Bankole A. Johnson *Editor*

Addiction Medicine

Science and Practice

Volume 1

Springer

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ISBN 978-1-4419-0337-2 e-ISBN 978-1-4419-0338-9
DOI 10.1007/978-1-4419-0338-9
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2010933193

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

For Carolina, and the beautiful dreams and great love that we share together, and the gift of our wonderful son. For Efun, and our eternal bond of family and love. For my father, whom I wish I understood better. For my mother, whom I remember, think of so very fondly, and pray for each day.

Preface

The book *Addiction Medicine: Science and Practice* is my attempt to bridge the gap between the explosion of neuroscientific and behavioral knowledge in the past three decades and treatment delivery in clinical practice. As such, it should fulfill the role of a comprehensive textbook that integrates addiction medicine from its scientific underpinnings to the treatment of patients in clinical settings.

In many ways, addiction is a spectrum of disorders that expands as our knowledge grows about the exposure and acquisition of habit-forming behaviors. This expansion shall eventually bring diseases not considered previously as addictions within its sphere. Due to our increasing use of in silico systems, technology-related behaviors might also become prominent areas of addiction research and treatment in the years to come. Our knowledge about the phenomenology and classification of addictive disorders is rising, and novel concepts related to the staging of disease are being developed.

We have learned that the neurobiological correlates of addictions related to substances, behaviors, or both appear to be similar. This discovery opens up new vistas for addiction treatments across a spectrum of disorders. Harnessing the power of understanding addiction at the level of the cell and molecular events across species with our ability to demonstrate the impact of these changes on the behavior of the organism shall usher in an era of personalized medicine. Innovative treatments and disease concepts are being advanced. New efficacious medicines for the treatment of addiction are being discovered. Indeed, our own immune system might someday be used to fight an addiction to various substances.

Culture, race, and ethnicity also have a major influence on how addictive behaviors can manifest or are expressed, and how they are viewed by society. Family traditions, religious beliefs and practices, and social setting characteristics are all very relevant and important in understanding addiction. Consequently, this book gives appropriate attention to these very relevant factors.

Taking all these essential factors into consideration, I conceptualized the bold design and challenge of a book that not only incorporated and highlighted cutting-edge science but also provided up-to-date and evidence-based treatments for addiction. This book provides a fresh approach that builds upon what the best experts know today—that for most, addiction is a

treatable disorder and the outcome need not always be poor. Modern addiction treatment is firmly in the arena of medicine, and is moving rapidly into general clinical practice, with evidence-based procedures replacing the much less well or formally evaluated and more expensive residential programs. For many individuals with an addictive disorder, an office-based approach enables optimum management of the disease whilst allowing engagement in work, play, social relationships, and the general business of daily life to continue.

I am most grateful to the distinguished group of leading experts who have come together to produce this book. These experts, united in their mission to deliver a scholarly and comprehensive book, came from the basic and clinical sciences and treatment delivery fields. I am glad for all that they have taught me through their contributions, for the knowledge they shall distill to all who read this book, and for their dedication to alleviating the suffering of those afflicted by the disease of addiction.

Charlottesville, Virginia Bankole A. Johnson, DSc, MD

Acknowledgment

I am most grateful to Robert H. Cormier, Jr., whose editorial assistance was instrumental in completing this project, and whom I also am proud to call my friend.

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Part I
History, Perspectives, Epidemiology, Diagnosis, and Classification

Emerging Health Perspectives

H. Westley Clark and Linda Hutchings

Contents

Introduction

This chapter will address a few issues that are emerging as critical health issues with substance use perspectives. First, there will be a brief review of the epidemiology of substance use; this will be linked to the growing problem of prescription drug abuse. Second, the issue of screening and brief intervention for substance use disorders will be addressed. Then, the issue of new technologies as a vehicle for enhancing substance use disorder services will be reviewed. Finally, the issue of how to pay for substance use disorder services will be reviewed.

The epidemiology of substance use makes it quite clear that clinicians of any stripe will encounter patients or clients who use or misuse alcohol or psychoactive drugs. Therefore, the inter-relationship between substance use disorders, brain function, and treatment outcome should be of interest to the clinician concerned with patient and client health.

Alcohol Use

The National Survey on Drug Use and Health annually interviews approximately 67,500 persons to establish national estimates of substance use [31]. More than half of Americans aged 12 or older report being current drinkers of alcohol in the 2007 survey; this means that almost 127 million people have had at least one drink in the past month. Other than underage drinking, current drinking is not inherently problematic. However, more than one-fifth (23.3%) of persons aged 12 or older admit to binge drinking, which the National Survey on Drug Use and Health defines as five or more drinks on a single occasion. Binge drinking is associated with a number of acute adverse events, including

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_1,

motor vehicle accidents, trauma, domestic violence, assaults, homicides, child abuse, suicide, fires, boating accidents, alcohol poisoning, and a number of high-risk activities which threaten the health and well-being of the consumer. Another confounding population of alcohol consumers is the heavy drinking population. It is estimated by the National Survey on Drug Use and Health that 17 million people or 6.9% of the population 12 or older admit to heavy drinking (binge drinking on at least 5 days in the past 30 days).

Naturally, alcohol consumption rates vary by—among other things—age, gender, and race/ethnicity. Among young adults aged 18–25 years of age, consumption rates are the highest in the current use, binge drinking and heavy alcohol use ranges. This age range is also associated with higher risk-taking and the consequences associated with risk-taking. Thus, physicians and other clinicians who provide primary and/or, emergency room care employment or college health practitioners are more likely to see patients in this age group for a variety of alcohol-related injuries or conditions.

Among adolescents and young adults under the age of 21, alcohol consumption rises fairly rapidly from 3.5% for those who are 12 or 13 to 50% for those who are between the ages of 18–20. Figure 1 shows the various levels of alcohol consumption for the 12–20 years olds by age grouping. It is apparent from these prevalence rates that late adolescents and young adults are likely to engage in substantial alcohol consumption. Knowing whether alcohol use is related to a presenting physical or psychiatric complaint should be helpful to the clinician. While many young adults, 18–25, will visit a clinician for very limited purposes, such as a job- or school-related physical, the epidemiology of alcohol use clearly offers the clinician an opportunity to address the issue of alcohol-related medical, social or behavioral problems. Clinicians should take advantage of such opportunities.

Illicit Drug Use

In 2007, there were an estimated 19.9 million Americans aged 12 or older who admitted to using at least one illicit drug in the past month according to the National Survey on Drug Use and Health. This represented an estimated 8.0% of the population 12 or older. For the purposes of the survey, illicit drugs included marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically. Marijuana is the most commonly used illicit drug by Americans, with 14.4 million people admitting to past-month use. The second category of prevalent drug use falls into the

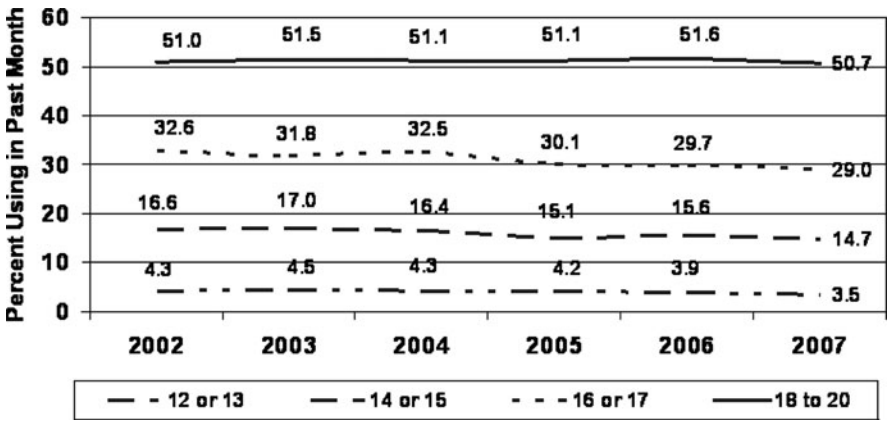

Fig. 1 Current alcohol use among persons aged 12–20: 2002–2007. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

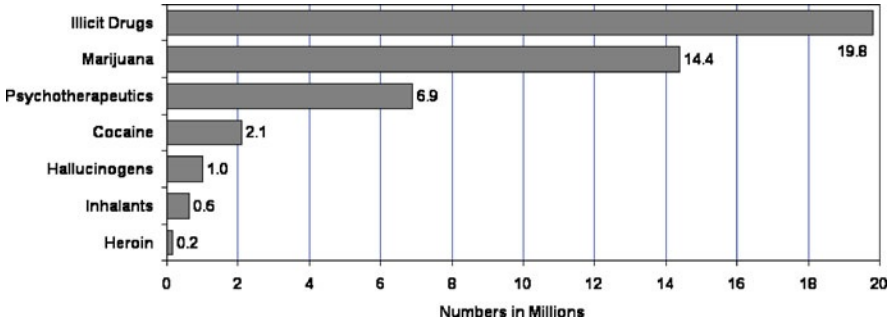

Fig. 2 Past-month use of specific illicit drugs among persons aged 12 or older: 2007. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

category of non-therapeutic or non-medical use of prescription drugs (see Fig. 2).

Specific categories of psychotherapeutics include a range of substances, including pain relievers, sedatives, tranquilizers, and stimulants. National Survey on Drug Use and Health data for those 12 and older reveal a consistent elevation of non-medical use of prescription pain relievers from 2002 to 2007 (see Fig. 3).

It has been recognized that prescription opioids are associated with higher rates of abuse and dependence than with other substances, as well as increased mortality [13]. The misuse of benzodiazepines in combination with therapeutic opioids can create problems with respiration and cardiac functioning, predisposing to respiratory depression or cardiac dysrhythmia leading to death.

Age Variations

However, as with alcohol use and misuse, there are age variations in illicit drug use. Among adolescents, National Survey on Drug Use and Health data indicate that there has been a progressive decline in the prevalence of drug use among adolescents aged 12–17 years of age (see Fig. 4). National Survey on Drug Use and Health data are supported by the Monitoring the Future Data, both surveys revealing the same basic trends [18].

It is important for primary care clinicians to recognize that the progress being made in reducing the substance use of adolescents has not resulted in an elimination of the problem of drug use. While substantial progress has been made, much effort needs to be exercised to keep up the

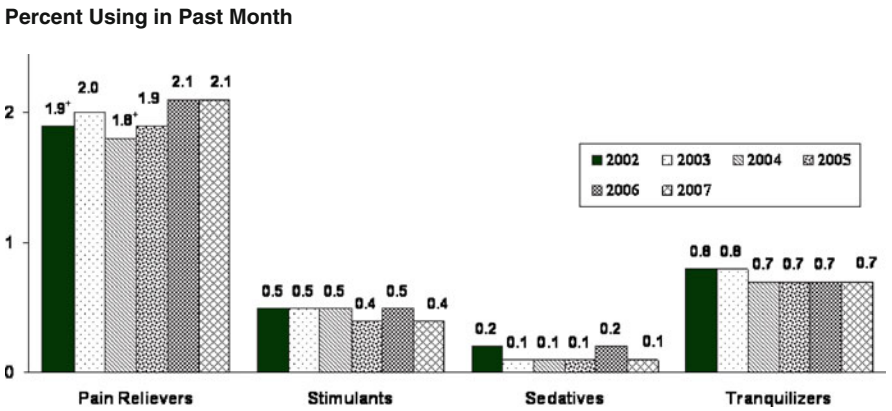

Fig. 3 Past-month non-medical use of prescription drugs (psychotherapeutics) among persons 12+: 2002–2007. +Difference between this estimate and the 2006 estimate is statistically significant at the 0.05 level. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

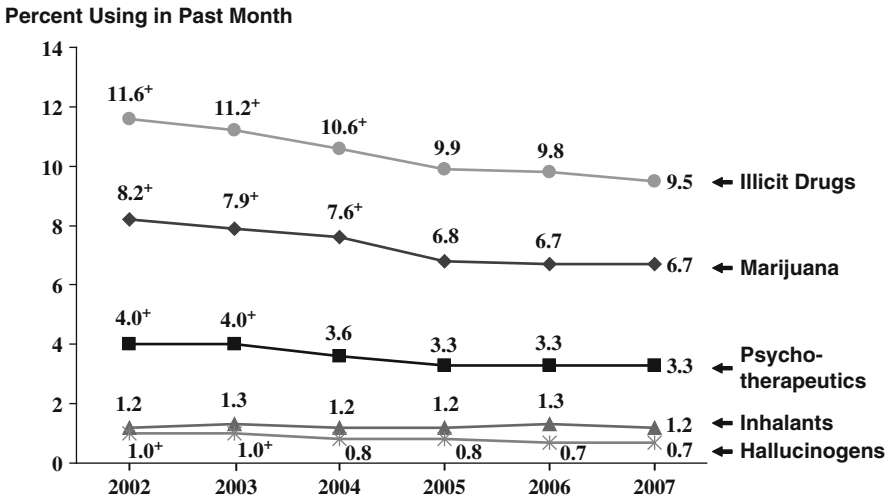

Fig. 4 Past-month use of selected illicit drugs among youths aged 12–17: 2002–2007. +Difference between this estimate and the 2007 estimate is statistically significant at the 0.05 level. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

pressure to continue to reduce the use of such substances among adolescents.

Another interesting trend seen in the National Survey on Drug Use and Health data involves adults aged 50–59. According to the 2007 National Survey on Drug Use and Health data, this age group showed an irregular increasing trend between 2002 and 2007 regarding current illicit drug use. For those 50–54, illicit drug use (past month) increased from 3.4% in 2002 to 6.0% in 2006, ending in 5.7% in 2007. There was a greater increase in past-month use of illicit drugs for those in the 55–59 age group — with an overall increase from 1.9% in 2002 to 4.1% in 2007. These trends may partially reflect the aging "Baby Boomer" population, whose lifetime rates of illicit drug use are higher than older adults (see Fig. 5).

For physicians—particularly those who specialize in the care of older patients—these trends indicate some of the challenges that may develop as the Baby Boomer population continues to age. According to the United States Census Bureau, one in five United States residents will be 65 or older in 2030. By 2050, it is projected that 88.5 million seniors will be 65 years or older, with 19 million of them 85 years or older [34].

Non-medical Use of Prescription Drugs

From an applied emerging issues perspective, the non-medical use of prescription drugs has become a major public health problem. The fact that the non-medical use of prescription drugs is now recognized as the second most prevalent pattern of illicit substance use should be of great interest to substance use disorder prevention and treatment specialists and to those in primary care, especially those who prescribe such medications.

As with alcohol misuse, there are age variations in the non-medical use of prescription drugs. National Survey on Drug Use and Health data show a gradual decline in the non-medical use of pain relievers in the past month, from 3.2 to 2.7% over the time period 2002–2007. However, when looking at young adults, 18–25 years of age, there has been a gradual *increase* in the non-medical use of prescription drugs from 4.1 to 4.6% for the same time period. Concomitantly, there has been a gradual increase for adults 26 or older from 1.3 to 1.6% during that time period. In 2007 alone, an estimated

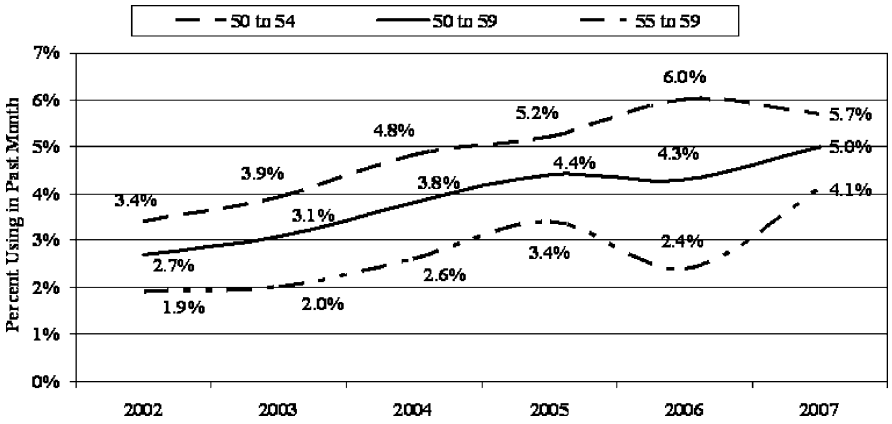

Fig. 5 Past-month illicit drug use among adults 50–59: 2002–2007. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

5.2 million individuals were currently misusing prescription pain relievers (see Fig. 6).

Additional data from the National Survey on Drug Use and Health highlight the fact that the majority of those who acquire prescription drugs for non-medical use get them free from friends and family members. Furthermore, when asked where the friends and family members got the prescription drugs, the majority of the respondents reported getting their drugs from a single physician (see Fig. 7).

It is now well established that individuals aren't just consuming prescription drugs "recreationally". Many are developing problems associated with their use. The National Survey on Drug Use and Health looked at those who meet criteria for abuse or dependence and found that figure to be more than two million individuals 12 or older. Within the prescription drug category, prescription pain relievers account for 1.7 million of the individuals who meet criteria for abuse or dependence, making prescription drugs the second most common category of drugs of misuse and the second most common category of abuse and dependence.

Thus, it is clear that the misuse of prescription drugs is a public health problem of growing proportion. However, that problem is complicated by the therapeutic need for the various agents, especially pain relievers, for clinical purposes. There does not seem to be any question about the need to treat pain adequately.

Among the implications of these findings are that prescribers of prescription drugs must assume some role in the education of patients or clients about the appropriate use of prescription drugs, and that the appropriate disposition of unused prescription drugs by patients and clients needs to be emphasized. Since prescription drug misuse is intimately tied to the

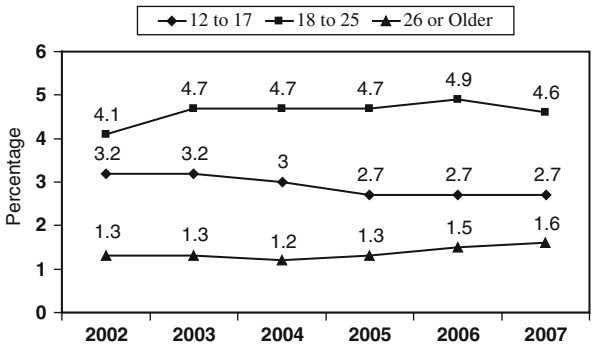

Fig. 6 Non-medical use of prescription pain relievers in the past month, by age group: percentages, 2002–2007. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

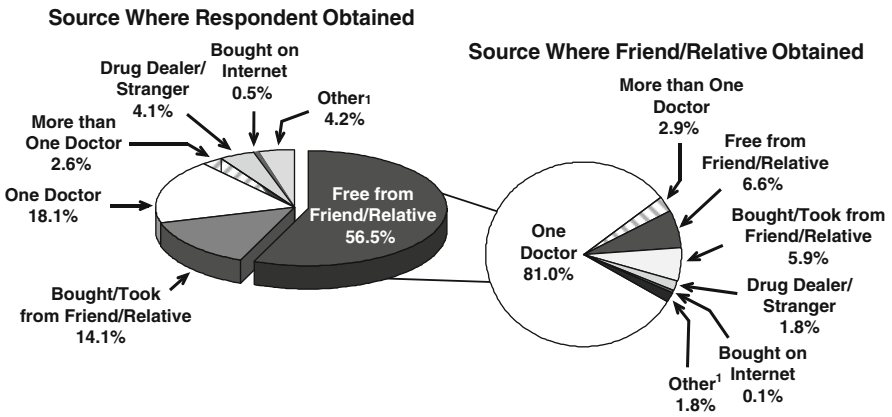

Fig. 7 Source where pain relievers were obtained for most recent non-medical use among past-year users aged 12 or older: 2007. Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown. [1]The "Other" category includes the sources "Wrote Fake Prescription", "Stole from Doctor's Office/Clinic/Hospital/Pharmacy", and "Some Other Way". Reprinted from the Substance Abuse and Mental Health Services Administration [31]

therapeutic use of critical medications, strategies that simply address drug dealing, internet sales, misprescribing clinicians, and doctor shopping are inadequate. Nevertheless, many jurisdictions have adopted prescription monitoring programs as a way of tracking the behavior of both patients and prescribers. The Drug Enforcement Administration notes that 38 states have enacted legislation that require prescription drug monitoring programs: 29 of those programs are currently operating and 9 are in the start-up phase [25]. (The 38 states with prescription drug monitoring programs and/or enacted legislation are: Alabama, Alaska, Arizona, California, Colorado, Connecticut, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Massachusetts, Michigan, Minnesota, Mississippi, Nevada, New Jersey, New Mexico, New York, North Dakota, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Virginia, Vermont, Washington, West Virginia, and Wyoming. Currently, the state of Washington uses its program only for disciplinary purposes; however, legislation has been introduced to expand the program statewide.)

Prescription monitoring programs are evolving with information technology. Some programs are hampered by the fact that they are not currently operating in real time, but promise to become real time in the future. Another limitation of prescription monitoring programs is that they are often limited to specific states and do little to address patient or physician behavior across state jurisdictional lines.

As suggested above, the category of prescription drugs that ranks highest in abuse is that of analgesics, particularly pain relievers in the Controlled Substances Act schedules II and III [9]. The treatment of pain in American society is the fundamental basis for use of controlled substances, and access to appropriate pain medication is essential. Strategies designed to monitor the prescribing of pain relievers were historically not proffered as efforts to limit access to pain medication, but to discourage the misprescribing of pain medication. However, among prescribing practitioners the fear of legal consequences may have a "chilling" effect.

A recent study by Goldenbaum et al. notes that only 725 physicians between 1998 and 2006 were criminally charged and/or administratively reviewed for offenses associated with the prescribing of opioid analgesics [16]. This represented only 0.1% of the estimated 691,873 patient-care physicians active in 2003. Furthermore, the Goldenbaum et al. study concluded, "Practicing physicians, including Pain

Medicine specialists have little objective cause for concern about being prosecuted by law enforcement or disciplined by state medical boards in connection with the prescribing of CS [controlled substances] pain medications" [16].

The policy discussion about pain and the use of controlled substances for the management of pain in patients is an important one. With an estimated 50–60 million people within the United States suffering from chronic pain, and a larger estimate of the prevalence of various acute pain syndromes, the availability of appropriate treatment strategies is of critical importance.

The legitimate role of controlled substances in the treatment of the spectrum of pain-related conditions is often discussed. Clinicians are admonished to use clinical guidelines, transparent practices with documentation, and conservative strategies when monitoring patient compliance and dysfunctional patient behavior. Clinicians are also told to anticipate that some percentage of their patients or clients may develop substance use disorders associated with their treatment regimens or may present to treatment with pre-existing substance use disorders or vulnerabilities.

Prescription opioid dependence is also associated with other psychiatric conditions. Depression and anxiety disorders are two *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition axis I diagnoses found to be related to opioid dependence disorder in patients being treated for disabling spinal disorders who suffered from pain [11]. Managing co-occurring disorders and chronic pain conditions requires specific treatment strategies that take into account the full spectrum of the patient's conditions.

Further research will need to be done to appropriately map out the dimensions of the prescription drug misuse problem. Clinical treatment strategies for those suffering from pain and needing controlled substances will need to be refined, while substance abuse prevention and treatment programs will need to develop targeted treatment protocols.

As previously mentioned, recent survey data indicate that approximately 57% of diverted pain relievers are obtained free from friends and family members. Another 8.9% of individuals bought their pain relievers from a friend or a relative, with another 5.2% stealing their pain relievers from their friend or relative. In short, almost 71% of individuals who admit to the non-medical use of pain relievers got them from friends or family.

Clinicians, researchers and others interested in the public health implications of prescription drug abuse should obviously focus more energy on addressing the social and behavioral aspects of the social network aspects of prescription drug transactions. An emphasis on appropriate prescribing, with minimal excess, and appropriate storage with limited access, should be incorporated into clinician–patient interactions. Clinicians also should advise patients or clients about the appropriate disposal of excess controlled substances; this enlists the patient further in accepting responsibility for the medication and enhances the awareness that controlled substances can be dangerous if misused. Substance use disorders specialists should also be aware of the increase in prevalence of prescription drug abuse, with a particular recognition that prescription opioids are a growing problem among those with abuse and dependence who might present for treatment.

Combat Methamphetamine Epidemic Act of 2005

Clinicians in general should be aware that an ongoing problem of prescription drug misuse, particularly with narcotic analgesics, will produce calls for increased regulation and control of prescribing authority and patient access [22]. An example of this cause and effect is the Congressional response to the use of pseudoephedrine in recent years.

Because pseudoephedrine can be a precursor to methamphetamine production in illegal laboratories set up for methamphetamine production, the Combat Methamphetamine Epidemic Act of 2005 was incorporated into the USA

Patriot Improvement and Reauthorization Act of 2005, which was signed into law on March 9, 2006 [36]. This act banned the unmonitored over-the-counter sales of cold medicines that contain pseudoephedrine, resulting in the implementation of a comprehensive system of controls regarding the distribution and sale of drug products. It is important to realize that pseudoephedrine is found in both prescription and over-the-counter products used to relieve nasal or sinus congestion caused by the common cold, allergic rhinitis, sinusitis, hay fever, and other respiratory allergies [29].

The availability of pseudoephedrine over-the-counter made it a consumer friendly medication that was inexpensive and available in a dosage form that allowed for self-medication. Over 20% of adults in the United States suffer from allergic rhinitis requiring some form of intervention; this means that over 60 million people fall into this category. Over 30 million people suffer from sinusitis and 17.6 million people suffer from hay fever. In fact, people in the United States suffer 1 billion colds each year, according to some estimates. The Centers for Disease Control and Prevention estimate that 22 million school days are lost annually in the United States due to the common cold. This means that annually over 60 million people are affected by requirements of the Combat Methamphetamine Epidemic Act of 2005, limiting the number of tablets of ephedrine, pseudoephedrine, or phenylpropanolamine that can be purchased in a 30-day period. The Act also requires buyers to present either government issued photo identification or some form of acceptable identification and enter personal information such as name, address, date and time of sale, and signature into a logbook. It does not ban the sale of over-the-counter pseudoephedrine, however. Nevertheless, pseudoephedrine is being phased out as an over-the-counter drug by some pharmaceutical companies and replaced by less effective alternative decongestants such as phenylephrine.

Since the annual prevalence of methamphetamine use is less than 2 million people, while the current use of methamphetamine is less than 1 million [31], the authors of the Combat Methamphetamine Epidemic Act of 2005 obviously believed that some restrictions on the ability of the over 60 million people who might require pseudoephedrine to get that medication over-the-counter were tolerable in order to keep a minority of individuals from having ready access to a methamphetamine precursor. This same logic may be extended by policy makers to the phenomenon of the non-medical use of prescription drugs, with a special focus on prescription narcotics. As the over-the-counter use of pseudoephedrine is being replaced with a less effective phenylephrine, attempts may be made by supply reduction advocates and policy makers to alter the prescribing practices of clinicians in order to stem the flood of prescription drugs, particularly the opioids, into the non-medical use arena.

With one in four adults in the United States saying they suffered a day-long bout of pain in the past month, and 1 in 10 saying the pain lasted a year or more [6], the issue of treatment of pain in America is quite real. These numbers amount to 76 million people who have suffered from a day-long bout of pain in the past month and 30.5 million who have suffered from pain lasting a year or more. With 5.2 million people admitting to the non-medical use of opioid pain relievers, the larger number of individuals potentially affected by legal or regular constraints of the prescription of controlled substances for therapeutic purpose would be those who suffer from pain, not those who misuse or divert pain medications. Nevertheless, if the experience with over-the-counter pseudoephedrine is an example, organized medicine should take advantage of its head start and begin addressing the myriad of issues associated with pain medications' use and misuse.

Common chronic pain complaints include headache, low back pain, cancer pain, arthritis pain, neurogenic pain (pain resulting from damage to the peripheral nerves or to the central nervous system itself), psychogenic pain (pain not due to past disease or injury or any visible sign of damage inside or outside the nervous system). Whether all of these conditions require the

use of specific opioid medications for any specific patient should be determined by research and clinical evidence. However, concerns have produced demands for change. Already the Food and Drug Administration has issued letters to companies that make opioid drugs, including morphine, oxycodone and methadone; furthermore, the Food and Drug Administration will meet with pharmaceutical companies to review risk-management plans for medications [37].

The misuse of opioids can produce abuse and dependence requiring treatment. There are three treatment strategies: use of methadone, use of buprenorphine and the use of Naltrexone. Methadone has been used for more than 40 years in treatment of drug addiction. Its use for treatment of pain has increased in the last 5–10 years. Methadone can cause fatalities among individuals who have not developed any tolerance to opiates: children and adults who accidentally take methadone, and fatal intoxications during first weeks of treatment and adjustment of the methadone dose. Several risk factors have been identified for methadone mortality: the concomitant use of benzodiazepines and other opioids, and/or alcohol; an elevated risk of some individuals for torsade de pointes; inadequate or erroneous induction dosing and monitoring by physicians, primarily when prescribing methadone for pain; and drug poisoning that occurs as a result of diversion of the drug and its non-medical use.

It is important for the clinician to recognize that there are differences between prescribed methadone for pain and dispensed methadone for medication assisted therapy. When methadone is used for pain treatment no required risk management plan has been required. However, the Food and Drug Administration modified the labeling of methadone in 2006, and the Drug Enforcement Administration imposed a voluntary restriction on distribution in 2008.

When methadone is used for addiction treatment, the distribution is limited to certified, accredited, and registered programs. There are limits on the initial dose and restrictions on dispensing. The federal government, through the Substance Abuse and Mental Health Services Administration, recognizes the following entities as accrediting bodies: Joint Commission on Accreditation of Health Care Organizations, Commission on Accreditation of Rehabilitation Facilities, Council on Accreditation, National Commission on Correctional Health Care, and the state authorities of Missouri and Washington. There are only about 1200 opioid treatment programs licensed by the federal government. Those programs treat approximately 257,000 individuals. Incidentally, there are approximately 760,000 individuals receiving methadone for pain treated primarily outside of the opioid treatment system.

Another public health concern associated with the therapeutic use of opioids is the phenomenon of deaths associated with their use. The Centers for Disease Control and Prevention reported that there has been a significant increase in methadone-related deaths (see Fig. 8). Furthermore, there has been a steep increase in methadone-related deaths as a percentage of all poisoning deaths.

Within the opioid treatment community, there is an evolving concern about the prolongation of the rate-corrected QT interval and its

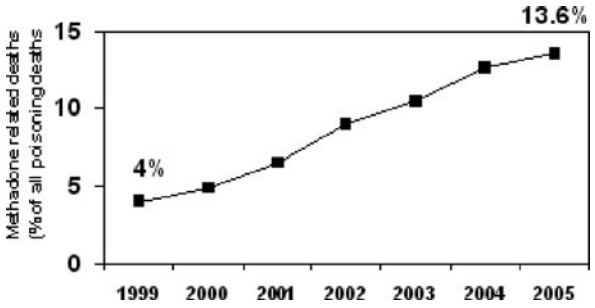

Fig. 8 Methadone-related deaths (percentage of all poisoning deaths). From 1999 to 2005, poisoning deaths increased 66% from 19,741 to 32,691. However, the number of poisoning deaths mentioning methadone increased 468% (from 786 in 1999 to 4,462 in 2005). Reprinted from Fingerhut [13]

relationship with torsade de pointes, potentially leading to sudden death. That concern is amplified by the increase in the number of methadone-related deaths. As more methadone is being used for the treatment of pain, it has become clear that even in the treatment of opioid dependence some risk exists for patients. Special concern applies to those who are being induced onto methadone.

SAMHSA's Center for Substance Abuse Treatment convened two expert panels over a 4-year period to examine associated etiologic factors related to methadone mortality. As a result of those reviews, it became clear that there were those in the medical community who believed that a routine pre-induction electrocardiogram screening should occur for all patients to measure the QTc interval and a follow-up electrocardiogram should occur within 30 days and annually thereafter. Particular sensitivity should be exhibited for those with histories of cardiac dysfunction [19].

While this advice is directed to opioid treatment programs, it applies to those who are receiving methadone for the treatment of chronic pain. Such advice recognizes that there are clinical challenges in the use of opioid medications, such as methadone, that extend beyond the issue of abuse and dependence. A preoccupation with abuse and dependence may detract from the physiological phenomenon that results from the greater use of a class of medications that play a critical role in preserving the public health.

Buprenorphine

Under the Drug Addiction Treatment Act of 2000, qualified physicians can treat individuals addicted to heroin or prescription opioids under a waiver provision administered by the Substance Abuse and Mental Health Services Administration and the Drug Enforcement Administration. To qualify, a physician must meet certain requirements (e.g., trained by a medical organization such as the American Psychiatric Association). Buprenorphine is the only Food and Drug Administration—approved medication that can be prescribed for this purpose.

In July 2005, Congress removed the 30-patient restriction on medical groups that prescribe buprenorphine for opioid dependence and addiction. The 30-patient limit was then applied to each physician's caseload, rather than to that of the entire clinic. The Office of National Drug Control Policy Reauthorization Act of 2006 increased the number of individuals a physician can treat with buprenorphine to 100 if specific conditions are met.

As of October 1, 2008, 19,000 physicians have been trained by a Drug Addiction Treatment Act–recognized medical organization and 16,000 physicians are authorized to prescribe buprenorphine. Approximately 300,000 individuals were treated in 2007, which is an 80% increase over 2006. (The Center for Substance Abuse Treatment is working with the Food and Drug Administration, the Drug Enforcement Administration, and the manufacturer to address reports of increasing diversion and abuse.)

There are a number of issues associated with the increased use of buprenorphine. Foremost is the need for medical schools, internships, residencies, and fellowships to increase the underlying issues of abuse and dependence of prescription opioids and/or heroin. Buprenorphine offers the primary care, specialist, or addiction medicine physician the opportunity to address opioid abuse or dependence at the patient level. However, training is a necessary precursor. An evolving twist in the practice of medicine is the use of buprenorphine for the treatment of pain. Of course, increased focus is also needed on those patients who have a pain condition and who suffer from addiction to opioids.

As buprenorphine gained in popularity, it was inevitable that adverse event reports would increase in occurrence. The increased use of buprenorphine magnifies the risk to children in homes in which it is used. Clinicians should remain vigilant for pediatric exposures [15]. Clinicians should *not* assume that because

Suboxone® is a combination of buprenorphine and naloxone, pediatric patients are not at risk for opioid toxicity [27]. Individuals receiving buprenorphine on an outpatient basis should be educated regarding steps they can take to ensure that it is not accessible to any young children in their homes.

In 2006, of 346,946 reported emergency department visits, 47,538 involved opioid analgesics—and only 356 of these involved buprenorphine or a combination of buprenorphine and other medications. Of those involving buprenorphine: 52 were due to adverse reactions, 63 were seeking detoxification, 225 were due to non-medical use, and 11 were due to accidental ingestion [35]. Most common pattern of abuse involves crushing the sublingual tablets and injecting the resulting extract. When injected intravenously, addicts claim buprenorphine effects are similar to equipotent doses of morphine or heroin. Indications are that buprenorphine obtained for non-medical purposes in the United States is diverted from prescriptions written for treatment of addiction or obtained through "doctor shopping" [30].

More than one-third of buprenorphine abusers reported that they took the drug in an effort to self-medicate and ease heroin withdrawal. A majority of buprenorphine abusers are young white males with extensive histories of substance abuse [8]. When asked in a National Association of State Alcohol and Drug Abuse Directors study, 33% of physicians considered Subutex® to be a significant abuse and/or diversion threat in their states [5]. In the same study, only 6% of physicians considered Suboxone® to pose a significant abuse threat, and only 8% considered it to be a significant diversion threat in their states.

Monitoring of discussions within Internet newsgroups and interviews found that the buprenorphine products are viewed primarily as medications to avoid or ease withdrawal symptoms rather than a means of getting high. There is evidence of experimental use and illegal diversion of buprenorphine; however, the extent of abuse and diversion does not come close to that of methadone or OxyContin®. Intravenous use of either Suboxone® or Subutex® appears to be rare, but it is evident from street interviews [10].

Physician Training and Buprenorphine

While the Drug Addiction Treatment Act of 2000 prescribes a minimum of 8 h of education for physicians not otherwise exempted, it became clear that additional support was needed for a number of practitioners new to the effort to provide care to those who abused or were dependent on opioids using buprenorphine. Therefore, the Center for Substance Abuse Treatment created the Physician Clinical Support System for Buprenorphine. The Physician Clinical Support System was created in collaboration with the American Society of Addiction Medicine; this public private partnership permits physicians who prescribe or dispense buprenorphine to contact the Physician Clinical Support System for support. The Physician Clinical Support System is a free, national service staffed by 45 trained physicians' mentors, a Physician Clinical Support System medical director and five physicians who are national experts in the use of buprenorphine. The Physician Clinical Support System offers support via telephone, via email, and/or at the place of the individual physician's practice. Access to information about the Physician Clinical Support System can be acquired from the Web site: www.PCSSmentor.org.

The Physician Clinical Support System has a steering committee made up of representatives from over 20 organizations, including such physician groups as the American Medical Association, the American Psychiatric Association, the American Osteopathic Academy of Addiction Medicine, the American Academy of Pediatrics, the Society of General Internal Medicine, the American Academy of Addiction Psychiatry, and the American Society of Addiction Medicine. It is believed that providing

physicians with collegial support will enhance treatment strategies and patient education, thus diminishing the prospect of adverse events and medication diversion.

Utilization of Substance Abuse Treatment Services

The National Survey on Drug Use and Health presents findings about utilization of substance abuse treatment services in addition to a comprehensive overview of substance use. In 2007, an estimated 22.3 million persons aged 12 or older were classified with substance dependence or abuse in the past year; this represented 9% of the population. Of these, 3.2 million were classified with dependence on or abuse of both alcohol and illicit drugs, 3.7 million were dependent on or abused illicit drugs but not alcohol, and 15.5 million were dependent on or abused alcohol but not illicit drugs.

In 2007, only 3.9 million of the 22.3 million persons who met criteria for substance dependence or abuse received some form of treatment for a problem related to the use of alcohol or drugs. Treatment was reported to be received in a range of settings: self-help groups, outpatient rehabilitation, inpatient rehabilitation, outpatient mental health centers, hospital inpatient, private doctor's offices, emergency room, or prisons or jails. Looking beyond the full universe of treatment options and focusing only on hospital inpatient units, drug or alcohol rehabilitation facilities (inpatient or outpatient), or mental health centers as specialty substance abuse treatment settings, the National Survey on Drug Use and Health reported that only 2.4 million people, 12 or older, who met criteria for substance abuse or substance dependence received treatment. What is striking about the findings is that 20.8 million people in 2007 who were classified as needing substance abuse treatment did not receive it.

Of the 20.8 million people who met criteria for needing treatment but did not receive it, 93.6% did not feel that they needed treatment and made no effort to get treatment. Another 4.6% felt that they needed treatment but did not make an effort to get it, while 1.8% or 380,000 people felt that they needed treatment, made an effort to get it, but did not receive it. In short, 98.2% of the 20.8 million people who met criteria for needing treatment made no effort to receive it.

These findings created the basis of two evolving concepts. The first is that the "true" waiting list is made up of only 380,000 people: the individuals who made an effort to get treatment, but who were not successful. The second is that the overwhelming majority of individuals who meet criteria are not seeking treatment despite being symptomatic (see Fig. 9). It is not clear why the overwhelming majority of individuals who

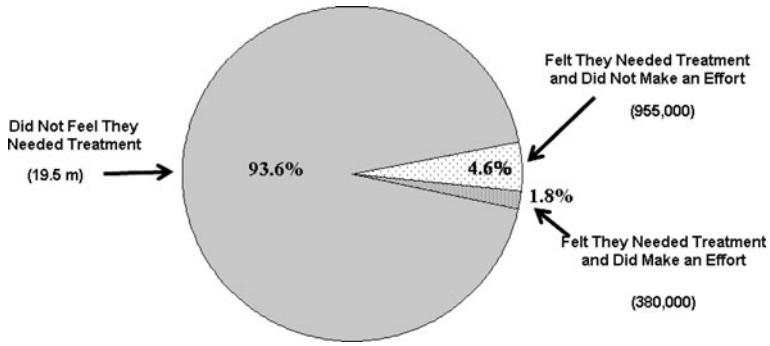

Fig. 9 Past-year perceived need for and effort made to receive specialty treatment among persons aged 12 or older needing but not receiving treatment for illicit drug or alcohol use: 2007. 20.8 million needing but not receiving treatment for illicit drug or alcohol use. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

meet criteria for needing treatment do not seek it. However, it is clear that these individuals must have some psychosocial decrements of function noticeable not only to themselves, but to those in their environment. Environmental motivators can include: family, employers, health care practitioners, law enforcement, faith leaders, friends, and associates. Therefore, from a public health perspective and a public safety perspective, it is important to determine the role of substances of misuse in the lives of individuals. It is also important to understand the developmental significance of alcohol and drugs to those in the 18- to 25-year age range, for these young adults account for the peak misuse of alcohol, traditionally illicit drugs and now prescription drugs. The data above clearly show that our efforts to reach young adults need to be intensified.

Social Determinants of Health

There are many social determinants of health, with varying influence depending upon the individual's unique condition (see Fig. 10). The use of alcohol or drugs has many cultural, biological and social precursors. The misuses, then, are similarly disposed. The question of why a substance is used beyond the obvious reality of the physiological and psychological effects remains a mystery. This is clearly seen among those who meet criteria for treatment, but who do not seek assistance. The World Health Organization has an established focus on the social determinants of health. The conceptual model depicted in Fig. 10 recognizes that there are structural determinants of health inequities coupled with intermediate determinants of health that influence the equity in health and well-being. The socioeconomic and political context of an individual's life plays a role in that individual's health. A modified version of the World Health Organization's model includes drug laws and laws governing the use of alcohol. A person's socioeconomic position in society also contributes, with material circumstances, behavioral and biological factors and psychological factors figuring into access to a health system and impacting on the health system available to a person. Health does not occur in a vacuum. Also, substance use and misuse do not occur in a vacuum. One recent survey showed that respondents feel that persons who are addicted to illicit drugs such as cocaine and heroin are much more of a danger to society than those addicted to alcohol, prescription drugs, or marijuana [33]. In fact, the

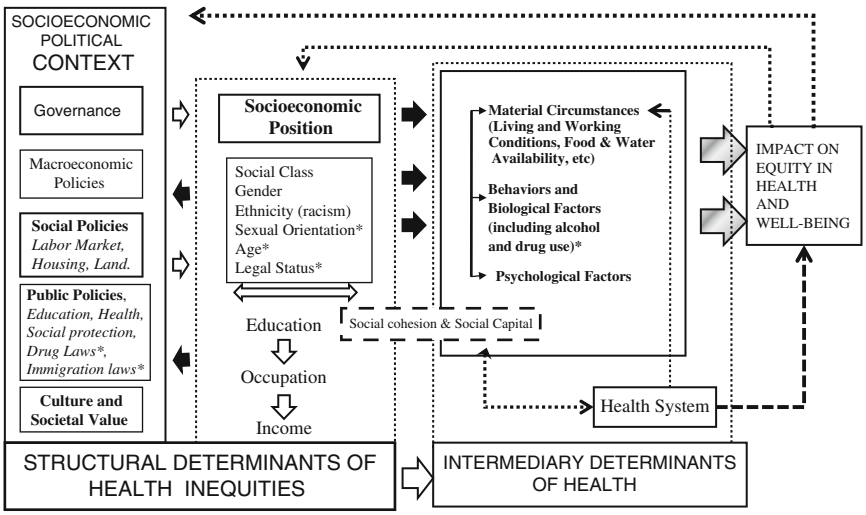

Fig. 10 The social determinants of health. Adapted from the diagram in section V.9 on p. 48 of: World Health Organization, Commission on Social Determinants of Health [38]

survey found that respondents viewed addiction to alcohol and prescription drugs to be more dangerous than addiction to marijuana. These data reflect the cultural imperatives, public opinions, and socioeconomic benefits associated with use of the substances in question.

Addressing Barriers to Treatment

Consequently, the reasons for *not* seeking treatment can also be complex, including lack of health care, lack of transportation, the fear of stigma and not knowing where to go for treatment or if any available program has appropriate treatment.

The United States government decided to embark on two different strategies to address the issue of the 20.8 million Americans who needed treatment for substance use disorders but who were not receiving treatment. The first effort, called the Access to Recovery initiative, targeted the 380,000 people who were seeking treatment but could not get it. The second effort recognizes that the overwhelming majority of people in need of care were not presenting to specialty treatment programs, but many were presenting at alternative sites of care, specifically trauma centers, community health centers, and other primary care venues.

Access to Recovery

In the Access to Recovery initiative, consumers are empowered to purchase substance abuse services using vouchers issued by state grantees. In addition to using such vouchers, increased emphasis is placed on a system of support services classified as recovery support services. Recovery support services are predicated on the notion that community support extends the reach of specialty delivery services. State or tribal grantees work with a network of public, private, and non-profit entities to help the affected individual. Thus, professional, peer, faith-based, and community-based support services were wrapped around the treatment focus. The Access to Recovery initiative served over 198,000 individuals in its first 3 years, primarily those individuals who lacked the financial resources to access treatment. Such services as transportation, child care, literacy training, self-help facilitation, recovery-based training and relapse prevention, assistance with the criminal justice system, transitional housing, and employment coaching are considered an integral part of the recovery process (see Fig. 11).

The basis for recovery support services is predicated on the work of the National Institute on Drug Abuse. The critical components of treatment are captured in the National Institute on Drug Abuse "Wheel". According to the National Institute on Drug Abuse's data, individuals without community or family supports are more vulnerable to relapse than those with such supports.

The combination of vouchers, which provide more freedom of choice, with the integration of recovery support services into the treatment plan, has proven to be effective. The Access to Recovery initiative maintains performance data for the jurisdictions participating; these data indicate that at 6-month follow-up, there was a reduction in substance use, decreased involvement with the criminal justice system, and an increase in stable housing.

The initial cohort of Access to Recovery programs involved 15 jurisdictions. The second phase of the program has increased to involve 24 jurisdictions: 18 States, Washington, DC, and five tribes or tribal organizations.

Screening, Brief Intervention, and Referral to Treatment

The second effort, Screening, Brief Intervention, and Referral to Treatment, recognizes that the overwhelming majority of people in need of care are not presenting to specialty treatment programs, but many are presenting at alternative

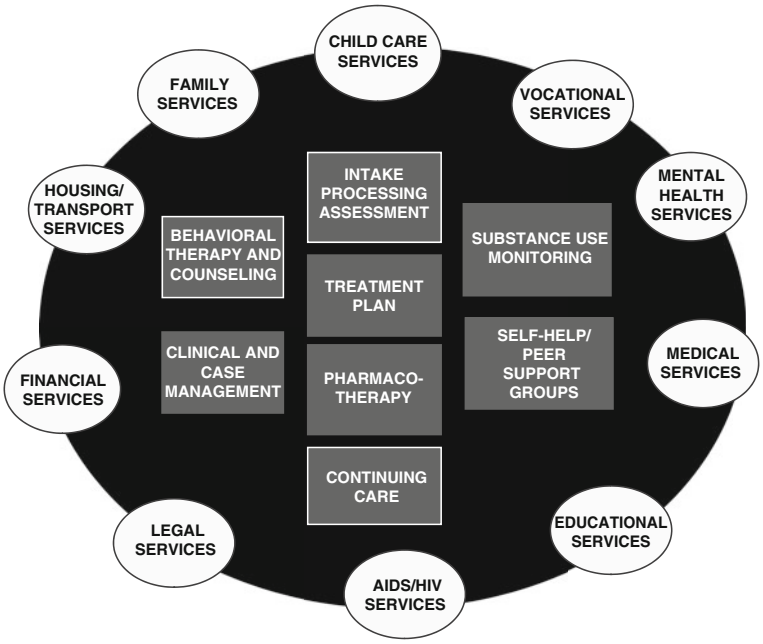

Fig. 11 Treatment services. Reprinted from the National Institute on Drug Abuse [23]

sites of care, specifically trauma centers, community health centers and other primary care venues (see Fig. 12).

Cherpitel and Ye analyzed the National Alcohol Survey for the year 2005. The Survey canvassed 6,919 adults using a random digit dial computer-assisted telephone interview with an over-sampling of blacks and Hispanics [7]. The respondents were asked if they consumed any alcohol in the 6 h prior to a reported injury (alcohol-related) and whether they felt the injury was related to their alcohol consumption (alcohol-caused). Seven percent of the respondents reported an alcohol-related injury treated in an emergency department; 6% reported receiving any treatment for their alcohol-related injury, and 5.3% reported alcohol-related injuries treated in primary care settings.

Of those seen at emergency departments who reported alcohol-related injuries, 28% reported that the injuries were alcohol caused; of those presenting to primary settings, 14.9% reported their injuries as alcohol caused; and for those presenting to any treatment, 18.9% reported their

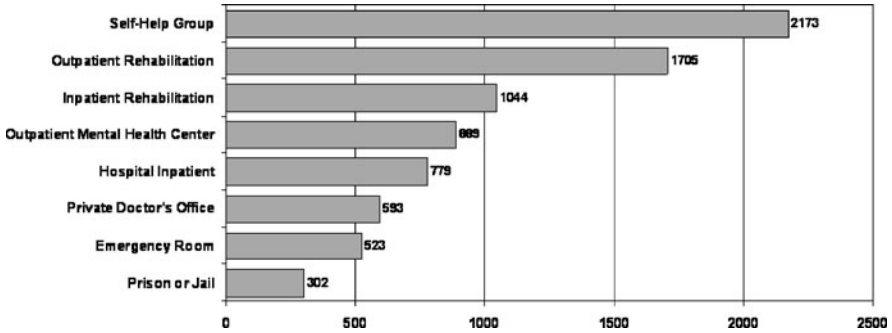

Fig. 12 Locations where past-year substance use treatment was received among persons 12+: 2007. Reprinted from the Substance Abuse and Mental Health Services Administration [31]

injuries as alcohol caused. One recent convenience sample of urban family medicine patients by Fogarty et al. found a prevalence rate of 16.7% for alcohol use disorders [14]. Fogarty et al. also noted that, inter alia, an alcohol use disorder was related to twice the odds of reporting more than one emergency department visit over the previous year, 16% fewer primary care provider visits, and 238% more non-psychiatric hospitalizations. In other words, while the prevalence of alcohol-related injuries is small in the general population, individuals presenting in the primary care setting who have an alcohol use disorder are more likely to use more expensive health care settings.

According to the National Survey on Drug Use and Health, the 19.5 million people who meet criteria for alcohol use disorders, but perceive no need for treatment and are not receiving treatment, are not going to specialty care settings. Thus, from a public health approach, if those affected by alcohol use disorders will not go to formal treatment, some form of treatment must go to them. Consequently, such entities as the World Health Organization, the United States Preventative Services Task Force, the Committee on Trauma of the American College of Surgeons, and the Academic Emergency Department Screening, Brief Intervention, and Referral to Treatment Research Collaborative all recommend routine screening for alcohol problems in various health care settings.

It has long been known that screening for problem drinking and brief counseling by primary care providers is an effective approach to reducing alcohol consumption [17, 28]. In fact, the United States Preventive Services Task Force recommends screening and behavioral counseling interventions to reduce alcohol misuse by adults, including pregnant women, in primary care settings [1]. Because it is recognized that a unique opportunity exists also to address illicit drugs in the primary health care setting, the question of whether it is practicable to screen for these substances has been raised. At this point in time, the United States Preventive Services Task Force has concluded: "for adolescents, adults, and pregnant women, the evidence is insufficient to determine the benefits and harms of screening for illicit drug use" [1]. Nevertheless, the Federation of State Medical Boards adopted a policy statement to develop "methods and/or modules of information to be used to educate medical students, residents and practicing physicians regarding the identification of substance use disorders, brief intervention and the proper prescribing of controlled substances" [12]. In addition, the Centers for Medicare and Medicaid Services added to the Healthcare Common Procedures Coding System new Level II billing codes for screening and brief intervention for alcohol and/or drugs that went into effect on January 1, 2007 [24]. The American Medical Association also has added to its current procedural terminology codes two new codes covering services related to alcohol and drug abuse screening and treatment [21].

Furthermore, researchers are exploring the utility of using screening and brief intervention as a tool to address more carefully the issue of drug abuse [2–4]. Use of such substances as marijuana, prescription drugs, and cocaine occurs with sufficient frequency to make them ideal targets for a screening effort. The epidemiology of a given community might elevate other substances of misuse to a level that makes screening in that community practical and feasible.

As noted, screening is not the only component of a process of detection and intervention. Screening, Brief Intervention, and Referral to Treatment is predicated on any of the three following strategies: brief intervention, brief treatment, or referral to treatment [32] (see Fig. 13). It became clear to the federal government that one of the engines that drive the demand for drugs is the lack of perceived need for care. At the same time, people were being seen for injuries and conditions related to drug abuse and misuse. The challenge was how to take advantage of the opportunity to provide this population with at least brief intervention or treatment.

The Center for Substance Abuse Treatment of the Substance Abuse and Mental Health Services Administration implemented a grant program in 2003 to encourage state jurisdictions and tribal organizations to initiate Screening, Brief

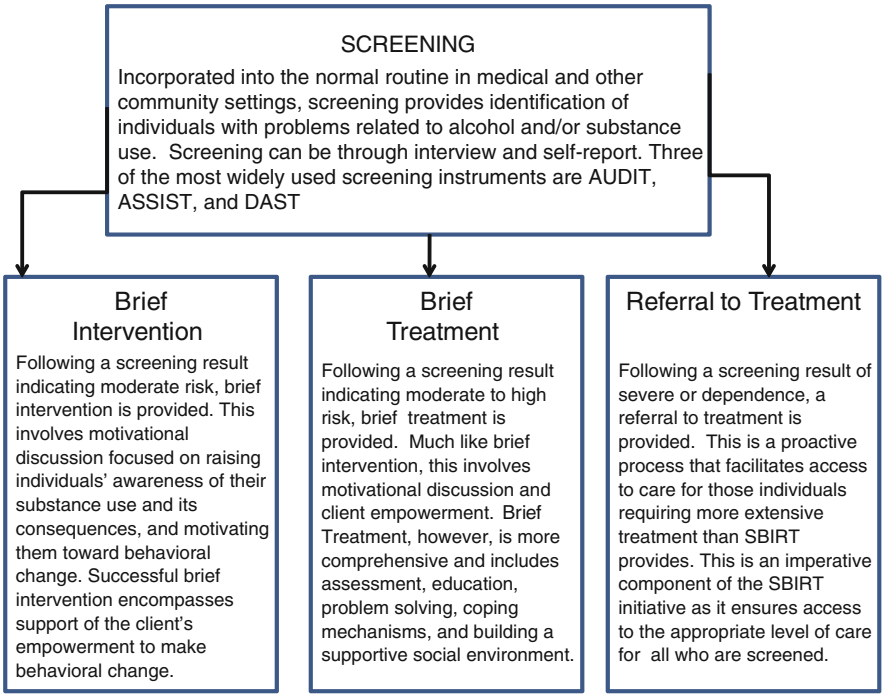

Fig. 13 Screening, brief intervention, brief treatment, and referral to treatment. Reprinted from the Substance Abuse and Mental Health Services Administration [32]

Intervention, and Referral to Treatment programs in a variety of healthcare settings, including inpatient programs, emergency departments, ambulatory care settings, community health centers and other primary care settings. The Center for Substance Abuse Treatment funded 5 state jurisdictions and one tribal organization to promote and implement Screening, Brief Intervention, and Referral to Treatment protocols in 2003 (California, Illinois, New Mexico, Pennsylvania, Texas, Washington, Cook Inlet Tribal Council of Anchorage, Alaska). Another four grants were funded in 2006 (Colorado, Florida, Massachusetts, and Wisconsin). Then, in 2008, another cohort of four grants was funded (West Virginia, Missouri, Georgia, and the Dena Nena dba Tanana Chiefs Conference of Fairbanks, Alaska). Performance data from the first two cohorts of Center for Substance Abuse Treatment Screening, Brief Intervention, and Referral to Treatment grantees revealed that by the end of September, 2008, over 700,000 individuals were screened in over 100 settings: community health centers, trauma care centers, schools and student assistance programs, occupational health clinics, and hospital emergency departments.

Recovery as a Holistic System

The Access to Recovery and Screening, Brief Intervention, and Referral to Treatment initiatives emphasize the need to move beyond the rather narrow world of treatment into the broader world of recovery. The process of change through which an individual achieves abstinence and improved health, wellness, and quality of life benefits from an integrated system of care that views the treatment agency as one of many resources needed to ensure the client's successful integration into the community. Just as each person's path toward substance misuse was different, the path to recovery will also look different for each client. The recovery system

must be person-centered and self-directed, drawing upon resources that meet the particular needs of the client. Hence, a recovery-oriented system of care model operates very much like the etiological model suggested by the model that the World Health Organization promulgates about the social determinants of health. Chronic care approaches, including self-management, family supports, integrated services, and intensive case management, improve recovery outcomes. Integrated and collaborative care not only optimizes recovery outcomes but also improves cost-effectiveness.

Health Insurance

In the health care delivery system, the cost of providing health care is a chronic issue. Total spending for health care was $2.4 trillion in 2007, or $7900 per person. Total health care spending represented 17% of the gross domestic product, with spending on substance abuse treatment rising from $9 billion in 1986 to $21 billion in 2003 and projected to increase to $35 billion in 2014. What is remarkable is that substance abuse treatment spending was only 2.1% of total health spending in 1986, and this had dropped to 1.3% in 2003, with further declines in share of total health spending in 2014 [20]. It is estimated that public payers are responsible for over 77% of the expenditures for substance abuse treatment in 2003, and this number is expected to increase to 83% of expenditures by 2014. This makes substance abuse disorder treatment unique in the pantheon of health expenditures.

In 2003, private insurers paid only 10% of the bill for substance abuse services, while state and local dollars paid for 40% of the bill for services; Medicaid paid for 18% of the substance abuse treatment services bill [20]. The burden on the public sector is demonstratively great, particularly at a time when state budgets are suffering under the weight of deficits. Yet, as with health care in general, the question is: if substance abuse treatment is to continue, "Who will pay for it?"

There are two emerging movements that shift substance abuse treatment services into a more contemporary payment scheme: health care parity and health care reform. How substance use disorder treatment services are compensated clearly plays a role in what treatment options are available to an affected individual. Furthermore, the clinical algorithm employed by the clinician will also be influenced by the patient's or client's ability to pay for services or to get services provided.

Parity for substance use disorder services was addressed in recent federal legislation, the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 [26]. In that law, which went into effect on January 1, 2010, health plans that offer mental health and substance use disorder treatment benefits must do so on par with other health benefits. Under the law, insurance plans are not mandated to offer addiction and mental health benefits, but plans that do have those benefits must provide them on a non-discriminatory manner. Parity is also extended to coverage for out-of-network providers—increasing access to treatment for many insured individuals. Plans have the right to manage the benefit as they see fit and can decide which mental health and substance abuse treatment services they cover, as long as their decisions do not discriminate. However, they must provide to individuals and providers the medical necessity terms and conditions for any denials [26].

The law also acknowledges the fact that some states have already implemented parity laws, some of which may be stronger than the federal laws. In such cases, stronger state laws will not be pre-empted.

In short, the Wellstone/Domenici bill does not require the inclusion of substance use disorder treatment services in a health insurance benefits plan; it only requires parity of benefit structure with other health benefits if the substance use disorder treatment benefit is offered. Thus, the evolving debate about health care reform, centering on universal access to health care services, poses the greater challenge for those who require substance abuse treatment services, those

who provide such services, and those who refer patients to such services.

Critical themes in health care reform will be the issues of cost of services, the quality of the services provided, accountability for the provision of the services, and access to the services. Decision-making within the province of substance abuse treatment services will have to be transparent, with a clear view of the qualifications of the providers, and assessment tools used to determine the various treatment components necessary for treatment, documentation of services provided through electronic health records, and the appropriate use of evidence-based practices with some evidence of fidelity to those practices and verification of acceptable outcomes in choosing the relevant practices.

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The Epidemiology of Alcohol and Drug Disorders

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What is Epidemiology?

The field of epidemiology involves investigation of the distribution and determinants of health conditions in populations or population subgroups. Epidemiological investigations fall under two common domains: descriptive and analytic. Descriptive epidemiologic studies provide estimates of the incidence and prevalence of illnesses or health behaviors. Incidence refers to the proportion of new cases of a particular health outcome during a specific period of time in a specific at-risk population (i.e., among individuals free of the outcome at the beginning of the time period). Prevalence refers to the proportion of a group or population affected with a health condition at a particular point in time. This includes new cases as well as chronic cases that began earlier and continued into the period of observation. Analytic epidemiologic studies focus on identifying causes/risk factors (e.g., genetic variants, contextual circumstances) of illness, often done through retrospective comparison of cases with non-cases or prospective study of disease development among individuals exposed versus unexposed to a particular hypothesized causal factor.

This chapter covers the epidemiology of alcohol and drug abuse and dependence (referred to together as "substance use disorders"). From an epidemiologic standpoint, substance use disorders have common as well as unique characteristics. This chapter identifies common characteristics of the epidemiology of alcohol and drug use disorders, and highlights

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_2,

some important characteristics unique to specific substances.

Substance Use in the United States: A Historical Overview

Alcohol Consumption

The use of substances to alter mood states has been a part of civilization from pre-historic through modern time periods. Archeological records document the conversion of sugar into fermented beverages for recreational use, as part of religious ceremonies, and as an analgesic or disinfectant as early at 10,000 B.C. [1, 188]. Alcohol remains incorporated into the fabric of many cultures for a variety of uses, including social and recreational use, as a part of religious ceremonies, secular festivities, and as a normative aspect of daily life. Further, moderate consumption is associated with health and longevity, and is considered to be protective against several adverse health outcomes including cardiovascular disease [13].

Long-term historical information on United States alcohol consumption is available through per-capita alcohol consumption statistics derived from sales records. These records show drinking levels in the United States varied greatly over time from the early days of the United States to the twenty first century [169, 172]. Per-capita consumption levels ranged from extraordinarily high levels during the United States colonial period (from an estimated 5.8 gallons per year per capita in 1790 to 7.1 gallons in 1830) to very low levels before and during Prohibition (from an estimated 1.96 gallons in 1916 to 0.97 gallons in 1934). Prohibition refers to the time period during which the United States prohibited the manufacture, sale, and transportation alcoholic beverages were prohibited by the 18th Amendment to the Unites States Constitution. This period began in 1920, and ended in 1933 with the repeal of the 18th Amendment by the 21st Amendment. From 1935 until 1982, shown in Fig. 1, per-capita alcohol consumption increased steadily to a peak of nearly 2.8 gallons of ethanol per year in 1982 [169]. Since then, consumption has declined, leveling off at about 2.2 gallons of ethanol per year in 1993, and

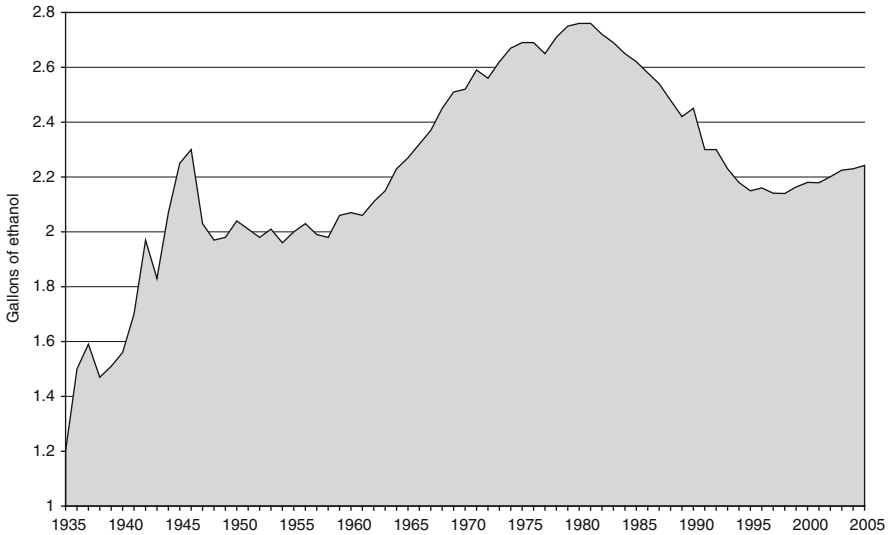

Fig. 1 Total per-capita ethanol consumption, United States, 1935–2005. Source: Lakins NE, LaVallee RA, Williams GD, Yi H (2007) Surveillance report #82: apparent per capita alcohol consumption: national, state, and regional trends, 1977–2005. NIAAA, Division of Biometry and Epidemiology, Alcohol Epidemiologic Data System, Rockville, MD, August 2007

remaining at around that level until 2005, with a slight increase from 1999 to 2005. These data are generally consistent with liver cirrhosis mortality statistics, which show similar variations over time [287].

Worldwide, alcohol consumption patterns vary considerably. Consumption is lowest in predominately Muslim countries (e.g., individuals in Afghanistan and Pakistan consume 0.03 and 0.31 l pure alcohol per capita, respectively) and eastern Mediterranean countries, and highest in eastern European countries (e.g., individual in Ukraine and the Russian Federation consume 15.58 and 15.23 l pure alcohol per capita, respectively) and western European countries such as France, Germany, and the United Kingdom [285].

Alcohol consumption is also heterogeneous within countries. For example, about one-third of United States adults do not drink, although per-capita consumption is 9.3 l [216, 224]. Abstainers are rare In Eastern Europe (including Russia and Ukraine), where per-capita consumption, 13.9 l, is the highest in the world [216]. After immigration, immigrants tend to retain the drinking levels of their country of origin rather changing to the patterns of their new country, for example, Mexican immigrants in the United States [89] and Russian immigrants in Israel [107, 214].

Drug Use

Drugs such as cannabis, opium, and cocaine have been cultivated and used medicinally as well as recreationally for centuries. Opium poppies are believed to have been first grown in the region near modern-day Iraq as early as 3400 B.C. Opium was used primarily as an analgesic and anesthetic, but medical use did not become widespread until the development of the hypodermic needle in the early 1800s [200]. Historical analysis also indicates that marijuana was smoked recreationally and medically in ancient China as early as 2737 B.C. [199]. In South America, societies have grown and consumed coca, the plant grown to create cocaine, for centuries. The most common mode of administration is to chew the leaves of the coca plant, or to mix the leaves into a tea [252]. In the twentieth century, innovations in pharmacological knowledge led to the development of synthetic drugs such as lysergic acid diethylamide, categorized as a hallucinogen, and methylenedioxymethamphetamine (or "ecstasy"), categorized as an amphetamine.

In Western countries prior to the 1960s, drug use was rare and the few studies that addressed prevalence focused on heroin, with widely varying results [56, 90, 243]. Morphine is believed to have been prescribed often in the nineteenth and early twentieth centuries mainly as a cough suppressant to ease the suffering of individuals with tuberculosis [199], although no data are available to empirically estimate incidence and prevalence. During the Civil War, it is believed that more than 400,000 soldiers became dependent on morphine, as it was liberally prescribed for pain associated battle wounds [199]. More systematic surveys of United States drug use began in the 1960s. A series of national household surveys on drug use conducted by the National Institute on Drug Abuse and later by the Substance Abuse and Mental Health Services Administration showed that illicit drug use, especially marijuana, increased greatly after the late 1960s (Fig. 2). Heroin use also increased in the late 1960s, when the profile of users changed from "bohemians" to inner-city, unemployed males. Yearly surveys of United States youth [140] since 1975 indicate that ~50% of 12th-grade students have used an illicit drug, with a high of 66% in 1982, a low rate of 41% in 1992, and 51% in 2004. Since 1975, over 80% of students felt that marijuana was easily available, ranging from 82.7% in 1992 to 90.4% in 1998.

Substance Use in the United States: A Public Health Problem

While alcohol and drug use is common both in the United States and in many countries worldwide, excess alcohol consumption is estimated to be the 3rd largest cause of United States

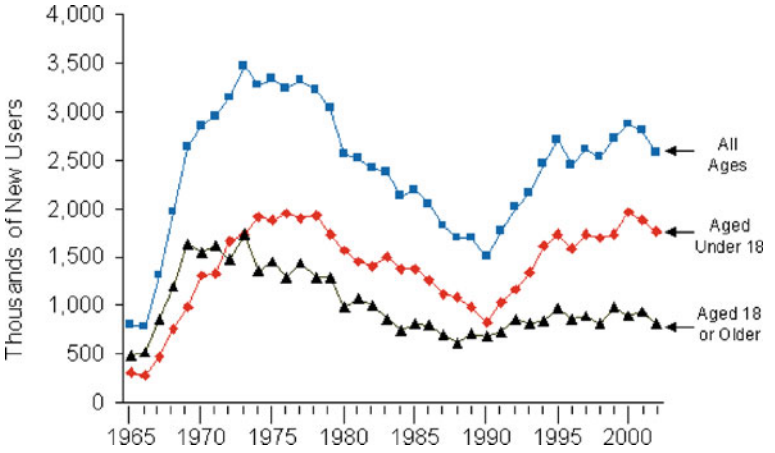

Fig. 2 New users of cannabis in the United States, 1965–2002. Source: Substance Abuse and Mental Health Services Administration (2004). Results from the 2003 National Survey on Drug Use and Health: National Findings

preventable mortality [197] and the 5th largest cause of preventable disability worldwide [66]. Excess substance use and substance use disorders are associated with a broad range of adverse outcomes including but not limited to accidents and traffic fatalities [126], domestic violence [25], fetal alcohol syndrome and other pre- and perinatal insults [211, 246], neuropsychological impairment [11], poor medication adherence (e.g., HIV) [229], economic costs and lost productivity [98], psychiatric comorbidity [21, 114], and functional disability [114]. Thus, prevention and intervention of excess substance use is an important public health priority.

When Does Use Become Pathological? Substance Abuse and Dependence

The two major nomenclatures, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, define psychiatric disorders within a common framework for individuals and groups with different training, experience, and interests. Users include medically and behaviorally trained clinicians, neuroscientists, geneticists, investigators conducting clinical trials, epidemiologists, policy makers, insurance companies and others. Both the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the research version of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision enable diverse groups to arrive at common definitions of disorders by providing specific, generally observable criteria for each disorder. For substance use disorders, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision provide diagnostic criteria for two disorders, dependence and abuse (shown in Tables 1 and 2). The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision also provide symptoms for diagnosing substance-specific intoxication and withdrawal syndromes, and methods for diagnosing substance-induced psychiatric disorders. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition was developed in the United States by the American Psychiatric Association and is used in the United States and internationally in research studies. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision was developed by the World

Table 1 Dependence criteria: International statistical classification of diseases and related health problems, 10th revision (ICD-10) and *diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV)

Substance	ICD-10	DSM-IV
All substances	*Three* or more of the following six symptoms occurring together for *at least 1 month, or* if less than 1 month, occurring together *repeatedly within a 12-month period*: 1. Tolerance: need for significantly increased amounts of alcohol to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount of alcohol. 2. A physiological withdrawal state of the characteristic withdrawal syndrome for alcohol, or use of alcohol (or closely related substance) to relieve or avoid symptoms. 3. Difficulties in controlling drinking in terms of onset, termination, or levels of use: drinking in larger amounts or over a longer period than intended; or a persistent desire or unsuccessful efforts to reduce or control drinking. 4. Important alternative pleasures or interests given up or reduced because of drinking; *or* a great deal of time spent in activities necessary to obtain or use alcohol or to recover from its effects. 5. Persisting with drinking despite clear evidence and knowledge of harmful physical or psychological consequences 6. A strong desire or sense of compulsion to drink.	A maladaptive pattern of drinking, leading to clinically significant impairment or distress as manifested by *three* or more of the following seven symptoms occurring *in the same 12-month period*: 1. Tolerance: need for markedly increased amounts of alcohol to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of alcohol. 2. The characteristic withdrawal syndrome for alcohol (or a closely related substance) or drinking to relieve or avoid withdrawal symptoms. 3. Persistent desire or one or more unsuccessful efforts to cut down or control drinking. 4. Drinking in larger amounts or over a longer period than the person intended. 5. Important social, occupational, or recreational activities given up or reduced because of drinking. 6. A great deal of time spent in activities necessary to obtain, to use or to recover from the effects of drinking. 7. Continued drinking despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by drinking.

Health Organization and is used internationally, mainly for clinical purposes and governmental reporting.

Substance Disorders in the Diagnostic and Statistical Manual of Mental Disorders

The substance dependence criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, shown in Table 1, are based on the alcohol dependence syndrome [62], which was generalized to drugs in 1981 [286]. Dependence was considered a combination of physiological and psychological processes leading to increasingly impaired control over substance use in the face of negative consequences. Dependence was one "axis" of substance problems, and the consequences of heavy use (social, legal, medical problems, hazardous use) a different axis of substance problems. This bi-axial concept [61] led to the distinction between abuse criteria (social, role, legal problems or hazardous use, most commonly driving while intoxicated) and dependence (tolerance, withdrawal, numerous indicators of impaired control over use).

The focus on *dependence* is based on its centrality in research and on its psychometric properties. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined dependence and International Statistical Classification of Diseases and Related Health Problems, 10th Revision—defined dependence have good to excellent reliability across samples and instruments [24, 26, 83, 99, 101, 108, 265], with few exceptions (rare substances; hallucinogens). Dependence validity has also been shown to be good via several study designs. These include: multi-method comparisons [40, 80, 108, 115,

Table 2 Abuse/harmful use criteria: international statistical classification of diseases and related health problems, 10th revision (ICD-10) and *diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV)

Substance	ICD-10	DSM-IV
All substances	**A**: Clear evidence that alcohol use contributed to physical or psychological harm, which may lead to disability/adverse consequences. **B**: The nature of harm should be clearly identifiable (and specified). **C**: The pattern of use has persisted for at least 1 month or has occurred repeatedly within a 12-month period. **D**: Symptoms do not meet criteria for any other mental or behavioral disorder related to alcohol in the same time period (except for acute intoxication).	**A:** Criteria for alcohol dependence have never been met. **B:** A maladaptive pattern of drinking, leading to clinically significant impairment or distress as manifested by at least *one* of the following four symptoms occurring within a 12-month period: 1. Recurrent use of alcohol resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household). 2. Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol use). 3. Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct). 4. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication).

213, 226, 231]; longitudinal studies [88, 100, 101, 109, 233, 235]; latent variable analysis [16, 97, 201], and construct validation [105, 113]. Animal models of a syndrome of cocaine dependence symptoms (as distinct from use patterns) [50, 222, 266] lend credence to the dependence syndrome not only as a cross-cultural phenomenon, as suggested by a World Health Organization study [40, 101, 213], but a cross-species phenomenon as well.

Substance *abuse* is a different case. Contrary to clinical assumptions, abuse does not necessarily lead to dependence [88, 100, 109, 116, 233, 235]. Further, not all cases of alcohol or drug dependence have abuse symptoms [110, 111]. Dependence is more familial than abuse [103, 109]. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol abuse is most often diagnosed in the general population based on one symptom, driving while intoxicated [104, 106, 156]; preliminary analyses of national data show this is also the case for drug abuse. A *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined diagnosis of abuse may thus depend on the availability of a car, while dependence is a heritable, complex condition.

Various psychometric analyses have been conducted to examine the validity of the Edwards and Gross taxonomy of two distinct, correlated factors for substance abuse and dependence criteria. Confirmatory factor analysis on the alcohol abuse and dependence items has provided mixed evidence; several studies show that a two-factor model best describes abuse and dependence items [84, 97, 201, 202], while several others found evidence of similar model fit for one- and two-factor models, preferring the

one-factor model on the basis of parsimony and high factor correlations [187, 212]. Factor analyses of cannabis abuse and dependence items have generally found support for a one-factor model or similar fit of one- and two-factor models [3, 73, 187, 203, 257], although results from a general population survey support a two-factor model [16]. Taken together, these studies show some support for combining abuse and dependence albeit with some evidence to the contrary. Differences across study may also have occurred due to characteristics of the populations studied (e.g., general population versus community sample, adults versus adolescents). A current unresolved issue for those preferring a single substance use disorder that combines abuse and dependence criteria is a valid threshold for differentiating between cases and non-cases. This issue will need to be resolved if the criteria are to be combined, for example, in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.

Substance Disorders: A Categorical or Dimensional Trait?

Recent psychometric analyses of the substance abuse and dependence criteria have suggested that these disorders are not categorical entities; instead, evidence supports an underlying continuum of alcohol severity across a variety of samples and populations [112, 142, 164, 185, 212, 228]. Such information may be critical when statistical power is limited, as it often is in studies of gene–gene or gene–environment interaction. If *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol dependence in categorical form is psychometrically sound (i.e., reliable and valid) but dichotomizes an inherently dimensional condition, then converting its elements to a dimensional measure may produce a more informative phenotype for etiologic studies [112]. Future versions of the diagnostic nomenclature will likely incorporate a dimensional form of substance dependence [122], but further psychometric and etiologic work validating dimensional forms of substance disorders remains necessary.

Descriptive Epidemiology: The Incidence and Prevalence of Substance Disorders

Prevalence and Incidence of Substance Disorders

The most comprehensive epidemiologic United States information on the incidence and prevalence of alcohol disorders comes from the National Epidemiologic Survey on Alcohol and Related Conditions, a longitudinal survey of 43,093 respondents aged 18 years and older conducted in 2001–2002 [81, 82, 85] with a 3-year follow-up of 34,653 respondents [82]. The diagnostic interview was the Alcohol Use Disorder and Associated Disabilities Interview Schedule—*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition Version [82], a structured interview for non-clinicians with high reliability and validity for substance use disorders [26, 83, 108, 227, 265].

In the National Epidemiologic Survey on Alcohol and Related Conditions, the prevalence of current (past 12 months) alcohol abuse and dependence was 4.7 and 3.8%, respectively, for a total prevalence of 8.5% for any current alcohol use disorder [114]. The prevalence of lifetime alcohol abuse and dependence was 17.8 and 12.5%, respectively, for a total prevalence of 30.3% for any lifetime alcohol use disorder [114]. Current and lifetime alcohol disorders are more prevalent in men (current: 12.4%, lifetime: 42.0%) than in women (current: 4.9%, lifetime: 19.5%). Compared with individuals of White race/ethnicity, among whom the current and lifetime prevalence of alcohol disorders was 8.9 and 34.1%, respectively, Blacks, Hispanics, and Asians have a lower prevalence of current and lifetime alcohol disorders (6.9 and 20.6% for current and lifetime alcohol disorders among

Blacks, 7.9 and 21.0% Hispanics, and 4.5 and 11.6% among Asians. Alcohol disorder prevalence is inversely related to age; those in younger age groups are most likely to have an alcohol disorder, with mean ages at onset of alcohol abuse and dependence at 22.5 and 21.9, respectively [114]. The incidence of alcohol dependence was 1.66 per 100 person-years [85], meaning 1.66 cases per year of alcohol dependence for every 100 individuals without alcohol dependence at the beginning of that year. Incidence of alcohol abuse was slightly lower at 1.03 per 100 person-years [85]. In general, predictors of incidence were similar to predictors of prevalence.

Drug disorders were substantially less common than alcohol disorders. The prevalence of current (past 12 months) drug abuse and dependence was 1.4% and 0.6%, respectively, for a total prevalence of 2% for any current drug use disorder [227]. The prevalence of lifetime drug abuse and dependence was 7.7 and 2.6%, respectively, for a total prevalence of 10.3% for any lifetime drug use disorder [227]. Current and lifetime drug disorders are more prevalent in men (current: 2.8%, lifetime: 13.8%) than in women (current: 1.2%, lifetime: 7.1%). Drug disorder prevalence is inversely related to age; those in younger age groups are most likely to have a drug disorder, with mean ages at onset of drug abuse and dependence at 19 years. There is no consistent trend by race for drug disorders [227]. In the National Epidemiologic Survey on Alcohol and Related Conditions, incidence of drug dependence was estimated at 0.32 per 100 person-years of observation [85]; incidence of drug abuse was slightly lower at 0.28 per 100 person-years. In general, predictors of incidence were similar to predictors of prevalence.

The Course of Substance Disorders

Initiation of alcohol consumption and drug use often occurs during adolescence. Onset of alcohol abuse and dependence is most likely among individuals aged 18–29, although 15% of alcohol dependence cases begin before age 18 [127]. Often, substance disorders are not lifelong conditions. Indeed, a high rate of recovery has been documented in general population samples, even among individuals who have never sought treatment. Studies of alcohol disorders in the general population also show that a high proportion of recovered individuals return to moderate drinking as opposed to abstinence [47, 277]. Data from the National Epidemiologic Survey on Alcohol and Related Conditions indicated that approximately 75% of individuals diagnosed with alcohol dependence at some point in the past did not have a current (i.e., past year) diagnosis, but that only about 20% of these individuals were abstinent from alcohol [47]. However, prospective follow-up of this sample has indicated that low-risk drinking represents a risk factor for relapse to an alcohol disorder compared with abstinence [45]. Longer term prospective follow-up of this general population sample will help to clarify the role of alcohol consumption in recovery from disorder.

The transition to adulthood represents a key developmental phase in which alcohol disorders often remit, in a process termed “maturing out” [8, 46]. Major predictors of recovery include key lifestyle components, such as employment, marriage, and childbirth. Whether or not these factors have a causal influence on recovery or reflect common factors underlying the positive lifestyle components and the recovery remains unknown.

Despite substantial progress in the development of treatments for alcohol and drug disorders, only about one-fifth of those individuals with an alcohol disorder [34, 114] and one-sixth of individuals with a drug disorder [35] seek treatment for the condition during their lifetime. Further, the delay from onset of disorder to treatment is typically 8–10 years [276]. Finally, in contrast to sharp increases in treatment utilization for disorders such as depression between 1990 and 2003 [153], a corresponding increase in the proportion of individuals seeking treatment for an alcohol and drug disorders did not occur during this period [114].

The path from first use to dependence to treatment also differs by gender. Women who

use alcohol and drugs often start using later than men, have a faster progression from first use to dependence, and enter treatment sooner than men given equal ages of dependence onset [209, 215], although no such differences have been observed for crack-cocaine users [55, 171]. This phenomenon has been termed "telescoping".

Evidence is accumulating that these well-documented gender differences in the course of alcohol disorders are converging. Studies of adolescent alcohol use have consistently shown a convergence in rates of alcohol and drug use initiation in younger birth cohorts, especially those born after World War II [139, 141]. Further, several genetically informative samples have researched gender differences in *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol and drug disorders over time, unanimously finding support for such a convergence [128, 220]. Similarly, large, representative cross-sectional studies in the United States support gender convergence in rates of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol abuse and dependence [92, 155]. Finally, evidence indicates that the traditional "telescoping" phenomenon whereby women exhibit later onset of drug use and disorder but earlier treatment and shorter course may be diminishing, as women are more closely approximating men in both onset and course of disorder [129]. Searches into the causes of these shifts are ongoing, but this evidence indicates increased social acceptability of alcohol use by women in younger generations [91].

Analytic Epidemiology: The Etiology of Substance Disorders

Substance use disorders have a complex etiology involving genetic and environmental factors. These occur along a continuum ranging from the macro level consisting of broad social influences, to the micro level, consisting of molecular-level influences. These can be thought of as external to internal levels (Fig. 3). In the remainder of this chapter, we address these levels in turn. We begin with macro/external factors, including societal availability and desirability of the substances, geographic and temporal differences, pricing, laws, and advertising. We next consider externally imposed stress. Intermediate-level factors include religiosity, parental and peer social influences. Moving increasingly toward the micro and internal levels, we consider cognitive and personality variables, subjective responses to substances, and specific risk as well as protective genes. We conclude by discussing gene-by-environment interaction, addressing the idea that since etiologic influences work at various levels, a factor at any level may emerge more clearly if other levels are considered conjointly.

Availability—Temporal and Geographical

Political Events

Political events, both local and global, influence the availability of substances and thus the risk

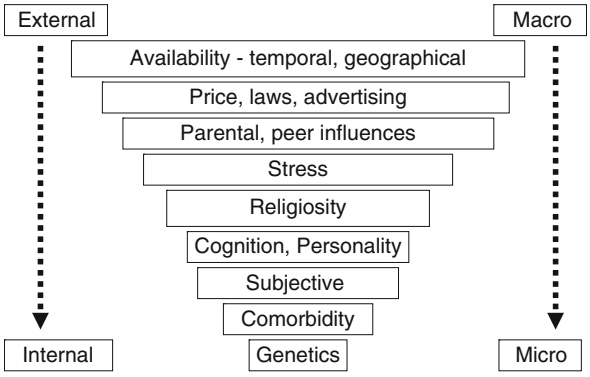

Fig. 3 Factors affecting substance use and substance use disorders

of substance use and dependence. In 2004, for example, religiously motivated attacks on alcohol retailers in Iraq (*BBC World News*, July 22, 2004) reduced the availability of alcohol locally for that region. After the Taliban government fell in Afghanistan in 2001, heroin production in Afghanistan increased greatly [165], coinciding with increased heroin use among American teenagers [255]. Political instability in South American countries such as Bolivia and Colombia, especially in the 1970s, influenced the production of cocaine and increased the availability of cocaine in the United States [251]. Thus, political events at a great geographic distance may influence local substance use availability and patterns of use.

Outlet Density

Counties, cities or states with higher density of alcohol outlets (places were alcohol is sold) have higher alcohol consumption and higher rates of alcohol-related problems, including hospital admissions, pedestrian injury collisions, and crashes and crash fatalities [33, 237, 256, 261, 262]. Ecologic and multilevel analysis controlling for individual level factors indicates that outlet density is related to higher mean group rates of consumption and drinking norms scores and to driving after drinking [93, 237]. Community-based interventions to limit access to alcohol by reducing the density of outlets have been shown to reduce alcohol-related traffic injury and self-reported consumption [130]. While information regarding outlet ("dealer") density is unavailable for drugs, the vigorous efforts of parents, schools, and law enforcement agencies to keep drug dealers away from schools are consistent with the same idea.

Pricing, Laws, and Advertising

Pricing

Alcohol taxation is the major determinant of state variation in the price of alcohol, and is thus a government intervention. An inverse relationship exists between state-level price of alcohol and per-capita consumption or adverse consequences of drinking [30]. Further, higher state-level beer tax is associated with lower prevalence of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol dependence [123]. Outside the United States, cutting the tax on spirits has been followed by increased per-capita alcohol consumption [120, 223].

Laws and Law Enforcement: Alcohol

Laws and their enforcement also affect consumption patterns. In the United States, the 18th Amendment to the Constitution outlawed the manufacture, transport, and sale of alcohol from 1920 to 1933. Figure 1 shows that in 1935, per-capita ethanol consumption was very low, but increased steadily afterwards, consistent with cirrhosis mortality rates from the same period [171, 287]. Thus, the 18th Amendment achieved its purpose, but was repealed because it was unacceptable to the public. Similar events occurred in the former Soviet Union, an area of very high per-capita alcohol consumption [285]. In the mid-1980s, the government attempted to restrict consumption. The policies were successful in reducing consumption, but so unpopular that they contributed to the downfall of the government and were eventually reversed [240].

More recently in the United States, enforcement of laws related to drinking and driving has been shown to be an important deterrent to alcohol-related crashes and fatalities. These include driver's license suspensions [268], and lowering the maximum legal blood alcohol concentration among drivers [69, 259, 269]. In addition, stricter driving-under-the-influence laws and their enforcement are consistently related to decreased hazardous use [182] and alcohol-related traffic fatalities [6, 268].

Minimum-age drinking laws influence the availability and acceptability of consumption among young people. Laws vary considerably by country both in scope and in minimum age [285]. For example, the minimum consumption

age in the United States is 21, while in Cyprus it is 12. Israel did not have a minimum legal drinking age until 2004, but public concern about increased risky drinking among young adults led to the establishment of a national minimum drinking age (18 years) at that time [248]. Some countries have separate age restrictions for consumption and purchase. For example, in Greece the minimum consumption age is 14 while the minimum purchase age is 17. In Italy, there is no age restriction on consumption in private, but a minimum age requirement of 16 to drink in public.

Minimum drinking age laws have a positive effect on community health as well as the health and safety of adolescents. Research in the United States and other developed countries has indicated that minimum drinking age laws reduce traffic crash and fatality rates [68, 241, 268, 271]; positive effects among adolescents include reducing in alcohol consumption and high risk drinking [206]. Additionally, several studies have documented an association between minimum drinking age laws and a reduction in youth suicide [15, 21].

State Distribution Policies

In the United States, states differ in the ways they control availability of alcohol. Some states exert more control through operation of state alcoholic beverage sales, while others exert less control through the licensing of alcohol outlets. This difference impacts sales and consumption patterns [270]. Compared with "wet" counties, "dry" counties, where alcohol is not sold, have lower rates of alcohol-related accidents, driving-under-the-influence arrests, and cirrhosis mortality [283]. International studies corroborate these findings; in Norway, stringent alcohol regulations, such as mandatory closing on Saturdays, led to lower detoxification admissions [223].

Grass-Roots Efforts

Mothers Against Drunk Driving was started in 1980 by a group of women after a teenage girl was killed by a repeat-offense drunk driver. Mothers Against Drunk Driving, a very active organization, national since the early 1980s, has been highly effective in influencing state legislation pertaining to intoxicated driving, such as increasing the minimum drinking age from 18 to 21, and enforcement of maximum-blood-alcohol-level laws among drivers [95]. In particular, a highly publicized media campaign called "Rate the State" in which states were graded A through D on driving-under-the-influence countermeasures, put pressure on legislators to increase the stringency of these laws, shown as an effective strategy in reducing alcohol-impaired driving [242, 267].

Alcohol Marketing and Advertising

Product development and marketing aim to increase sales and consumption [29]. Alcohol companies allocate substantial resources to researching consumer preferences, developing new products and promoting them [138]. For example, the alcohol beverage industry spent 696 million dollars on magazine advertising alone between 1997 and 2001, largely targeted to adolescents [74]. The alcohol industry does not publish the results of its marketing research, and resources necessary for definitive public health studies of advertising and other marketing effects are limited by comparison.

Public health concerns often focus on marketing that targets adolescents [28, 39]. Existing data from longitudinal studies show associations between late childhood-early adolescent exposure to advertising and subsequent drinking initiation and frequency [37, 64, 249]. Cross-sectional studies also show associations of various marketing and advertising strategies with positive attitudes about drinking and drinking frequency [71, 167]. Further, an imaging study of adolescent response to alcohol advertising indicated greater brain activation in areas linked to reward and desire among adolescents with alcohol use disorders than infrequent drinkers [254], suggesting that advertisements are especially salient to vulnerable adolescents.

Laws and Law Enforcement: Drugs

A literature on government efforts to reduce drug use by reducing availability is inconsistent. Some studies suggest the strategies are ineffective [17, 279, 284], while others find supply reductions efficacious [48, 278]. Reducing the supply of specific drugs can have unintended consequences, including increases in other substances [260]. Data from United States college studies, however, indicate that increased restrictions on alcohol use does not increase marijuana use, as has been hypothesized, but instead serves to decrease both alcohol and marijuana use [281]. Thus, the evidence is inconsistent on the efficacy of government attempts to limit drug use by reducing supply.

Parental and Peer Influences

Parental Modeling of Substance Use

Twin studies indicate that up to half the liability to alcohol dependence is environmental [225]. Parental modeling has been proposed as one such environmental factor affecting subsequent substance use in their children [65]. Adoption studies do not support this, however, since rates of alcoholism in adoptive children of alcoholics are not elevated [132]. One etiologic model with empirical support from twin studies posits that influential factors for substance use and the progression to dependence change over time; environmental and social factors mediate the initiation and use of substances in childhood and adolescence, while genetic factors become more influential in the adult substance use and dependence [151].

Parenting Practices

Poor parental monitoring increases association with substance-abusing peers [117], a risk factor for alcohol misuse (see below, peer influences). Harsh, inconsistent parenting predicts earlier initiation of alcohol use, conduct problems and poor regulatory competencies [166, 217]. On the other hand, warm yet authoritative parenting styles protect adolescents from alcohol problems [207].

Peers

Peer influence is a strong predictor of adolescent drug and alcohol use and problems [143, 250, 272]. Twin studies show that shared environmental influences such as peers have a significant effect on initiation of alcohol and any drug use [157, 219]. Two models have been proposed to explain peer influence on adolescent substance use, social selection, and socialization [144]. The social selection theory proposes that young adolescents selectively "mate" with friends; those children who display deviant behavior as children will be prone to choose deviant friendships in adolescence [70]. This can lead to initiation of drug use (especially marijuana use) and may be a factor in the transition to "heavier" drugs. It has been further proposed that an underlying trait such as sensation seeking (see below) influences both the selection of peers and substance use [53]. In contrast, the socialization theory proposes that adolescents can be influenced to use substances by peers in their environment [49] via modeling, offers, development of expectancies, and social norms [18, 236]. Substance use by older siblings is also associated with individual substance use [23, 75, 136, 190]. Studies that could examine these various environmental effects while controlling for genetic influences are needed to resolve the social selection/causation debate.

Peers may also be protective. Some United States ethnic/immigrant groups use substances less than the norm [89]. Adolescents from these groups with ethnically homogeneous peers encounter less pressure to use substances [22].

Stress

Drug disorders are often preceded and accompanied by disruptive behavior and conduct

problems [168] that have a shared genetic vulnerability with drug disorders [149]. These behaviors evoke negative reactions from the environment, resulting in stressful life events that are not always independent of the individuals, making a causal direction between stress and disease onset difficult to discern. In animal studies where stress can be experimentally applied, cause and effect are clearer, as is also the case in studies of early stressful experiences in humans that antedate the onset of substance use disorders.

Animal Models

In animal studies, the timing of stress relative to normal development can be experimentally manipulated. In adult animals, substance use increases after physical stressors [76, 210] and social stressors [44, 85, 96, 194].

Early life stressors also contribute to drug-using behaviors in animals. Neonatally isolated rats are more likely to acquire stimulant self-administration behaviors [134, 160, 179] and show higher dopamine levels in response to cocaine than handled rats, suggesting that early stress leads to greater cocaine reward [20, 161]. Early-life rearing stressors predict ethanol seeking in primates [10]. Isolated rearing led to increased drinking of morphine solution under various conditions [5, 184]. Recently developed animal models of Δ9-tetrahydrocannabinol self-administration [19] may allow similar studies for cannabis.

Early Stressors and Drug Use in Humans

Childhood stressors, including parental separation, neglect and abuse (physical and sexual) are associated with later substance use, problems and dependence [54, 150, 152]. However, most studies failed to control for parental history of substance abuse, a potential confounder given that substance abuse is associated with poor parenting [174]. One informative study showed that among adolescents with a substance-abusing parent, strong family cohesion (the opposite of neglect) protected against drug problems [133]. Twin studies allow the study of environmental stressors while controlling for genetic influences and have shown that childhood sexual abuse is an environmental risk factor for substance use disorders [147, 204]. Effects of other childhood adversities (e.g., neglect, physical and emotional abuse) have not been examined in twin studies.

Religiosity

Religiosity has been called "one of the more important environmental factors that affect the risk for substance use and dependence" [148]. An inverse relationship between religiosity and drinking is cross-cultural [4, 7, 208]. Longitudinal studies of adolescents, college and professional students show that religiosity protects against later heavy drinking [9, 183]. Religiosity is strongly correlated within twin pairs due to shared environmental effects [148, 158, 263]. Heritability of drinking differs between religious and non-religious twins, an example of gene-environment interaction [159]. In twins studied longitudinally [148], religiosity predicted later drinking more than drinking predicted later religiosity, suggesting that religiosity is more likely to influence drinking than the reverse. These studies indicate that religiosity is largely environmental and protects against alcohol use disorders. Religiosity also protects against drug disorders [31, 198], although this literature is less extensive.

Cognition, Personality

Substance Expectancies and Motivations

Positive substance expectancies constitute an important risk factor for the development of alcohol dependence [78, 238]. For example, alcohol expectancies are considered the beliefs that drinking alcohol will result in decreased

negative emotions or enhanced positive emotions [77, 245]. These expectancies can be derived from parents and peers, and are believed to be environmentally influenced rather than genetically influenced [244]. Motivations for drinking often fall under four main domains: (1) drinking to obtain social rewards or enhance social interactions; (2) drinking to enhance positive mood; (3) drinking to reduce negative mood, and (4) drinking to avoid social rejection and conform to social norms. While individuals with alcohol disorders often rate all motivations highly, reduction of negative affect and enhancement of positive affect have been prospectively associated with heavy use and alcohol and drug disorders [14, 27, 137].

Personality Traits

No single personality trait predicts alcoholism [239], but traits associated with the development of alcohol use disorders include novelty seeking [32] and sensation seeking [186, 289], traits that are often associated [58, 282]. The heritability of sensation seeking is unclear, with some twin studies suggesting that approximately half of the variance can be attributed to genetic factors [119, 121, 135], and another suggesting a much weaker influence of genetic factors [195]. Additional personality traits related to alcohol use disorders, albeit less consistently, are neuroticism/negative emotionality [288], impulsivity/disinhibition [191], and extraversion/sociability [125]. Similar traits have been examined in relation to drug use disorders. For example, research has shown that impulsivity/inhibition is reliably lower among individuals with drug abuse/dependence [38, 190], whereas negative emotionality tends to be higher [253, 282].

Subjective Reactions

Level of response to alcohol indicates the quantity needed to obtain an effect. Individuals with a low level of response need to drink more to obtain an effect. This is a genetically influenced characteristic associated with enhanced risk for alcohol use disorders [234]. Level of response varies by ethnicity. Several groups at high risk for alcohol use disorders show low response, including children of alcoholics, Native Americans, and Koreans [63, 198, 273], while high response is found among Jews [234], a group with relatively low levels of alcohol disorders [107, 174]. A low level of response predicts later onset of alcohol dependence in young adult males [232], and may contribute to transition from lighter to heavier drinking in individuals in a heavy-drinking environment [230]. Several chromosomal regions have shown suggestive linkage results to level of response [280] and an association with variations in the ADH1B gene (one of the genes that influences metabolism of alcohol in the liver) has been documented [57], but replication is needed.

Subjective reactions can also be characterized by whether they are positive or negative. A stimulating (reinforcing), rather than sedating, effect of alcohol has been identified in moderate/heavy drinkers [131], as well as untreated alcoholics [258]. In contrast, a flushing reaction to alcohol includes unpleasant physical sensations [124], found among Asians. A strong flushing reaction precludes drinking, while moderate flushing protects against alcohol dependence. Individuals also vary in their subjective responses to marijuana, and positive and/or negative responses are moderately heritable [180].

Psychiatric Comorbidity

Individuals with substance use disorders exhibit higher rates of mood, anxiety, and personality disorders as compared with the general population [35, 86, 87, 114, 154, 221]. For example, national surveys indicate that individuals with an alcohol disorder are approximately 3.0 times more likely to be diagnosed with major depression; the association between drug disorders and major depression is even stronger,

with odds ratios around 7.0 [36, 102]. A strong association has also been documented between substance disorders and antisocial personality disorder. The National Epidemiologic Survey on Alcohol and Related Conditions survey estimates that 39.3 and 72.4% of individuals with antisocial personality disorder meet criteria for lifetime drug disorders and alcohol disorders, respectively [79].

The strong and consistent relationships between substance disorders and other psychiatric disorders have prompted etiologic researchers to evaluate evidence for an underlying vulnerability to psychiatric disorder in general. Adult twin studies indicate at least moderate genetic heritability across disorder [146, 149, 182], and recent genetic studies have indicated specific genes associated with the transmission of several psychiatric disorder in general, rather than particular disorders [52, 274]. "Internalizing" and "externalizing" domains have been proposed as a means of organizing individual disorders into larger, more meaningful groups. Internalizing disorders are often characterized by the anxiety and depression domains, whereas externalizing disorders are often characterized by alcohol, drug, and antisocial personality disorders. Research into the validity and utility of broad versus narrow categorizations of disorder has been a major area of psychiatric research for decades [192], and remains ongoing [162, 163].

Genetics

Family and Twin Studies of Alcohol and Drug Dependence

Alcoholism [41, 205] and drug disorders [193] are familial. Genetic epidemiology studies of heritability use twin samples to compare concordance for a disorder between monozygotic (identical) vs. dizygotic (non-identical) twins. In these studies, significantly higher concordance in identical twins, who share 100% of their genes, compared with non-identical twins, who share only an average of 50% of their genes, indicates genetic heritability for a disorder. Twin studies of alcohol dependence show substantial heritabilities (50–60%) [118, 218]. Heritability estimates from studies of illicit drugs are more variable, perhaps due to more varied phenotypes (use, heavy use, abuse and dependence); for drug dependence, heritability estimates are similar to alcohol dependence [72, 147, 219]. For all substances, environmental factors appear to influence initiation and continuation of use, while genetic factors move individuals from use to dependence. Also, as noted above, environmental and social factors mediate the initiation and use of substances in childhood and adolescence, while genetic factors become more influential in the adult substance use and dependence [151]. Some twin studies investigating shared heritability of dependence on different substances showed high shared genetic variance between substances [149, 264] while other studies suggest that dependence on different classes of drugs is not genetically interchangeable [264]. Molecular genetics studies may be able to clarify these issues.

Genetics in Epidemiology Studies and Gene × Environment Interaction

The last 5 years have seen considerable progress in the genetics field in general, as well as in identifying genes whose variants show replicated results on relationships to the risk for alcohol and drug dependence. Some of the genes involved include those that affect the process of alcohol metabolism in the liver such as alcohol dehydrogenase 4 (*ADH4*), related to both alcohol [60, 94, 175, 177] and drug dependence [175, 177, 178]. Other well-replicated findings on genes related to the risk for substance dependence involve processes linked to neurotransmission. These include genes influencing gamma-aminobutyric acid, the major inhibitory neurotransmitter in the brain. Genetic variants in *GABRA-2* predict alcohol dependence in United States [42, 43, 59], Russian [170], and German [67, 247] samples, and the outcome of a behavioral treatment for

alcohol dependence in a multi-site study [12]. *GABRA-2* variants were also related to the risk for drug dependence [2]. The functioning of muscarinic cholinergic receptors underlies many brain functions, including attention, learning, memory, and cognition, all potentially related to addictive disorders. Genetic variants influencing this process include *CHRM2*, shown to affect the risk for alcohol and drug dependence [51, 176, 275] and related personality traits [60].

Although twin studies show that genetic and environmental factors are both important, few studies have addressed whether the relationship of specific genetic variants to alcohol and drug dependence is modified by environmental circumstances. This type of research question could be addressed by appropriately designed epidemiologic studies that collect DNA as well as interview information on risk factors. Until recently, a limitation on such studies was the need to extract DNA from blood samples, a difficult task in survey research due to many practical considerations. Fortunately, methods have recently become available to collect DNA through the use of saliva samples, making the inclusion of genetic variables much more feasible in epidemiologic research. An example of this approach includes a study showing that being exposed to childhood maltreatment interacted with a gene influencing stress reactions to predict early onset of drinking among adolescents [145]. Additional studies of this type are under way in Israel [248] and are being planned in the United States.

Studying the interaction between certain genes and specific environmental factors has important implications for the prevention and treatment of alcohol and drug use disorders. First, better knowledge in this area may help early identification of individuals who are unlikely to be able to use drugs or alcohol in moderation for early education, additional support or supervision. Second, the knowledge may help identify individuals exposed to particular stressors that would particularly benefit from intervention. Finally, clearer knowledge of the interaction of environmental with genetic effects may suggest new lines of investigation to determine the biological mechanisms of protective or risk-enhancing environmental events or conditions, which may eventually aid in developing better treatments.

Conclusion

In summary, a number of factors influencing the risk for substance dependence have been identified. Through trans-disciplinary research, epidemiologists and others can work together in the future to address multi-level factors conjointly.

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United States Federal Drug Policy

Angela Hawken and Jonathan D. Kulick

Contents

Introduction

The United States federal government takes an active role in setting and implementing drug-control policy, directly and in concert with state and local authorities and with international partners—even as the other polities' policies may be widely at variance with federal policies. Over the last century, the government's formal policies, budgetary commitments, and actions reflect enduring tensions between different conceptions of the problem of drug abuse: civil liberties versus public order, public health versus criminal justice, use reduction versus harm reduction, and demand driven versus supply driven. Accordingly, the balance among the three pillars of treatment, prevention, and law enforcement has shifted with changes in drug use; public sentiment; external political, economic, and social forces; and research findings. Even so, the span of federal drug-control policy is best characterized as periods of perfervid law enforcement, driven by acute concern about the menace of particular drugs, alternating with periods of routine management of one of many social ills.

This chapter addresses the development of federal drug-control policy, and current policies and functions of the federal government. In particular, it considers the role of research in influencing policy. It is necessarily synoptic, and the interested reader is referred to more detailed source materials.

History

The use of some drugs that are now illicit, especially cannabis and opiates, was commonplace and uncontroversial in the United States before the late nineteenth century [56] (milestones in federal drug-control policy are outlined in Table 1). Opium appeared in many patent medicines, and the medical benefits were considered to outweigh the acknowledged harms [6]. Morphine and, later, heroin, were introduced in the 19th century, and were widely prescribed into

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_3,

Table 1 Milestones in federal drug-control policy

Year	Measure	Effect or goal
1906	Pure Food and Drug Act	Required medicines to have labels of ingredients.
1909	Smoking Opium Exclusion Act	Prohibited import of opium for smoking.
1912	Hague Convention	Required signatories to pass domestic legislation to combat international drug trade.
1914	Harrison Narcotics Tax Act	Regulated trade in opium and coca products; effectively prohibited their use.
1918	Rainey Committee	Found illicit drugs to be a serious threat; called for stricter law enforcement.
1919	Heroin Act	Prohibited trade and possession of heroin, even for medical purposes.
1922	Narcotics Drugs Import and Export Act	Prohibited non-medical use of opiates and cocaine; established Federal Narcotics Control Board.
1925	*Linder v. United States*	Allowed for prescription of illicit drugs for addiction treatment.
1928	*Nigro v. United States*	Upheld constitutionality of Harrison Act.
1929	Porter Act	Created Public Health Services Narcotics Division and prison hospitals for addicts.
1930	Federal Bureau of Narcotics	Created enforcement structure in Treasury Department, under a Narcotics Commissioner.
1932	Uniform State Narcotic Act	Encouraged state governments to control marijuana use in line with 1922 Act, in lieu of federal legislation.
1936	*Reefer Madness*	Documentary about the dangers of marijuana distributed by government.
1937	Marihuana Tax Act	Effectively criminalized distribution of marijuana.
1942	Opium Poppy Control Act	Prohibited growing opium poppies without a license.
1951	Boggs Act	Established mandatory-minimum prison sentences, with uniform penalties for opiates, cocaine, and marijuana.
1956	Narcotic Control Act	Increased penalties under the 1951 Boggs Act.
1960	Narcotics Manufacturing Act	Placed controls on legal manufacturers of opiates and cocaine.
1961	Single Convention on Narcotic Drugs	Consolidated earlier drug-control treaties, and added cannabis; superseded 1912 Hague Convention.
1963	President's Advisory Commission on Narcotics and Drug Abuse (Prettyman Commission)	Called for using all resources of federal government to combat trafficking.
1965	Drug Abuse Control Amendments	Placed controls on stimulants and depressants, and restricted research into hallucinogens.
1966	Narcotic Addict Rehabilitation Act	Diverted some addicts to treatment as an alternative to incarceration. Authorized support to states' rehabilitation programs.
1968	Bureau of Narcotics and Dangerous Drugs	Created from merger of Federal Bureau of Narcotics and Bureau of Drug Abuse Control.[a]
1969	Operation Intercept	Closed Mexican border and searched vehicles crossing it.
1970	Controlled Substances Act[b]	Consolidated many drug-control laws, placing all controlled drugs into one of five schedules. Addressed prevention and treatment, and interdiction. Repealed mandatory-minimum penalties.
1971	War on Drugs	Comprehensive policy announced by White House to combat domestic and international production, distribution, and use.
1972	National Commission on Marihuana and Drug Abuse	Federal study recommended marijuana decriminalization [56].
	Drug Abuse Office and Treatment Act	Established national network of treatment programs. Created Special Action Office for Drug Abuse Prevention in Executive Office of the President.

Table 1 (continued)

Year	Measure	Effect or goal
	Drug Abuse Warning Network and National Household Survey on Drug Abuse	Surveys initiated under the Special Action Office for Drug Abuse Prevention.
1973	Methadone Control Act	Established federally funded clinics for prevention and treatment of heroin addiction.
	Heroin Trafficking Act	Increased penalties for drug traffickers and established strict bail procedures.
	Drug Enforcement Administration	Created to supersede the Bureau of Narcotics and Dangerous Drugs.
	Alcohol, Drug Abuse, and Mental Health Administration	Created to oversee the National Institute of Mental Health, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism.
	National Institute on Drug Abuse	Established as focal point for research, treatment, prevention, training, services, and data collection.
	National Drug and Alcohol Treatment Unit Survey	Initiated at the National Institute on Drug Abuse to characterize prevention and treatment programs.
1975	Monitoring the Future Survey	Initiated at the National Institute on Drug Abuse to measure use and attitudes in young adults.
1976	Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act Amendments	Directed attention to prevention and treatment for women and youth.
1978	Drug Abuse Education Amendments	Coordinated state and federal education programs. Established Office of Alcohol and Drug Abuse Education in Department of Education.
1980	Drug Abuse Prevention, Treatment, and Rehabilitation Amendments	Encouraged foreign cooperation in eradication and interdiction. Strengthened federal leadership in prevention, education, treatment, and rehabilitation. Reimposed mandatory-minimum sentences.
1982	National Research Council marijuana-policy study [41]	Called for allowing states to decriminalize.
1986	Controlled Substances Analogue Enforcement Act	Established controls for enforcement of "designer drugs" (e.g., 3,4-methylenedioxymethamphetamine); allowed for immediate scheduling.
	Drug-Free Workplace	Executive order required federal agencies to institute urine-testing programs.
1988	Drug Free Workplace Act	Required federal contractors to institute urine-testing programs.
	Anti-Drug Abuse Act	Authorized funds for school-based prevention programs. Established different penalties for powder and crack cocaine.
	Office of National Drug Control Policy	Created in Executive Office of the President.
1991	National Commission on Acquired Immune Deficiency Syndrome	Report called for expansion of treatment and decriminalizing needle sale and possession.
1992	Substance Abuse and Mental Health Services Administration.	Established in the Department of Health and Human Services. Transferred the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute on Alcohol Abuse and Alcoholism to the National Institutes of Health. Abolished the Alcohol, Drug Abuse, and Mental Health Administration.

Table 1 (continued)

Year	Measure	Effect or goal
1993	Departments of Labor, Health and Human Services, and Education FY 1994 Appropriations Act	Prohibited funding for sterile-needle programs.
	Domestic Chemical Diversion Control Act	Instituted Drug Enforcement Administration registration requirement for many precursor chemicals for controlled substances.
	International Counternarcotics Policy (Presidential Decision Directive 14)	Provided policy framework for international drug control.
1995	Heroin Control Policy (Presidential Decision Directive 44)	Provided policy framework for source-country eradication and trafficker-financing efforts.
1996	Methamphetamine Control Act	Established new controls over methamphetamine precursor chemicals, and increased penalties for their possession.
1997	Drug-Free Communities Act	Provided funds to community anti-drug coalitions.
1998	Drug-Free Workplace Act	Provided federal funds to small businesses for mandatory employee drug testing.
	Drug Free Media Campaign Act	Required the Office of National Drug Control Policy to conduct a national youth-targeted media campaign.
	Office of National Drug Control Policy Reauthorization Act	Expanded the Office of National Drug Control Policy's mandate and elevated it to cabinet status.
2000	Drug Addiction Treatment Act	Allowed physicians to provide opiates to addicts outside of drug-treatment clinics.
	Ecstasy Anti-Proliferation Act	Increased penalties for trafficking in 3,4-methylenedioxymethamphetamine.
	Children's Health Act	Repealed the Narcotic Addict Rehabilitation Act. Waived parts of the Controlled Substances Act of 1970 to permit office-based treatment of opiate dependence. Authorized expansion of National Institute on Drug Abuse research on methamphetamine and 3,4-methylenedioxy-methamphetamine.
	Plan Colombia	Emergency Supplemental Act funded counter-drug activities of Government of Colombia.
2001	National Prevention Research Initiative	National Institute on Drug Abuse effort to promote science-based prevention strategies.
	National Research Council comprehensive federal policy study [47]	Found that data and research are "strikingly inadequate" to support policymaking.
2002	Vulnerability to Ecstasy Act	Provided for prosecution of owners and managers of facilities hosting drug use, trade, or manufacturing.
2004	Anabolic Steroids Control Act	Significantly expanded list of scheduled anabolic steroids.
2005	Combat Methamphetamine Epidemic Act	Regulated retail sales of medicines used in the manufacture of methamphetamine.
	Gonzales v. Raich	Upheld right of Congress to ban marijuana use, under the Commerce Clause.

[a]Formerly the Federal Bureau of Narcotics had been responsible for heroin, cocaine, and cannabis, and the Bureau of Drug Abuse Control (in the Food and Drug Administration) had been responsible for depressants, stimulants, and hallucinogens

[b]The Controlled Substances Act of 1970 was Part II of the Comprehensive Drug Abuse Prevention and Control Act

the 1920s. Cocaine appeared first in beverages, and then in many prescription medicines around the turn of the century [41].

The anti-alcohol temperance movement grew in force in the late 19th century, leading to calls for the prohibition of alcohol, but the movement leaders were not concerned with other drugs, which they did not regard as degrading to character [67]. Nonetheless, the success of the temperance movement established a precedent that "prohibition was the only logical or moral policy when dealing with such a great national problem" [42].

Until the turn of the century, the federal government had not exercised general police powers over public health. The rise of the progressive movement and public concerns about the depredations of the patent-medicine industry led to the passage of the Pure Food and Drug Act of 1906, which imposed labeling and purity requirements. While it did not prohibit any ingredients, it is regarded as having reduced the rate of opiates addiction [34].

The first federal prohibition against drug use addressed opium, driven by concerns about opium smoking by Chinese immigrants, by foreign-policy interests in China and the Philippines, and by the observation that merely restrictive laws had spurred smuggling without much reducing supply. A 1905 law that prohibited the import and sale of opium in the Philippines, then a United States colony, was the first federal law to prohibit trafficking in a drug, although opium for smoking had been subject to a special duty since 1862 [25]. The Smoking Opium Exclusion Act of 1909 prohibited the import of opium for smoking, but did not cover other forms of opium, which was widely used for medicine and recreation throughout the United States. The United States was also signatory to several international conventions restricting the trade in opium.

As opium smoking was associated with Chinese immigrants, so did cocaine snorting become associated with poor blacks around the turn of the century, even as whites dominated cocaine consumption [74]. Similarly, marijuana became associated with Mexican immigrants, and concern about its use was highest in the border regions where they were concentrated [42].

The Harrison Narcotics Tax Act of 1914 [26] was positioned as a revenue measure, rather than as prohibition, and as required for the United States to comply with the Hague Convention of 1912 [30]; the congressional debate on the act saw almost no mention of moral concerns. The Act required that any party involved in the distribution of opiates or coca products register with the federal government and pay a tax. It allowed for selling small quantities of the controlled drugs over the counter, and for larger sales authorized by a physician, so doctors (and the American Medical Association) did not feel that it threatened the practice of medicine [42]. Soon after passage, however, the act was interpreted to prohibit a physician from supplying the controlled drugs to addicts (who—as addiction was not considered a disease—were not legitimately patients). Under this interpretation, federal agents arrested many physicians, and made it clear that the government was not going to tolerate treatment of addicts that maintained their addiction [16]. The Narcotics Division of the Prohibition Unit of the Internal Revenue Service (Treasury Department) was given enforcement authority, which was transferred to the Prohibition Bureau in 1927.

There followed a series of committees to investigate the effects of the Harrison Act and the scope of the drug problem. A 1918 committee finding called for stricter law enforcement and greater coordination of state laws with federal statutes [34].

Many court rulings on whether Congress had the power to regulate physicians and punish drug possession established federal authority by 1925 [6], and a 1928 Supreme Court ruling affirmed that the Harrison Act was constitutional [48]. Alcohol prohibition, established by the Eighteenth Amendment in 1919, was by this time hotly debated, but the Harrison Act occasioned little controversy, despite the fact that drug violations accounted for a greater number of federal prisoners than any other class of offenses [48].

The growing scope of prosecutions under the Harrison Act spurred Congress to build an institutional structure to manage the consequences. The Porter Narcotic Farm Act of 1929 established two facilities where addicts could be held and treated. In 1930, the Federal Bureau of Narcotics was established in the Treasury Department, under the direction of Commissioner Harry J. Anslinger, who would go on to dominate federal drug-control policymaking and implementation for decades. (Anslinger was the nephew of the Treasury Secretary, Andrew J. Mellon; it is not apparent that Mellon shared what turned out to be his nephew's zeal for drug control [58].) Initially, the Federal Bureau of Narcotics focused its efforts on heroin, and Anslinger publicly downplayed the threat from marijuana [21]. In the 1930s, advances in the processing of hemp fiber threatened powerful petroleum and timber interests, who lobbied Congress for the prohibition of hemp and used their influence in the newspaper business to demonize marijuana users [56]. (As industrial hemp and marijuana are the same plant—albeit very different strains—it is difficult to distinguish between cultivation of the two in the law.)

The Federal Bureau of Narcotics responded to these pressures with the Marihuana Tax Act of 1937, and a media campaign to stir fears of marijuana use. The Act did not explicitly prohibit the possession or sale of marijuana, but imposed registration and transaction tax obligations on anyone trafficking in it, with heavy fines and prison terms up to 20 years. (The transfer tax was a contrivance, as a measure under treaty powers was infeasible and a revenue measure would be difficult to enforce [74].)

Drug use declined during World War II, and rose again thereafter [74]. The wartime decline was due, in part, to supply reductions from countries embroiled in conflict. The shortage of legal supplies spurred the growth of the black market, especially for heroin [33]. In response to the growing public perception that marijuana use led to the use of opiates, and urged on by the Federal Bureau of Narcotics, Congress responded with reinforcements of the Harrison Act. The Boggs Act of 1951 [8] was the first to impose mandatory-minimum sentences and to lump together marijuana, opiates, and cocaine, with uniform penalties [57]. National medical and legal associations questioned this stricter regime, and called for a Congressional study of the government's drug policy. The Daniel Committee found that drugs posed a great threat to the country, and recommended increased powers for the Federal Bureau of Narcotics and harsh measures, including denial of bail, making smuggling and heroin trafficking capital offenses, and the closing of treatment clinics [33]. The Narcotic Control Act of 1956 [43] implemented these recommendations.

The Narcotics Manufacturing Act of 1960 [44] established licenses and quotas for drug manufacturers, to bring the United States into compliance with international conventions on the medical and scientific uses of natural and synthetic opiates and cocaine. By the language of the conventions, barbiturates, amphetamines, and tranquilizers were not covered by the Act [26].

As public concern over drug abuse (including prescription drugs) grew in the 1960s, the White House established the President's Advisory Commission on Narcotics and Drug Abuse (Prettyman Commission). Its 1963 report called for marshaling all the powers of the federal government to combat drug use and trafficking [51]. In particular, it recommended: (1) that enforcement and investigative responsibilities be transferred to the Department of Justice, (2) a substantial increase in federal agents, and (3) extension of federal control over all drugs "capable of producing serious psychotoxic effects when abused".

Following on the report, the Drug Abuse Control Amendments of 1965 placed restrictions on the manufacture of prescription drugs with a potential for abuse, with the establishment of the Bureau of Drug Abuse Control in the Food and Drug Administration. As previous prohibitions had done for opiates, the Drug Abuse Control Amendments created shortages that drove up the street price (especially of amphetamine) and spurred the involvement of criminal organizations in manufacturing and

trafficking [16]. In 1968 the Bureau of Drug Abuse Control was merged with the Treasury Department's Federal Bureau of Narcotics to form the Bureau of Narcotics and Dangerous Drugs, in the Department of Justice.

Despite these efforts to control drugs (and similar measures in other countries), the use of marijuana and heroin continued to increase. Under President Nixon, the United States government redoubled its campaign against drug trafficking and abuse, formally declaring a "War on Drugs"; in 1971, President Nixon declared that drugs were "public enemy number one" [7]. In 1969, the United States closed the border with Mexico and instituted searches of vehicles crossing the border. The National Commission on Marijuana and Drug Abuse was created in 1970.

The Controlled Substances Act of 1970 [14] supplanted the Harrison Act as the basis of federal drug-control policy, and remains so today. Extant federal laws were reformulated under the federal power to regulate interstate commerce, and drugs were placed into five categories ("schedules") according to their medical utility and potential for abuse. (See Table 2 for a summary of the current schedules.) In earlier decades, courts had found that Congress did not have the authority to regulate the local production and distribution of drugs under its interstate-commerce powers, but opinions had shifted by the mid-1960s. Following the 1965 Drug Abuse Control Amendments model, the Controlled Substances Act of 1970 established administrative procedures for scheduling new drugs. The ongoing tension within the government over which agencies would have control over drug policy was evident in the drafting of the Controlled Substances Act of 1970. In the Senate version of the bill, the Attorney General was required only to "request the advice" of the Secretary of Health, Education, and Welfare (now Health and Human Services) and of a (non-binding) scientific-advisory committee before amending the schedule; in the House version, which was finally adopted, the Attorney General was not allowed to override the Secretary's determination *not* to schedule a new drug, and he was required to accept the Secretary's recommendation regarding medical and scientific considerations [59].

Drug control was a less visible priority under the Ford and Carter administrations. President Ford endorsed the findings of the Domestic Council Drug Abuse Task Force that the federal government could at most contain the problems of drug abuse, and should not operate under the model of eliminating them [23]. President Carter went so far as to publicly entertain the notion of marijuana decriminalization, but this idea gained no traction in Congress and public sentiment was against it [41].

The Drug Abuse Prevention, Treatment and Rehabilitation Act of 1979 [17] reflected the latest, slight swing of the pendulum away from law enforcement. It imposed minimum requirements on the National Institute on Drug Abuse for spending on prevention, and identified high-risk populations to be targeted with intervention programs.

The 1980s saw another escalation of the War on Drugs. President Reagan created the position of the White House Drug Policy Advisor in 1982, which was supplanted by an even more powerful Director of the Office of National Drug Control Policy in 1988, under the National Narcotics Leadership Act. (These officials are commonly known as the "Drug Czars". The Director of the Office of National Drug Control Policy has held cabinet-level rank, until the appointment of Gil Kerlikowske by President Obama [15]. For a comparative assessment of the performance of the Drug Czars, see [39].)

A series of measures increased federal penalties for many offences, increased drug-control spending, and improved the coordination of federal drug-control efforts. The Comprehensive Crime Control Act of 1984 [13] amended the Controlled Substances Act of 1970 to allow for fast-tracked scheduling of newly emerging "designer drugs" and when there exists an imminent public-safety hazard. Rising public concern about crack cocaine, catalyzed by the overdose death of a star college basketball player, led to the Anti-Drug Abuse Act of 1986 [2], which reinstated mandatory-minimum sentences for possession (large amounts were considered

Table 2 Schedule of controlled substances

Schedule I	
Criteria	• high potential for abuse • no currently accepted medical use in treatment in the United States • no safety for use under medical supervision
Major drugs	• cannabis • heroin • gamma-hydroxybutyric acid • lysergic acid diethylamide • 3,4-methylenedioxymethamphetamine (Ecstasy) • methaqualone (Quaalude) • peyote[a] and mescaline • psilocybin mushrooms
Schedule II	
Criteria	• high potential for abuse • currently accepted medical use in treatment in the United States • abuse may lead to severe psychological or physical dependence
Major drugs	• amphetamines • barbiturates—short acting • cocaine • methamphetamine • methylphenidate (Ritalin) • opiates (e.g., methadone, morphine, oxycodone, fentanyl)
Schedule III	
Criteria	• potential for abuse less than in schedules I and II • currently accepted medical use in treatment in the United States • abuse may lead to moderate or low physical dependence or high psychological dependence
Major drugs	• anabolic steroids • barbiturates—intermediate acting • codeine • ketamine • synthetic tetrahydrocannabinol (Marinol)
Schedule IV	
Criteria	• low potential for abuse relative to schedule III • currently accepted medical use in treatment in the United States • abuse may lead to limited physical dependence or psychological dependence relative to schedule III
Major drugs	• barbiturates—long acting • benzodiazepines (e.g., Valium, Xanax)
Schedule V	
Criteria	• low potential for abuse relative to schedule IV • currently accepted medical use in treatment in the United States • abuse may lead to limited physical dependence or psychological dependence relative to schedule IV
Major drugs	• codeine cough suppressant • opiate anti-diarrheals

Source: Drug Enforcement Administration

[a]Members of the Native American Church are allowed to use peyote in their rituals

prima facie evidence of intent to distribute) and allowed for the death penalty for some offenses.

Sentencing requirements were based on weight (see Table 3), with crack and powder cocaine treated dramatically differently; Congress justified the 100:1 powder-to-crack ratio on the basis of the social harms associated with crack, despite the identical chemical composition of the two forms. Whatever the original intent of Congress, this sentencing distinction

Table 3 Federal penalties for drug trafficking

Drug (Schedule)	Quantity	Penalties	Quantity	Penalties
Cocaine (II)	500–4,999 gm	1st Offense: 5–40 years. If death or serious injury, 20 years–life. ≤$2 M if an individual, $5 M if not. 2nd Offense: 10 years–life. If death or serious injury, life. ≤$4 M if an individual, $10 M if not.	≥5 kg	1st Offense: 10 years–life. If death or serious injury, 20 years–life. ≤$4 M if an individual, $10 M if not. 2nd Offense: 20 years–life. If death or serious injury, life. ≤$8 M if an individual, $20 M if not. 2 or More Prior Offenses: Life.
Cocaine Base (II)	5–49 gm		≥50 gm	
Fentanyl (II)	40–399 gm		≥400 gm	
Heroin (I)	100–999 gm		≥1 kg	
Lysergic acid diethylamide (I)[a]	1–9 gm		≥10 gm	
Methamphetamine (II)	5–49 gm		≥50 gm	
Phencyclidine (II)	10–99 gm		≥100 gm	

Drug	Quantity	Penalties
Other Schedule I and II	Any	1st Offense: ≤20 years. If death or serious injury, 20 years–life. $1 M if an individual, $5 M if not. 2nd Offense: ≤30 years. If death or serious injury, life. ≤$2 M if an individual, $10 M if not.
Schedule III	Any	1st Offense: ≤5 years. ≤$250 k if an individual, $1 M if not. 2nd Offense: ≤10 years. ≤$500 k if an individual, $2 M if not.
Schedule IV	Any	1st Offense: ≤3 years. ≤$250 k if an individual, $1 M if not. 2nd Offense: ≤6 years. ≤$500 k if an individual, $2 M if not.
Schedule V	Any	1st Offense: ≤1 year. ≤$100 k if an individual, $250 k if not. 2nd Offense: ≤2 years. ≤$200 k if an individual, $500 k if not.

Cannabis	Quantity	Penalties
Marijuana	50–99 kg or plants	1st Offense: ≤5 years. ≤$250 k if an individual, $1 M if not. 2nd Offense: ≤10 years. ≤$500 k if an individual, $2 M if not.
	100–999 kg or plants	1st Offense: 5–40 years. If death or serious injury, 20 years–life. ≤$2 M if an individual, $5 M if not. 2nd Offense: 10 years–life. If death or serious injury, life. ≤$4 M if an individual, $10 M if not.
	≥1,000 kg or plants	1st Offense: 10 years–life. If death or serious injury, 20 years–life. ≤$4 M if an individual, $10 M if not. 2nd Offense: 20 years–life. If death or serious injury, life. ≤$8 M if an individual, $20 M if not.
Hashish	≤10 kg or 1 kg hashish oil	1st Offense: ≤5 years. ≤$250 k if an individual, $1 M if not. 2nd Offense: ≤10 years. ≤$500 k if an individual, $2 M if not.
	>10 kg or 1 kg hashish oil	1st Offense: ≤20 years. If death or serious injury, 20 years–life. ≤$1 M if an individual, $5 M if not. 2nd Offense: ≤30 years. If death or serious injury, life. ≤$2 M if an individual, $10 M if not.

Source: Drug Enforcement Administration

[a]Lysergic acid diethylamide weights include the carrier medium (e.g., blotter paper)

has had hugely disproportionate racial impacts, as the majority of offenders sentenced for crack have been black, and the majority sentenced for powder have been white [32]. Congress has rejected repeated recommendations by the U.S. Sentencing Commission that the crack-powder distinction be eliminated, and has let die in committee every bill that would reduce or eliminate sentencing disparities [19].

The Anti-Drug Abuse Act of 1988 [3] states that "it is the declared policy of the United States Government to create a drug-free America by 1995." It established the White House Office of National Drug Control Policy to be the principal architect of national drug-control strategy. The Act also requires some federal contractors and all grantees to meet requirements for providing a "drug-free workplace," and extends mandatory-minimum sentencing requirements to conspiracy convictions. Under the statute, the Office of National Drug Control Policy is to set priorities, implement a national strategy, and certify federal budgets. The strategy is to be comprehensive and research based, with measurable objectives. Subsequent executive orders, reauthorization bills, and other legislative initiatives have added to the Office of National Drug Control Policy's authority and responsibilities, to include media campaigns, grants to communities, and cabinet-department budget assessments [65]. Smarting from criticism that the office was politically driven and insufficiently evidence based, it asked the National Research Council to establish a Committee on Data and Research for Policy on Illegal Drugs, which found that:

> [N]either the data systems nor the research infrastructure needed to assess the effectiveness of drug control enforcement policies now exists. It is time for the federal government to remedy this serious deficiency. It is unconscionable for this country to continue to carry out a public policy of this magnitude and cost without any way of knowing whether and to what extent it is having the desired effect [36].

The subsequent presidential administrations have seen smaller-bore legislative initiatives and less rhetorical emphasis on drugs, even as the War on Drugs has continued apace. At the same time, conflicts between federal law and state- and local-level statutes and enforcement have increased. In President Clinton's first term, he decimated the Office of National Drug Control Policy staff, appointed a low-key Director, and made almost no mention of drugs, occasioning criticism even from Democratic officials [5]. President Clinton reversed these positions during his reelection campaign and appointed a very visible Director.

In the same election season, voters in Arizona and California approved measures that legalized the use of marijuana for medical purposes, in direct contravention of the federal Controlled Substances Act. (Other state initiatives to allow for the medical use of marijuana date back to 1978, but were ineffective [37].) Top administration officials vowed to enforce federal laws and sought to prosecute physicians who prescribed marijuana. The George W. Bush Administration continued to campaign against increasingly lenient state laws and local decisions to make marijuana arrests a low priority, and went after (locally legal) sellers of drug paraphernalia [9].

Nonetheless, despite Drug Enforcement Administration raids on dispensaries, a few prosecutions of prescribing doctors, and a Supreme Court ruling upholding the federal government's authority to prohibit the use of cannabis [27], medical marijuana has proved popular, and the new Obama Administration has announced that it will no longer prosecute marijuana dispensaries that are operating legally in the 13 states that allow for them [38]. Meanwhile, states and localities have become laboratories for experimenting with reforms of drug policy—with sentencing, needle-exchange programs, and marijuana decriminalization. An accurate understanding of drug policy *as practiced* in the United States requires closer attention to state and local drug policies [53].

Federal Drug-Control Operations

The federal government budgets over 14 billion dollars to drug-control efforts, divided among twelve federal agencies with drug-control

Table 4 Federal drug-control fiscal year 2009 budget and activities

Agency	Drug-control programs and functions	Budget ($ million)
Department of Health and Human Services	National Institute on Drug Abuse (drug-abuse and addiction research), the Substance Abuse and Mental Health Services Administration (substance-abuse treatment and prevention), Indian Health Services (treatment and prevention), Centers for Medicare and Medicaid Services (screening and intervention for at-risk beneficiaries)	3,799
Department of Homeland Security	Office of Counternarcotics Enforcement, Customs and Border Protection, Immigration and Customs Enforcement, Coast Guard	3,696
Department of Justice	Drug Enforcement Administration, Interagency Crime and Drug Enforcement, Office of Justice Programs, Bureau of Prisons	2,896
Department of State	Bureau of International Narcotics and Law Enforcement Affairs, United States Agency for International Development	1,489
Department of Defense	Interdiction, intelligence, state and local assistance, prevention, and treatment programs	1,061
Department of Veterans Affairs	Veterans Health Administration	465
Office of National Drug Control Policy	High Intensity Drug Trafficking Area Program, Drug Free Communities program, National Youth Anti-Drug Media Campaign, Counterdrug Technology Assessment Center	422
Department of Education	Safe and Drug-Free Schools and Communities Act programs	218
Department of the Treasury	Internal Revenue Service, Office of Foreign Assets Control, Financial Crime Enforcement Network	59.2
Department of the Interior	Bureau of Indian Affairs	6.3
Department of Transportation	National Highway Traffic Safety Administration	2.7
Small Business Administration	Drug-free workplace grants	1.0
	Total	14,114

Source: Office of National Drug Control Policy

functions (unless otherwise noted, all budget figures are for fiscal year 2009). The lion's share of these resources (92%) is controlled by five cabinet departments: Health and Human Services, Homeland Security, Justice, State, and Defense (see Table 4). The Department of Health and Human Services has the largest share ($3.8 billion). It houses the National Institute on Drug Abuse, the largest supporter of drug-abuse and addiction research, and the Substance Abuse and Mental Health Services Administration, which funds substance-abuse treatment and prevention services. The Department of Homeland Security ($3.7 billion) enforces drug control at the borders, via Customs and Border Protection, Immigration and Customs Enforcement, and the Coast Guard. These agencies are responsible for cross-border protection, intercepting the movement of drugs and drug-related funds, and money laundering. Following the attacks of September 11, 2001, the drug-funds interception functions of the Department of Homeland Security were increased with the passing of the USA Patriot Act, which gave the Department of Homeland Security and federal security agencies additional authority to investigate and preempt future terrorist activities.

The Department of Justice budget is $2.9 billion. The Department of Justice supports prison- and community-based drug treatment through the Bureau of Prisons; enforces federal illicit-substance laws and regulations through the Drug Enforcement Administration, targets drug-trafficking and money-laundering organizations through the Interagency Crime and Drug Enforcement account, and manages drug-control–strategy programs through the Office of Justice Programs.

The State Department budget is $1.5 billion, for the Bureau of International Narcotics and Law Enforcement Affairs and the U.S. Agency for International Development. Roughly two-thirds is for eradication and interdiction efforts, and one-third for promoting alternatives to drug production in source countries.

The Defense Department budget is $1.1 billion, for drug-related threats to national security. The Department of Defense oversees interdiction and the disruption of illegal-drug flows toward the United States, collects and disseminates intelligence on drug activity, and trains American and foreign drug-enforcement agents (including foreign militaries). The Department of Defense's drug-control efforts include a demand-reduction program (random drug testing with sanctions, anti-drug education, and treatment) for the military.

Policymaking and Budgeting

While drug-control policy is implemented in many agencies of the executive branch, it is directed from, and coordinated by, the White House Office of National Drug Control Policy. Responsibility for drug-control legislation is spread across many House and Senate subcommittees (see Table 5 for those subcommittees with principal responsibility, and Table 6 for bills introduced in recent sessions).

When the Office of National Drug Control Policy was created in 1988, it was tasked with compiling a federal drug-control budget. Each year federal agencies submit drug-control–budget data to the Office of National Drug Control Policy, which produces a single federal budget. The Office of National Drug Control Policy has no budget-enforcement authority, so its budget is not prescriptive.

Federal agencies and the Office of National Drug Control Policy have some discretion in what they identify as drug-control expenditures, so the federal budget (and the balance between demand- and supply-side control measures) is sensitive to assumptions about what constitutes drug control [40]. In 2004, the Office of National Drug Control Policy changed its methodology for assembling the federal drug-control budget [77]. The Office of National Drug Control Policy's stated purpose was to more directly measure efforts targeting drug use itself, rather than its consequences [60]—that is, to exclude expenditures that were considered ancillary to drug control. Critics of this revision regard it as a manipulation by the Bush Administration to hide the costs of the War on Drugs. Previously, the

Table 5 Congressional subcommittees with drug-policy oversight

Subcommittee	Committee
Senate	
International Development and Foreign Assistance, Economic Affairs and International Environmental Protection	Foreign Relations
Western Hemisphere, Peace Corps, and Narcotics Affairs	Foreign Relations
Crime and Drugs	Judiciary
House of Representatives	
Early Childhood, Elementary and Secondary Education	Education and Labor
Health, Employment, Labor, and Pensions	Education and Labor
Western Hemisphere	Foreign Affairs
Border, Maritime, and Global Counterterrorism	Homeland Security
Crime, Terrorism, and Homeland Security	Judiciary
Criminal Justice, Drug Policy and Human Resources	Oversight and Government Reform
National Security and Foreign Affairs	Oversight and Government Reform
Research and Science Education	Science and Technology

Source: United States Senate and House of Representatives

Table 6 Recent congressional bills

Bill Number	Title	Purpose
110th congress		
H.R. 79	Powder-Crack Cocaine Penalty Equalization Act of 2007	To amend the Controlled Substances Act and the Controlled Substances Import and Export Act with respect to penalties for powder cocaine and crack cocaine offenses.
H.R. 174	Public Housing Drug Elimination Program Reauthorization Act of 2007	To reauthorize the public and assisted housing drug elimination program of the Department of Housing and Urban Development.
H.R. 970	Dextromethorphan Distribution Act of 2007	To amend the Federal Food, Drug, and Cosmetic Act with respect to the distribution of the drug dextromethorphan, and for other purposes.
H.R. 1118	Drug Trafficking Elimination Act of 2007	To amend the Controlled Substances Act to enhance criminal penalties for drug trafficking offenses relating to distribution of heroin, marijuana, and methamphetamine and distribution to and use of children, and for other purposes.
H.R. 1199	Drug Endangered Children Act of 2007 (enacted)	To extend the grant program for drug-endangered children.
H.R. 2294	Enhanced Participation in Drug Courts Act of 2007	To amend the Omnibus Crime Control and Safe Streets Act of 1968 to revise the definition of "violent offender" for the purpose of participation in drug courts.
H.R. 2425	Stop Marketing Illegal Drugs to Minors Act	To amend the Controlled Substances Act to provide enhanced penalties for marketing controlled substances to minors.
H.R. 3749	Methamphetamine Prevention Enhancement Act of 2007	To amend the Public Health Service Act to provide for the establishment of a Drug-Free Workplace Information Clearinghouse, to authorize programs to prevent and improve treatment of methamphetamine addiction, and for other purposes.
H.R. 4545	Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2007	To target cocaine kingpins and address sentencing disparity between crack and powder cocaine.
H.R. 5035	Fairness in Cocaine Sentencing Act of 2008	To amend the Controlled Substances Act and the Controlled Substances Import and Export Act to eliminate increased penalties for cocaine offenses where the cocaine involved is cocaine base, to eliminate minimum mandatory penalties for offenses involving cocaine, to use the resulting savings to provide drug treatment and diversion programs for cocaine users, and for other purposes.
H.R. 5842	Medical Marijuana Patient Protection Act	To provide for the medical use of marijuana in accordance with the laws of the various States.
H.R. 5843	Act to Remove Federal Penalties for the Personal Use of Marijuana by Responsible Adults	To eliminate most federal penalties for possession of marijuana for personal use, and for other purposes.
H.R. 6281	High School Sports Anti-Drug Act	To provide States with the resources needed to rid our schools of performance-enhancing drug use.
S. 1011	Recognizing Addiction as a Disease Act of 2007	To change the name of the National Institute on Drug Abuse to the National Institute on Diseases of Addiction and to change the name of the National Institute on Alcohol Abuse and Alcoholism to the National Institute on Alcohol Disorders and Health.
S. 1211	Saving Kids from Dangerous Drugs Act of 2008	To amend the Controlled Substances Act to provide enhanced penalties for marketing controlled substances to minors.

Table 6 (continued)

Bill Number	Title	Purpose
S. 1383	Drug Sentencing Reform Act of 2007	To reduce the disparity in punishment between crack and powder cocaine offenses, to more broadly focus the punishment for drug offenders on the seriousness of the offense and the culpability of the offender, and for other purposes.
S. 1685	Fairness in Drug Sentencing Act of 2007	To reduce the sentencing disparity between powder and crack cocaine violations, and to provide increased emphasis on aggravating factors relating to the seriousness of the offense and the culpability of the offender.
S. 1711	Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2007	To target cocaine kingpins and address sentencing disparity between crack and powder cocaine.
S. 2137	Methamphetamine Kingpin Elimination Act of 2007	To amend the Controlled Substances Act to expand the threshold criteria for designating an individual as a principal administrator, organizer, or leader of a continuing criminal enterprise involving methamphetamine.
S. 2274	Dextromethorphan Abuse Reduction Act of 2007	To amend the Controlled Substances Act to prevent the abuse of dextromethorphan, and for other purposes.
S. 3351	Drug Trafficking Interdiction Assistance Act of 2008	To enhance drug trafficking interdiction by creating a Federal felony for operating or embarking in a submersible or semi-submersible vessel without nationality and on an international voyage.
S. 3598	Drug Trafficking Vessel Interdiction Act of 2008 (enacted)	To amend titles 46 and 18, United States Code, with respect to the operation of submersible vessels and semi-submersible vessels without nationality.
111th congress		
H.R. 68	No More Tulias: Drug Law Enforcement Evidentiary Standards Improvement Act of 2009	To increase the evidentiary standard required to convict a person for a drug offense, to require screening of law enforcement officers or others acting under color of law participating in drug task forces, and for other purposes.
H.R. 265	Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2009	To target cocaine kingpins and address sentencing disparity between crack and powder cocaine.
S. 97	Drug Free Families Act of 2009	To amend title IV of the Social Security Act to require States to implement a drug testing program for applicants for and recipients of assistance under the Temporary Assistance for Needy Families program.

Source: GovTrack.us

drug-control budget reflected consistent annual increases in spending, and a stable 2-to-1 ratio between supply- and demand-side expenditures over the years. The revised methodology yielded a much smaller drug-control budget, with 90% of the apparent reductions appearing on the supply side. The most significant change was the exclusion of costs associated with prosecuting and incarcerating drug users [75].

The 1980s and 1990s saw a shift in spending from treatment to law enforcement. In real terms, the federal drug-control budget increased by 600% between 1981 and 2000, from about three to 18 billion dollars [68]. This increase was driven primarily by criminal-justice expenditures. The change in budgeting approach makes it difficult to track the federal budget over time. The Office of National Drug Control Policy recalculated earlier budgets using their new methodology, but only as far back as 1996. Figure 1 shows the federal drug-control budget from 1996 to 2009, which is the longest series for which consistent budget data are available (i.e., comparable budgeting methodologies were used). The federal drug-control budget

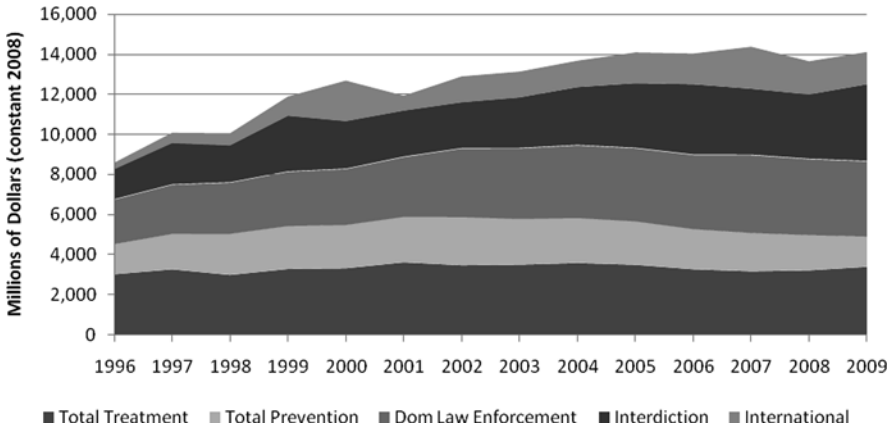

Fig. 1 Federal drug-control budget 1996–2009 (constant 2008 dollars). Data for 1996–2001 are from [61]. Data for 2002–2009 are from [62]. All data reflect budgets using the revised Office of National Drug Control Policy methodology. To correct for changes in the purchasing power of the dollar, we have adjusted the data to constant 2008 dollars, using the Consumer Price Index. Dom = Domestic

increased steadily over this period (even after controlling for inflation). The two lowermost areas in Fig. 1 represent the total demand-reduction budget, with the three uppermost representing the total supply-reduction budget. Demand-reduction spending has remained relatively stable over the period, while supply-reduction spending has increased substantially. Therefore, in spite of accounting revisions, demand-reduction spending has declined as a share of the total (from 43% in 2004, the first year of the revised methodology, to 35% in 2009).

Law Enforcement

The enforcement of federal drug laws entails the seizure of illicit drugs, and the arrest, prosecution, and punishment of traffickers and users. In addition to targeting the drug-supply chain, federal law-enforcement agencies also seek to reduce ancillary harms of the drug trade through, for example, Project Safe Neighborhoods, a national program to reduce gun and gang violence. Disrupting the supply chain increases the price of illicit drugs and reduces the quantity available for sale. Targeting users deters drug use by imposing consequences for purchasing drugs (through the probability of arrest and the severity of the sanction imposed). The federal government spends more than $9.2 billion (65% of the drug-control budget) on domestic and international law enforcement and interdiction [63]. These strategies target the entire supply chain, but federal agencies focus primarily on international and interstate actors.

Domestic law enforcement accounts for 42% of enforcement and interdiction spending [63]. Under the revised budget methodology, the drug-control budget no longer includes the (substantial) cost of prosecuting and incarcerating drug offenders; 52% of the 200,000 federal inmates were sentenced on drug charges [22]. The costs of investigations, intelligence, assistance to state and local authorities, and law-enforcement research are included. The Office of National Drug Control Policy highlights two programs that assist state and local authorities: the High Intensity Drug Trafficking Area and Organized Crime Drug Enforcement Task Force programs.

The Director of the Office of National Drug Control Policy has the authority to designate qualifying jurisdictions in the United States as High Intensity Drug Trafficking Areas, centers of production or distribution that have

harmful effects on other areas. When a jurisdiction is identified as a High Intensity Drug Trafficking Area, federal resources are provided to facilitate investigations and information sharing across enforcement agencies and to fund strategic intervention initiatives to reduce the production and distribution of drugs, and drug-related money laundering. As High Intensity Drug Trafficking Area initiatives are tailored to the needs of the jurisdiction, activities differ across sites. As such, there is no cross-site evaluation of a High Intensity Drug Trafficking Area. Each jurisdiction is responsible for developing and monitoring performance measures relevant to its High Intensity Drug Trafficking Area program. The Organized Crime Drug Enforcement Task Force coordinates federal, state, and local efforts against high-value drug trafficking and money-laundering organizations (Consolidated Priority Organization Targets), with the goal of disrupting the chain of command within these organizations. Key measures used to monitor the performance of the Organized Crime Drug Enforcement Task Force are the number of organizations that are disrupted or dismantled, and the number of defendants convicted:

> From 2002 to 2008, a total of 110 CPOTs [Consolidated Priority Organization Targets] have been identified, of which 81 percent have been indicted, 53 percent have been arrested, 25 percent have been extradited from other countries, and 3 percent have been killed either by other gang members or as a result of resisting arrest. Of the 110 existing CPOTs, 26 percent are linked to Foreign Terrorist Organizations [63] (pp. 23–24).

Other domestic law-enforcement efforts include the Drug Enforcement Administration Mobile Enforcement Teams and the U.S. Immigration and Customs Enforcement Border Enforcement Security Task Forces. The Drug Enforcement Administration focuses on major drug organizations involved in international and interstate trafficking. In 1995, Mobile Enforcement Teams were established to assist with lower-level enforcement efforts, by giving technical and investigative help to local law-enforcement agencies to fight traffickers and the violent crime related to trafficking, especially gang violence. Mobile Enforcement Teams are rapid-response teams, deployed in response to requests by local sheriffs, police, or district attorneys.

Border Enforcement Security Task Forces were established in response to the growing threat from trafficking across the Mexican border and drug-gang–related violence associated with the Mexican drug cartels. The Border Enforcement Security Task Forces facilitate information sharing among local, state, federal, and foreign law-enforcement agencies. Border Enforcement Security Task Forces have been responsible for many arrests and convictions, and seizures of drugs and weapons, equipment, and currency that support trafficking [71].

Suppressing drug production and trafficking in other countries, and preventing illicit drugs from entering the United States, are top priorities of federal drug enforcement; 58% of the law-enforcement budget is for international programs and interdiction. The United States provides direct assistance to foreign countries (primarily through the Departments of State and Defense), as well as multilateral assistance through international organizations, such as the United Nations Office on Drugs and Crime [69]. United States efforts target the Andean region (Plan Colombia [72], and the Andean Counterdrug Initiative [73], for Bolivia, Peru, Ecuador, Brazil, and Panama) and Afghanistan, with small initiatives in Pakistan and Haiti. Increasing attention and resources are being devoted to Mexico as violence associated with the major Mexican drug cartels has spilled over the border.

Foreign assistance consists primarily of bolstering law enforcement and anti-trafficking efforts, and crop eradication. Relatively little emphasis is placed on alternative development and crop-substitution programs. Most illicit-drug crops are in poor countries, tended by peasant farmers; eradication programs have been criticized for leaving locals without alternative livelihoods, sometimes threatening state stability and reversing eradication successes, as with coca eradication in Bolivia in the 1990s [21].

Colombia is the largest recipient of foreign assistance for drug control [10]. The United States has aided Colombia's military in countering drug production and trafficking since the 1970s, but by the late 1990s Colombia led the world in cocaine production and was a major supplier of heroin to the United States. In 1999 the Colombian president announced the six-year Plan Colombia, which aimed to halve drug cultivation, production, and distribution, and increase security in Colombia by taking back areas controlled by militia groups that used drug profits to finance their activities. United States funding was approved in 2000, and more than six billion dollars has been spent since, 74% for military support [24]. The plan has helped Colombia improve its security situation, but has done little to curb the flow of cocaine to the United States. The production-reduction goals of the plan were not met; coca production has increased since 2000 as producers moved into more-remote areas [24].

The many billions of dollars spent on international drug-law enforcement has yielded meager results; the mechanics of drug production and distribution militate against enforcement efforts bringing about lasting reductions in supply. Focused efforts that reduce drug production in one area are offset by increased production elsewhere. Also, since most of the profits accrue to actors at the end of the supply chain, street prices are relatively insensitive to supply shocks as retailers have latitude to adjust their profit margins [21].

Prevention

Preventing the initiation of drug use precludes later physiological and social harms, and so may be cost effective, but only 10% of the federal drug-control budget goes to prevention programs. This is due, in part, to the difficulty of appropriately targeting these programs, and to the lack of documented success of those existing prevention programs. In 2007, an estimated 8% of American youth aged twelve or older were using illicit drugs (according to the National Institute on Drug Abuse's Monitoring the Future Survey and the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health), making youth prime targets for prevention programs.

Among the better-known prevention programs are Drug Abuse Resistance Education (D.A.R.E.) and school-based random drug testing. Drug Abuse Resistance Education involves a uniformed police officer visiting classrooms and educating students on how to resist drug use. Successive evaluations of Drug Abuse Resistance Education have found no meaningful differences in knowledge, attitudes, or drug use for those students participating in Drug Abuse Resistance Education, compared with those who did not [31]. When it became apparent that Drug Abuse Resistance Education was an ineffective use of drug-control resources, the program was "retooled" into what became the New-Drug Abuse Resistance Education (New-D.A.R.E.) program [54]. New-Drug Abuse Resistance Education provides a more interactive curriculum, where students are exposed to brain imaging as proof of how drug use impairs brain functioning, provides data on actual levels of drug use among youth, and teaches refusal skills [35]. Evaluations of New-Drug Abuse Resistance Education fail to show any improvements over its predecessor [1]. The federal government has had a rocky relationship with Drug Abuse Resistance Education, and negative findings have led it to almost eliminate financial support for the program. In 2001, the Surgeon General identified Drug Abuse Resistance Education as a program that "Does Not Work" [55], and, in 2003, the U.S. Government Accountability Office concluded that Drug Abuse Resistance Education was potentially counterproductive in certain populations (i.e., it was associated with *increased* drug use) [31]. Remaining federal support for Drug Abuse Resistance Education is largely rhetorical; it continues to be listed as a model prevention program on the Office of National Drug Control Policy Web site [64], and President Obama declared a National Drug Abuse Resistance

Education Day to celebrate the work of the program [49].

The Office of National Drug Control Policy directly manages two prevention programs: The National Youth Anti-Drug Media Campaign and the Drug Free Communities Support Program. The National Youth Anti-Drug Media Campaign was created by Congress in 1998 with the goal of preventing and reducing drug use through radio, television, and other media. National Institute on Drug Abuse-funded evaluations have shown that, while it has positively affected parents' beliefs and behaviors, there has been no measurable impact on initiation or reduced use among targeted youth [50].

The Drug Free Community Program, funded by Congress in 1997, supports local initiatives to address drug use. The Drug Free Community Program is managed jointly by the Office of National Drug Control Policy and the Substance Abuse and Mental Health Services Administration and the program currently supports 769 community coalitions. An ongoing evaluation suggests that communities receiving support through The Drug Free Community Program have reduced drug use at a greater rate than non-recipient communities [4]. There are many inherent difficulties in drawing conclusions about the causal effect of this type of program. As communities have to apply for Drug Free Community Program support, selection bias can muddy findings: communities that opted into the program may be different from those that did not, in ways that may affect outcomes. Nonetheless, the evaluation findings warrant cautious optimism.

Other federal prevention programs are spread across several executive agencies [64]. For example, the Student Drug-Testing Institute in the Department of Education provides technical support for schools interested in establishing a school-based testing program. Random drug testing ostensibly serves a double function—it deters drug use and detects early drug involvement, thereby disrupting the path to addiction. By 2008, 16% of secondary schools had implemented drug-testing programs [52]. An assessment of school drug testing found no differences in student drug-use outcomes between schools with drug testing (whether for cause or at random) and those without [76]. To overcome the methodological limitations of the research design used in this study, a randomized controlled trial of school drug-testing programs is under way [29].

Despite some troubling instances of persisting support for unproven or even discredited programs, there are federal government efforts to bring research-based evidence to bear on prevention [12].

Treatment

In 2009, drug-treatment services (excluding treamtent research) account for 20% of the federal drug-control budget (about $2.4 billion) and are provided primarily through the Substance Abuse and Mental Health Services Administration. Implementation is mostly left to the states, as 86% of the Substance Abuse and Mental Health Services Administration's drug-treatment funding is distributed via block grants (lump sums allocated to states, with very few stipulations on how resources are to be spent). The Center for Substance Abuse Treatment within the Substance Abuse and Mental Health Services Administration works with states and local groups to improve and expand effective treatment services provided under the block grants.

The remaining 14% of the Substance Abuse and Mental Health Services Administration's funds are issued on a discretionary basis, under Programs of Regional and National Significance: capacity programs, which identify needed system changes and extend evidenced-based care, and science and service programs, which identify practices that might improve services and disseminate information about these practices. The federal government has made strides toward promoting treatment practices that are grounded in evidence [46], but the quality of the federally endorsed evidence base on "what works"

remains weak, and the standards for considering a treatment program "evidence-based" are low [20].

Research

Seven percent of the budget (about one billion dollars) goes to research. Of this, 60% goes to treatment and 40% to prevention. The National Institute on Drug Abuse, created in 1974, is the principal federal agency funding basic, clinical, and epidemiological research into drug abuse and addiction; the National Institute of Justice and the National Institute of Mental Health also fund research. National Institute on Drug Abuse-funded research has made major contributions to the science of addiction and has led to a number of innovations in drug treatment, including the clinical development of levo-alpha-acetylmethadol and naltrexone (medications used to treat opioid dependence). Despite being effective treatments for opioid addiction, levo-alpha-acetylmethadol and naltrexone faced market barriers to distribution and were ultimately of little policy significance. Levo-alpha-acetylmethadol is no longer produced and naltrexone is provided to few addicts [28]. The National Institute on Drug Abuse disseminates research findings to promote science-based practices and policies, through its *Research Monograph Series* (first issued in 1975) and the bi-monthly newsletter *NIDA Notes* (first issued in 1985). The National Institute on Drug Abuse accounts for some 85% of global biomedical research on drugs and addiction [70].

The National Institute on Drug Abuse's billion-dollar budget gives it high visibility, and the Institute has on occasion come under scrutiny for its role in shaping federal drug policy, through both the types of research it funds and the targeting of its research dissemination. The Institute has been criticized for promoting politically expedient research messages and a research agenda that reinforces the War on Drugs, to maintain its funding, while paying little attention to harm-reduction strategies [49]. However, Nora Volkow, a neuroscientist who was appointed director of the National Institute on Drug Abuse in 2003, maintains that its agenda is divorced from politics and is driven by science.

Issues in Policymaking

In the next decade, budget constraints may yield a welcome scrutiny of federal drug-control policies and programs. If outcomes are to improve, federal drug-control policymakers will have to take resource allocation seriously and prioritize their efforts. What will this mean for federal drug control?

Picking Battles

Drug policymakers will need to pick their battles, which will require clearly elaborating the mission and goals of the federal drug-control strategy. This may entail focusing on particular drugs and drug-control activities.

The stated goal of the national drug-control policy is "to reduce illicit drug use, manufacturing, and trafficking, drug-related crime and violence, and drug-related health consequences" [66].

It seems reasonable, then, that the strategy should focus on those drugs associated with the most severe crime, violence, and health consequences—and, further, that policymakers establish that the program's fiscal and social costs are outweighed by the benefits obtained. Under current law, alcohol—the costliest drug by far—is legal, while the scheduling of illicit and controlled substances is only loosely determined by social harms. As alcohol is legal, it is usually divorced from the drug-policy debate. If public health is to be the driving principle, the policy for each drug should reflect its social costs.

Setting Minimum Standards for "Evidence"

Few people will object to a call for "evidence-based" practices; indeed, the Office of National Drug Control Policy is required to "develop and implement a set of research-based principles" for drug-abuse–prevention programs [45]. But this desideratum compels stakeholders to justify their existence and continued funding by demonstrating that their programs "work," which may have the perverse effect of stifling progress. A low bar for "effectiveness" renders many ineffective programs "evidence-based," and makes it difficult to identify worthy programs. Good programs get lost in the mix, and weak programs persist. Clear, strict standards for the quality of evidence would shield policymaking from some of the malign influences of politics [35].

The Muddled "Wars"

Afghanistan, the world's leading producer of illicit opium poppies [69], is also a central front of United States counterterrorism operations. As the War on Drugs has become inextricably linked with the Global War on Terror, terrorism-related drug-control efforts (trafficking and money laundering) have received greater federal support. Conflating these two "wars" reduces policymakers' ability to optimize resource allocation toward programs that are most effective at reducing drug-related social harms. If national-security concerns are to drive drug-control policymaking, then it should be made explicit. Whatever the operating principles are, if they are not made clear and adhered to, the resulting policies are not likely to be effective.

The new Obama administration's top drug-policy appointments have been received with guarded optimism by advocates of reform, and are not identified as ardent drug warriors (although Vice President Biden has long been so), but no official changes of policy have been implemented. Whatever their orientation, previous administrations have called for evidence-based policymaking, but the political process has trumped science and program evaluation. Should policymakers be committed to thoroughgoing reform, there is ample evidence to inform their efforts.

Appendix

The Controlled Substances Act of 1970 created five schedules under which drugs of abuse are classified [18].[1] Scheduling of a drug determines, in part, federal penalties for possession and distribution, and the terms under which it may be prescribed.

The legislation created the initial listing, but the Drug Enforcement Administration and the Department of Health and Human Services determine adjustments to the Schedules, based on a drug's potential for abuse, accepted medical use in the United States, and potential for dependence. The Drug Enforcement Administration begins or accepts petitions for investigations, and then passes its findings to the Department of Health and Human Services, for a recommendation based on scientific and medical evaluations. The Drug Enforcement Administration then makes the scheduling decision.[2]

See Table 2 for the scheduling criteria and major scheduled drugs.

[1] Some states impose controls on the sale and use of substances not covered under the federal schedules, such as nitrous oxide and amyl nitrite [11]. Pseudoephedrine is widely used in the manufacture of methamphetamine, and medicines containing pseudoephedrine are separately regulated under an amendment to the USA Patriot Act [18].

[2] The scheduling procedure may be bypassed when an international treaty requires controlling a drug, or "to avoid an imminent hazard to the public safety" [2].

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Historical Perspectives of Addiction

Howard I. Kushner

Contents

Histories of Addiction

In the past quarter century, historians of addiction have focused on contextualizing the political, social, and cultural meanings of addiction. Building on Harry Gene Levine's classic 1978 article, "The Discovery of Addiction," historians have suggested that the classification of certain substances as illicit or licit tells us more about social norms and power relationships than about the psychopharmacological properties of the substances themselves [32]. Historians have contextualized the definitions of addiction, alerting us to the extent to which alcohol prohibition and the criminalization of narcotics and stimulants reflected dominant cultural values rather than robust scientific findings. These studies pose an *intellectual* challenge to the treatment and control of addiction. So far, however, they have made a less significant impact on addiction policy and treatment. In a recent article, I argued that historians of addiction should take biology seriously [44]. Here I hope to persuade addiction scientists and practitioners of the value of these recent histories for their research and practice.

Doing so requires an appreciation of historical methods. Academic historians are not simply engaged in telling a chronological story; nor, since the late nineteenth century, have they assumed that they can uncover "facts" that recreate the past as it was. Rather, academic historians insist that historical sources do not speak for themselves, but are subjects of contested interpretations framed by current and past cultural and political contexts. From this perspective, there can never be one final "factual" reading of the past; today's landmark interpretation is regularly subjected to tomorrow's reinterpretation because, odd as it may sound to the non-academic historian, the past is always subject to change as historians redefine the contexts in which events occur. The current scientific paradigm that addiction is a brain disease [56] is placed in social and cultural contexts. The implicit message is that, whatever its biological substrates may be, by acknowledging social, cultural, and political forces, addiction scientists,

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_4,

policy-makers, and practitioners can develop more effective policies and interventions.

Brain Disease Redux

Often, writes historian Nancy Campbell, what has been learned in addiction science has been ignored in succeeding paradigms. More than a half century ago, Campbell finds, addiction researchers Maurice S. Seever and Abraham Wikler had independently concluded that addiction was a chronic relapsing/remitting condition, a view presented in 2000 by then-National Institute on Drug Abuse director, Alan Leshner, as novel [48]. Campbell also points to a rhetorical resilience of a traditional "moral lexicon" of addiction. Citing the work of current National Institute on Drug Abuse director, Nora Volkow, and her colleagues as exemplars, Campbell finds that their notion of "disrupted volition" parallels nineteenth century constructions of addiction "as a 'disease of the will' subject to voluntary control." Thus, writes Campbell, with "amnesiac gesture toward its own repressed past, the addiction enterprise comes full circle into the present" ([12], pp. 221, 237).

As Campbell suggests, the claims that addiction is a brain disease would sound familiar to nineteenth century neurologists. In many respects, current views resemble degeneration theory as expounded by the French physician Théodule Ribot in his 1883 study *Les Maladies de la Volonté* (which was reissued in 32 subsequent editions in French and English) [64]. Degeneration theory offered a hereditarian explanation for a variety of disorders including retardation, depression, depravity, and sterility. Behaviors that today would include addictions such as alcoholism, diet, and sexual addictions were alleged to have a cumulative destructive impact on the nervous system that was inherited by succeeding generations [24]. Practitioners took extensive family histories and prepared elaborate pedigrees that sought to explain a current disorder by uncovering patterns of disease and behavior in a patient's family. Adherents sought to portray degeneration as organic, but much like addiction practices today, treatment revolved around an array of psychological and moral interventions under the rationale that alterations in habits had a direct physiological influence on the nervous system [24, 53, 58, 61].

Degeneration theory meshed with the views of the influential neurologist James Hughlings Jackson, whose "dissolution theory" was based on his claim that lesions in the neo-cortex reversed the evolutionary process in which the "higher" cortical structures restrained the "lower" emotive, limbic functions. Jackson's hydraulic theory reinforced the assumptions that addictions reflected a hijacking by these more primitive structures, often referred to as the "reptilian brain." Thus, addiction was a brain disease because the behaviors were enabled by the damage to cortical censors [32]. Because these behaviors appeared to run in families, it was a small step to connect Jackson's dissolution with degeneration.

Both degeneration and dissolution were translated into early twentieth century popular scientific explanations of the physical effects of alcohol and other drugs. For instance, historian Susan Speaker writes of Richmond P. Hobson, a retired naval officer and three-term congressman from Alabama, who published *Alcohol and the Human Race* in 1919 and portrayed it as based on the best "evolutionary science" of the time [35]. Hobson, who founded the American Alcohol Education Association in 1921, wrote that alcohol was a toxin that paralyzed white blood cells, making them unable to "catch the disease germ" that was "devouring" the drinker. This led to the destruction of the "centers of the brain upon whose activities rest the moral sense," resulting in what Hobson labeled "retrograde evolution." For Hobson, "alcoholic beverages, even in moderation reverse the process of nature." Ninety-five percent of "all the acts of crime and violence committed in civilized communities," Hobson claimed, "are the direct result of men being put down by alcohol to the plane of savagery" ([72], p. 214).

Hobson's "science" both influenced and was influenced by early twentieth century prohibitionist sentiments. With the end of Prohibition, a

new science of alcoholism emerged. Americans, according to Speaker, ceased "demonizing alcohol after Prohibition, and chose to deal with its risks largely through regulation, education, and harm-reduction strategies." However, she writes, "they have resisted" treating users of most other psychoactive drugs in a similar manner [72]. What emerged were distinct attitudes, policies, and sciences that separated alcohol from other addictive substances. However, Speaker implies, these distinctions were based less on objective evidence than on the cultural, social, and economic attitudes toward alcohol and other mind-altering substances. I begin with historians' interpretations of the science of alcohol addiction and then move on to other substances.

Alcohol and Other Drugs

The federal government has created two separate divisions for addiction research: (1) the National Institute on Alcohol Abuse and Alcoholism, which has focused exclusively on alcohol, and (2) the National Institute on Drug Abuse, which has studied the use of all other addictive substances. Despite this official separation of alcohol from other drugs, in a recent collection, *Altering American Consciousness: The History of Alcohol and Drug Use in the United States, 1800–2000*, historians Sarah W. Tracy and Caroline Jean Acker argue that bringing them together is justified: "Despite the chasm created by law, which separates them into legal and illegal categories, all psychoactive drugs share important commonalities" ([78], p. 22). "America's drug habits cannot be understood, nor effective drug policy made," they insist, "until we have a clearer picture of the range of drugs used yesterday and today, and the ways in which specific historical circumstances have shaped their use and regulation" ([78], p. 2).

The theme that runs through *Altering American Consciousness* is best summed up by historian Alan Brandt, who writes that although the addictive nature of nicotine may today be seen as an undisputed fact of its chemical properties, nicotine's classification as an addictive substance is rooted more in the history of attitudes toward smoking than in its neurochemical mechanisms [7]. Brandt believes that the history of nicotine provides a window to understanding the meaning of addiction. He rejects what he calls "universal, transhistorical approaches to the mechanisms of addiction" in favor of "specific historical contexts" that illuminate "the social processes by which addictions are created and experienced, categorized, and treated" ([7], p. 383).

The history of nicotine provides a context for the increased labeling of a variety of substance uses and behaviors—from carbohydrates and coffee to shopping and sex—as addictions. Perhaps this has occurred because, as William L. White [84] points out, there continues to be no consensus on the language and meaning of addiction itself [37, 69, 83]. "The rhetoric of addiction," White believes, "grew out of the multiple utilities" of the constituencies it served ([84], p. 43). Deconstructing the various definitions of inebriety, intemperance, drunkenness, and alcoholism, White argues that the contested rhetoric of addiction served as "a means of staking out professional territory." At stake was which institutions and professions could claim "legitimate ownership of the problem" ([84], p. 50).

Taking White's view further, anthropologist Helen Keane's *What's Wrong With Addiction?* focuses on how addiction rhetoric is constituted in current discourses [37]. Like Brandt, Keane eschews a universalist view, arguing instead that what has become characterized as addiction "is tied to modernity, medical rationality and a particular notion of the unique and autonomous individual" ([37], p. 6). Although addiction has been portrayed as restricting freedom and individual autonomy, Keane argues that discourses of addiction have tended to limit freedom as they have authorized the prohibitive power of the family, the state, and the corporation.

Keane's and White's claims are best examined in historical context. We begin with histories of alcohol use and then move on to other substances.

Alcohol: Predisposed or Culturally Determined

The histories of alcohol addiction have much in common with those of other drug addictions, but unlike illicit and (still) legal drugs such as nicotine, alcohol putatively poses a danger only to predisposed alcoholics. The prevailing view in America is that moderate consumption of alcohol by those without a predisposition is safe and not addictive. In contrast, the dominant media and scientific view today holds that, although some people are more prone to addictive behaviors than others, no predisposition is necessary for addiction to illicit substances and nicotine; any exposure potentially places any user at risk [19, 56].

Connected to the risk dichotomy is the widely accepted belief that alcoholism is a disease. Although a number of historians have pointed to a long genealogy supporting the notion that excessive and seemingly uncontrollable drinking was driven by forces beyond an individual's power, most agree with Griffith Edwards [25], former chairman of the UK's National Addiction Centre, that the modern concept defining alcoholism as a disease comes from the work of the director of the Yale Center for Alcohol Studies, Elvin M. Jellinek, in the 1940s [36]. Not all experts have been persuaded by the disease paradigm. Two types of challenges emerged: the first questioned the almost universal belief that alcoholics must abstain from drinking for their entire lives, and the second was aimed at the validity of the disease construct.

In 1962, the renowned British psychiatrist D. L. Davies published a report of seven alcohol-dependent individuals who returned to normal drinking without reverting to alcoholism [21, 25]. Edwards, who trained under Davies, followed these alcoholics and concluded that Davies' optimism was not sustained by their long-term behaviors ([25], pp. 159–161). In the 1970s, California psychologists Mark and Linda Sobell claimed that behavior modification could enable recovered alcoholics to return to what they called "controlled drinking" [70, 71]. The Sobells' research was the subject of a damning analysis published in *Science* in 1982, which concluded that "a review of the evidence, including official records and new interviews, reveals that most of the subjects in the controlled drinking experiment failed from the outset to drink safely. The majority were hospitalized for alcoholism treatment within a year after discharge from the research project." In fact, a 10-year follow-up revealed that only one of the original 20 subjects could be classified as having met the criteria of controlled drinking; four had died of alcohol-related causes ([25], pp. 148–164).

When a number of studies attacking the construction of alcoholism as a disease appeared in the late 1980s and 1990s, the response of the alcohol research community was hostile. These critiques, including highly publicized ones written by Herbert Fingarette [28] and Stanton Peele [60], have been the focus of sustained attacks from a wide range of alcohol researchers, and the authors have been marginalized and often stigmatized.

Although historians generally do not confront the controversy over controlled drinking, recent addiction histories can be read as providing support for the minority view questioning the robustness of the claims that alcohol addiction is a disease. Building on Levine, they have concluded that the separation and classification of alcohol addiction as substantially different from other drug addictions is a cultural construction.

Earlier histories of alcohol use have detailed the battles between pro- and anti-prohibitionists [47], but sociologist Ron Roizen believes that this focus has obscured the more important story of the depoliticization of alcohol [65]. The construction of alcoholism as a disease, according to Roizen, meshed with the values of both the "spiritual orientation" of Alcoholics Anonymous and the "disinterestedness, objectivity, and empiricism" of contemporary science. Ironically, the notion that alcoholism was a disease "also offered destigmatization to the alcoholic and a measure of new symbolic legitimacy for [the] beverage alcohol itself." From the disease perspective, alcohol "harbored little more

responsibility for alcoholism or alcohol related troubles than did sugar for the disease of diabetes" ([65], p. 64). The dominant belief remains that moderate drinking is safe for all but the potential and actual alcoholic. For Roizen, "the story of modern alcoholism" reveals "its strongly social-constructionist character and flimsy science base" and "invites our attention to the relationship between alcohol science and the wider society" ([65], p. 74). Roizen also has been particularly vocal in his opposition to what he sees as a new public health campaign to demonize alcohol [27].

One of the linchpins for the notion of alcoholism as a disease is the widespread popular belief that Native Americans are genetically vulnerable to alcoholism. This view has been challenged by a number of recent studies. In 2000, in the *American Journal of Public Health*, John W. Frank and his colleagues emphasize that beyond obvious "risk factors in contemporary life," there is the need to consider the historical sources of Native American drinking problems. "In contrast to other explanatory factors," they write, "the role of history seems to have been underemphasized in the voluminous literature attempting to explain the problem of drinking among Native Americans." For instance, one must acknowledge "the extraordinary barrage of inducements to drink heavily in the early years after European contact. The harmful drinking patterns established during those years have largely persisted." Thus they conclude that "the cultural dimensions of Native American drinking must be considered far more important than the notion that Native Americans' propensity for heavy and dependant drinking is primarily genetic" ([29], pp. 349–350).

Although historian Peter C. Mancall does not cite Frank et al., he endorses their findings [50]. Mancall agrees that some individuals "seem to possess an inherited predisposition toward alcohol abuse," but he insists that "there is no convincing evidence suggesting that Indians as a group are more inclined to possess these traits than the general American population" ([50], pp. 99–100). Historical research, according to Mancall, reveals that "there has been no single Native American response to liquor. Consumption patterns have differed over time by region and even in specific communities." They also have varied by age and gender. "Patterns of alcohol-related illness, disease … and trauma are not uniform within the Native American population today, and were not in past centuries either" ([50], p. 93). Europeans, Mancall reminds us, who had been exposed to alcohol for centuries, "had developed rules for its consumption." Nevertheless, they too experienced "periods of wide-spread alcohol-related problems," including the so-called gin craze in the mid-eighteenth century, which "occurred in part because of wider availability of more potent alcohol during the early phases of the industrial revolution when the English and other Europeans drank more alcohol" in an attempt to "escape from the disorienting social changes of their everyday lives" ([50], p. 100). For Mancall then, like Frank et al., "history, not biology, holds the key to understanding Native American drinking patterns, just as history, not biology holds the key to understanding alcohol consumption in other American populations" ([50], p. 101).

Mancall's thesis is built on a number of studies [41], including Craig MacAndrew and Robert B. Edgerton's 1969 cultural anthropology classic, *Drunken Comportment: A Social Explanation*, which explored variations in behaviors observed in different populations when they are drunk [49]. In relatively simple societies, people learn how they are supposed to behave when intoxicated; in more complex societies, the cultural expectations may vary, but the same principle holds. Edwards supports MacAndrew and Edgerton's anthropology. Acknowledging that "alcohol is a drug which has the inherent capacity to interfere with brain function and produce a state of intoxication," Edwards, nevertheless, argues that "intoxication is not, however, a fixed and monolithic state." Rather, based on narratives of South African and Bolivian drinking behaviors, Edwards explains behavioral reactions to alcohol intoxication as "plastic." By this he means that "drunkenness behavior can be molded by influences which

include the immediate context, the way people react to drunkenness, the drinker's personality, and the expectations given by culture and society." From this perspective, "drunkenness is more like clay than concrete" ([25], p. 56).

The history of attempts to treat drunkenness suggests that clay was often mistaken for concrete. This response can be seen in historian Katherine A. Chavigny's discussion of nineteenth century drinking reform [15]. She focuses on the emergence—from the antebellum period to the 1880s—of a consensus among a group whom she labels as "inebriety physicians" that drunkards were suffering from an inherited disease. If the cause of drunkenness was a degenerative inheritance, "those persons who had inherited a constitutional weakness for alcohol had little chance of becoming sober without long-term quarantine from temptation." These physicians urged the construction and maintenance of facilities to house and treat the afflicted, many of whom were poor, homeless, and criminal. Legislatures were not persuaded, and other more traditional reformers rejected "hereditarian interpretations of inebriety" because they "believed that such views discouraged drunkards from trying to reform and provided them with a ready excuse for backsliding" ([15], p. 118). Nevertheless, the failure of inebriety physicians to persuade legislatures and other reformers that drunkenness was a disease was a temporary setback.

In contrast, historian Sarah Tracy's "Building a Boozatorium" examines a successful attempt to medicalize habitual drunkenness in turn-of-the-century Iowa [76]. Similar to the physicians discussed by Chavigny, Tracy's reformers relied on degeneration theory and its eugenic offspring. Unlike the experts in Chavigny's narrative, this cohort of clinicians, clergy, and social reformers persuaded the Iowa legislature to designate a facility for confinement and treatment of the disease of intemperance. Tracy connects this success to its context in wider Progressive social reform. "As much as any reform passed in turn-of-the-century Iowa," writes Tracy, "the creation of inebriate hospitals embodied a diversity of elements that characterized Progressivism in America: the search for order." These include "the rise of 'issue-focused coalitions,' the secular institution of Protestant moral values; the growth of an increasingly regulatory state with a well-articulated, efficiently organized, social reform mission; the maturation of the professions; and the expansion of scientific and medical authority" ([76], p. 149).

While Chavigny uncovers the roots of the contemporary triumph of the medicalization of alcoholism in earlier reformers' ideology, Tracy finds a disconnect. A number of factors, writes Tracy, "worked against the wholesale adoption of the medical perspective" on alcohol abuse. Foremost was the failure of these institutions to demonstrate a robust cure rate. Moreover, these institutions "addressed a small percentage of the alcoholic population," and, as a result, medical care never was able to supplant the criminal justice system. "Prohibition and World War I cut short the medical efforts of physicians, drying up much of the political concern for the drunks" ([76], p. 153). Thus, "Iowa's efforts to medicalize habitual drunkenness were unsuccessful for as wide a range of reasons as they were initiated" ([76], p. 153).

Tracy's 2005 volume, *Alcoholism in America: from Reconstruction to Prohibition*, finds no medical consensus that alcoholism was a disease. However, like Chavigny, Tracy uncovers a persistent attempt by practitioners and social reformers to attach drunkenness to forces beyond individual choice [77]. Thus, reformers located the etiology of alcoholism in social forces, biological destiny, or some combination. Therefore, the current dominant discourse, in which alcoholism is considered a disease, has deep, if contested, historical roots.

Although today alcoholism is widely assumed to be organic, mid-twentieth century psychiatry focused on psychogenic etiologies, often tied to gender role confusion. Alcoholic males, writes Michelle McClellan, were characterized as effeminate with homosexual tendencies manifested by employment difficulties. In contrast, psychiatrists portrayed female alcoholics as displaying "masculine traits such as aggressiveness," and they "were often promiscuous or

frigid" women and inadequate mothers ([52], p. 274). Given the psychoanalytic paradigm that underpinned these views, gender identity and behavior issues were tied to childhood conflicts resulting from poor parenting. "Experts," according to McClellan, found that "many alcoholic women had displayed masculine and therefore deviant behavior as children—some had acted like tomboys, for example, while others exhibited unfeminine temper tantrums" ([52], p. 279). When later life stressors and emotional difficulties arose, particularly those tied to sexual and reproductive issues, these vulnerable women turned to alcohol.

Gendered assumptions, according to historian Lori E. Rotskoff, also informed psychiatric views about the role that sober wives played in their husbands' alcoholism [66, 67]. Underlying many of these observations was the tension of post-war readjustment of gender role expectations, with returning males displacing working women. The task, seen by many psychiatrists and social workers in the 1940s and 1950s, was to reestablish traditional gender roles within the American family. A number of psychiatrists suggested that "wives had a vested interest in maintaining their husbands' incompetence" ([67], p. 302). Some practitioners suggested that a husband's alcohol abuse was triggered by his wife's neuroses, manifested in dominating their emasculated husbands. Others saw the domination as resulting from the stress of their husband's addiction. Nevertheless, both of these perspectives suggested that alcoholism was a "family illness" and that "the whole family would need to convalesce" ([67], p. 307). Thus, by the 1950s, psychiatrists and social workers advocated group therapy for alcoholics' wives. "Given the nation's deep psychological investment in marriage," Rotskoff concludes, "it is apt that alcoholism's deleterious effects would increasingly be measured in marital terms. In large part, the cultural construction of the 'recovering' alcoholic marriage—comprised of sober husbands and supportive wives—gained public acceptance because it reflected and reshaped familial values in American society at large" ([67], p. 321).

What these historians have shown is that the theories that informed these arguments, interventions, and policies—degeneration, psychoanalysis, and eugenics—reflected dominant social values in the guise of science. One might argue that current scientific claims about alcoholism as a disease rely on a completely different science, informed by neurobiology, biochemistry, and genetics [9, 59]. However, having shown the culture-bound nature of earlier scientific theories supporting the idea that drunkenness is a disease, historians are skeptical of current scientific assertions that alcoholism is a disease.

Opiates and Other Illicit Drugs

The same science and psychiatry that have consistently viewed host predisposition as the trigger for alcohol addiction have, just as consistently, viewed opiates as posing an addictive risk for all who use them. According to Edwards, this is because alcohol intoxication "is remarkably susceptible to cultural prescriptions and proscriptions" and alcohol is "a widely accepted recreational drug," whereas, "in contrast, intoxication with crack cocaine, or injected amphetamines, or with a heavy dose of lysergic acid diethylamide (known more commonly as LSD), is not so easily shaped, and these are not drugs which society is ever likely to accord a licit recreational status" ([25], p. 57).

Alcohol prohibition was attempted, and, despite some revisionist arguments that it reduced drunkenness and alcohol addiction substantially [11], Prohibition was a social and political failure [46]. The contrast between the rejection of alcohol prohibition and the expansion of opiate prohibition is underlined by the triumph of the belief that alcohol use had a wide range of possible individual effects from benign to deadly. Where these effects fell on the spectrum was a consequence of host differences and excessive drinking. The refusal to accept a similar range of possibilities for opiates and other mind-altering substances, including marijuana, stimulants, and amphetamines, framed both the

official response and individual behavior of users [55]. Nevertheless, there remains a deeply held belief that there is such a thing as an addictive personality that leads one to drugs. This concept, as we will see, has deep historical roots, often attached to an array of negative character traits. In contrast to the alcoholic, predisposition toward narcotic use became evidence that drug addicts were sociopaths. As a result, prohibition of drugs and punishment for dependence were framed by a combination of claims about the nature of the substances and that of the addicts.

In *Creating the American Junkie* (2002) and her subsequent publications, Caroline Acker traces this history of opiate prohibition through an examination of the experience of users as they negotiated a world in which opiate use increasingly became criminalized [1]. Acker's work reinforces David Courtwright's study, *Dark Paradise* (2001), which, using similar narratives, demonstrates that "what we think about addiction very much depends on who is addicted" ([16], p. 4). In the early twentieth century, addicts could seek medical treatment that included prescriptions of maintenance doses. Beginning with the Harrison Narcotics Act in 1914, however, non-medical use or purchase of cocaine and opiates was restricted and all narcotics sold or prescribed were required to be registered. As a result, physicians were no longer able to treat addicts through maintenance, and ceased treating them altogether. This shift, writes Acker, transformed the context of opiate use and "as the context for the use of opiates changed, so did the meanings for those who used them" ([1], p. 166). Thus, "addicts developed their own strategies for maintaining their addiction," which resulted in "a new form of addict identity as the behaviors to maintain addiction were criminalized" ([1], p. 167).

Courtwright has a slightly different take. With the decline of medical (iatrogenic) addiction in the late nineteenth century, "opiate addiction . . . began to assume a new form: it ceased to be concentrated in upper-class and middle-class white females and began to appear more frequently in lower-class urban males, often neophyte members of the underworld. By 1914 the trend was unmistakable." For Courtwright, "the trend toward criminalization . . . was well underway before the basic narcotic statutes were enacted" ([16], p. 3).

Part of that identity, according to historian Timothy Hickman, was the emergence of "a double meaning of addiction," in which some of the addiction was attributed to disease and some to hedonism and antisocial behavior ([34], pp. 185–186). "The addiction concept of habitual narcotic use was embedded in the early twentieth century paradigm of professionalizing medical authority" ([34], p. 185) because it placed juridical addicts under medical authority and criminal addicts under criminal jurisdiction. Anti-narcotic legislation, argues Hickman, reflected this dichotomy, and, by the early 1920s, "volitional addicts came to be defined as *criminals*" while "juridical addicts . . . were defined as innocent *patients*" because of their willingness to seek medical treatment ([34], p. 188, italics in original). Hickman does not distinguish between alcohol and narcotic use, but his evidence and the wider historical record indicate that the division between those who were considered diseased and those who were classified as criminal mirrored the division between alcoholics and drug addicts.

Although Hickman does not make the connection, his essay provides a context for the emergence of the psychoanalytic construct of the "addicted personality," which first appeared in Lawrence Kolb's 1925 article, "Types and Characteristics of Drug Addicts" [38], and in his subsequent works [39]. Despite Kolb's insistence that addiction was a medical issue, federal officials adopted Kolb's construct as evidence of the general character defects of addicts and as justification to extend the criminalization of drug use [16, 78].

Speaker explains such results as almost inevitable given the rhetoric that informed drug addiction from the 1920s to the 1940s [72]. Acknowledging that "drug abuse is a significant and difficult public health problem," Speaker, nevertheless, points to accumulated evidence that suggests "that at least some persons can use drugs moderately without becoming abusers,

that even heavy abuse may not be a lifelong pattern, and that many 'outbreaks' of drug abuse are self-limiting and fairly short-lived" ([72], p. 203). Illicit drugs and nicotine were demonized with similar, if not the same, adjectives and hyperbole that once framed alcohol prohibition campaigns: "The drugs in question are powerful, seductive, and rapidly addictive; that everyone is at risk for addiction; that drugs *by themselves* are sufficient to cause any imaginable deviant behavior and are directly responsible for most crime and violence" ([72], p. 204, italics in original). Although, as Speaker asserts, with the end of Prohibition alcohol consumption was destigmatized, the use of other psychoactive drugs has not been. Indeed, made illicit, their use is not only illegal, but also immoral ([72], p. 205).

As medical treatment for alcohol addiction became the norm in the mid-twentieth century, maintenance clinics for the treatment of narcotics addiction became illegal. From 1923 to the opening of the first methadone treatment center in 1965 in New York City, writes Jim Baumohl, "addicts were demonized, hounded, subjected to draconian criminal penalties, and never treated except in the confines of a hospital or jail." Aside from a very few wealthy private clients, "abstinence was the only legitimate goal of treatment" [5]. By the 1930s, even the supporters of maintenance programs "believed most addicts to be incurable" ([5], p. 228).

It was in this context that in 1935 the U.S. Public Health Service established the Center for Drug Addiction at the federal prison hospital in Lexington, Kentucky [12]. Informally labeled as "Narco," the facility, which continued its addiction research until 1979, was designed to be a treatment hospital for incarcerated addicts. In 1948, the research unit became the first basic research laboratory of the newly formed National Institute of Mental Health, the Addiction Research Center. Inmates became voluntary participants in Addiction Research Center experiments that tested reactions to a wide variety of substances including alcohol, barbiturates, heroin, methadone, major and minor tranquilizers, and psychedelics. Campbell's *Discovering Addiction* examines the Center for Drug Addiction and Addiction Research Center in detail. She found that inmates often were re-addicted and some of the information obtained "was used by pharmaceutical companies seeking to bring drugs to market" ([12], p. 76). Nevertheless, Campbell concludes that "the research program yielded broadly distributed benefits to persons from the addicted class" ([12], p. 142).

The Center for Drug Addiction's benign approach to addicts was an exception, but the venue for its research, a federal prison, reflected the policies of Henry Anslinger, the influential director of the Federal Bureau of Narcotics (1930–1962). With bipartisan support, Anslinger advocated incarceration as the only deterrent. It didn't matter to Anslinger, writes Baumohl, whether addicts were confined to a jail or a hospital, but "the more like a jail, the better he liked the hospital" ([5], p. 254).

Anslinger's role in shaping and extending the criminalization of drug use policy, writes Rebecca Carroll, cannot be overestimated [13, 14]. Anslinger "influenced Americans' attitudes toward narcotic drugs and drug users and sellers, depicting both users and sellers as criminals." This is evident in Anslinger's 1937 Congressional testimony in which he claimed that marijuana "is dangerous to the mind and body, and particularly dangerous to the criminal type, because it releases all of the inhibitions." It causes some individuals to "have an increased feeling of physical strength and power," which is dangerous because they "fly into a delirious rage, and they are temporarily irresponsible and may commit violent crimes" [4].

Although a number of influential experts, including leaders of the American Medical Association and the American Bar Association, argued for the medicalization and clinical treatment of addicts, Anslinger stifled their voices [75]. In 1944, at the urging of New York City Mayor Fiorella La Guardia, the New York Academy of Medicine conducted a study on the effects of marijuana, the findings of which contradicted Anslinger's claims. The commission found that cannabis did not cause violence and, despite Anslinger's insistence otherwise,

concluded that marijuana could be medically beneficial. Anslinger denounced the report and instructed the Bureau of Narcotics agents to investigate the commission members' own drug use. Further, he threatened prison sentences for anyone carrying out independent research on cannabis.

In the post-war era, Anslinger altered his views of marijuana's effect on its users but not his policy toward its use. Testifying in Congress in 1948, Anslinger claimed that cannabis caused the user to become peaceful and pacifistic; thus, the Communists were recruiting Americans into cannabis use as part of a plot to weaken their will to fight [75].

Like Anslinger, those who continue criminalizing marijuana use in the United States today claim to base their views on scientific research, but, also like Anslinger, their antipathy toward marijuana use reflects deeper cultural values rather than robust science. A similar claim can probably be made about those who support unrestricted availability of marijuana. The point here, as much of recent addiction history reveals, is that the classification of substances as licit or illicit has less to do with science than with politics.

This political influence can be seen in attempts to control demand. Historian William B. McAllister's examination of international drug control shows that increasing regulation and criminalization of drugs has ended up pretty much as it began, with incarceration of drug users and a failure to stem the activities of suppliers [51]. What has changed, according to McAllister, is the "nature and scope" of anti-drug efforts. "Governments and international agencies constructed massive bureaucracies, engaged in considerable legislative activity, and attempted to implement policies intended to change the behaviors of millions of individuals, with varying degrees of success" ([51], p. 175). Although McAllister finds that "since the late nineteenth century, the American drug experience has largely mirrored that of other Western industrialized nations," he notes that the United States "has acted as the center of demand" for all types of drugs and has been the greatest force of "regulatory activism." As a result, McAllister concludes, "policy-makers, legislators, and citizens of the United States, much like addicts, cannot escape their relationship to the global drug scene" ([51], pp. 201–202). If, as a number of historians have indicated, the century-long activism failed to stem the drug addiction that it was aimed at curing [73], the rhetoric surrounding drug use, combined with the increasing classification of substances as addictive, has exacerbated the problem.

In a recent book, Richard Davenport-Hines argues that the criminalization and prohibition of drugs have resulted in an epidemic of use and an exacerbation of fatal encounters. The almost paranoid response of puritanical American policy-makers has, according to Davenport-Hines, led to a black market and growth in all types of criminal activity [20]. David Courtwright finds this argument unpersuasive: "What is unique about [Davenport-Hines'] *The Pursuit of Oblivion* is that it combines the simplification inherent to world history with the simplification peculiar to polemical exertion. The result is a book that, for all its length and erudition, is almost startlingly reductive: the story of a bad idea imposed upon a doubtful world by aggressive fools" ([18], p. 445).

Licit Mind-Altering Drugs

Neuroscientists typically attribute the heightened anti-drug rhetoric to a more sophisticated understanding of how these substances work on the human brain, a view shared by historian turned bio-ethicist Steven Novak [57]. He finds that when it came to lysergic acid diethylamide (i.e., LSD), despite the desires and pressures from researchers, their pharmaceutical sponsors, and influential lay persons, clinical and neurobiological research determined its ultimate classification. LSD became suspect because research data revealed suicide risks, prolonged psychotic sequelae, and anti-social behaviors. Meanwhile, LSD was being used

illegally for recreational purposes with many of the same dangerous effects. Although for some—Timothy Leary and his followers—it was LSD's mind-altering, liberating effect that spelled its doom, Novak's history suggests otherwise. The ongoing thalidomide revelations and resultant increased Congressional oversight led to legislation requiring prior Food and Drug Administration approval for all investigational drug trials, as well as a finding that a substance was safe and efficacious before it could be marketed. LSD met neither test and was eliminated from medical investigation, albeit with some resistance [57]. The importance of this history is that it was the biochemical action of LSD that determined its marginalization and eventual criminalization [79].

In contrast to LSD is the history of antidepressants—often addictive, mind-altering, but licit, drugs. With the introduction of a new class of antidepressants in the late 1980s called selective serotonin reuptake inhibitors (fluoxetine hydrochloride [Prozac®], paroxetine hydrochloride [Paxil®], and sertraline hydrochloride [Zoloft®]), antidepressant use has grown exponentially. Spurred on by massive advertising efforts in the late 1990s and Peter Kramer's best-selling book, *Listening to Prozac* [40], selective serotonin reuptake inhibitors, according to psychiatrist Nicholas Weiss, have become "consumer products appropriate for wide usage or general lifestyle enhancement." Selective serotonin reuptake inhibitors' predecessors, monoamine oxidase inhibitors and tricyclic antidepressants, were viewed as "disease therapies to be kept strictly in the medical domain" [83]. Why, asks Weiss, had "no one listened to [the tricyclic antidepressant] imipramine?" ([83], p. 329). His answer, like so much else connected to addiction, lies in the history of alcoholism.

The definition of "alcoholism" as a distinct disease affecting only a minority of drinkers, writes Weiss, has removed the blame for alcohol-related social problems from the substance to a subgroup of susceptible individuals. Thus, alcohol use, though not abuse (drunkenness), is socially acceptable. "This enabled the alcohol beverage industry to sell its product, despite widespread concerns about the dangers and evils of alcohol, as long as drinking was officially proscribed for that susceptible population" ([83], p. 349). The diagnosis of depression, according to Weiss, "functioned in an analogous, though inverse manner." A diagnosis of depression identified a susceptible group "who *should* become users, those with a current or potential medical depression" ([83], p. 349, italics added). Therefore, dependence on selective serotonin reuptake inhibitors is authorized, even though they are mind-altering (and often addictive) substances, because depression has been constructed as a disease. The risks of selective serotonin reuptake inhibitor use are downplayed because the condition that they treat is defined as illness, despite a spate of warnings about the hazards associated with selective serotonin reuptake inhibitors [10, 30, 33].

Similarly, although Weiss does not make this connection, a diagnosis of attention deficit hyperactivity disorder authorizes placing individuals (mainly children) on addictive stimulant medications such as Ritalin® (methylphenidate) [22]. According to historian Nicholas Rasmussen, the current amphetamine epidemic should be viewed in the context of the medical use of stimulants to treat depressive disorders and how this resulted in a wider epidemic of stimulant use by the mid-twentieth century. Building on this history, Rasmussen connects the present methamphetamine epidemic to the earlier iatrogenic epidemic [62, 63]. This history appears to be repeating itself as Ritalin® and other stimulants prescribed for the treatment of attention deficit hyperactivity disorder become widely used as recreational drugs on American college campuses and beyond.

Recognizing how prescription medication use once again has morphed into recreational and self-medicating substance use and abuse has important implications for those who wish to understand and treat the current wave of addiction and substance abuse. For Rasmussen, these evolutions have resulted as much from changing populations who use stimulants as from the biological actions of these drugs. A similar

argument has recently been made by psychologist Richard DeGrandpre in *The Cult of Pharmacology* (2006) [23].

In fact, for most illicit addictive substances, there is a companion licit substance, such as methylphenidate, the action of which mirrors that of the proscribed drug. As DeGrandpre points out, although Ritalin® and cocaine act similarly on the brain, the former is widely prescribed for children while the use of cocaine is a felony. Similarly, the street drug ecstasy acts on the same serotonin receptors as selective serotonin reuptake inhibitors. Although far from controversial, the risk of addiction to mind-altering pharmaceuticals has been justified because of the putative benefit conferred by their consumption. This returns us to the tensions that exist regarding alcohol and nicotine use. Each has been sanctioned because of their alleged benefits and vilified because of their harms.

Smoking and Nicotine

As Alan Brandt points out, although the addictive potential of nicotine in tobacco was often noted long before the 1988 Surgeon General's report on nicotine and addiction [82], attitudes toward cigarette smoking have a complex history. The prohibition of alcohol in 1919, writes Brandt, "had the effect of further legitimating the use of cigarettes. Cigarettes now assumed many of the positive cultural and social attributes previously associated with drinking—leisure, pleasure, and sociability—without the risks of intoxication with its consequent social and familial pathologies" ([7], p. 386). For the next several decades, moderate smoking was portrayed in the media, including in medical journals, as risk free and possibly beneficial to overall health. Smoking, Brandt argues, was contrasted with drug addiction and characterized as "a habit that could be broken without much trouble" ([7], p. 387). In fact, "often cigarettes were seen as a vehicle for assisting in breaking addictions to more dangerous substances like alcohol or opiates" ([7], p. 388). As late as 1964, the Surgeon General's advisory committee on the health consequences of smoking concluded that "the evidence indicates this dependence to be psychogenic in origin" and "the biological effects of tobacco, like coffee . . . are not comparable to those produced by morphine, alcohol, barbiturates, and many other potent addicting drugs" [80]. As a result of the dramatic decline of smoking because of its associated health risks, its recategorization as addictive in the 1980s was, according to Brandt, "far less problematic than would have been the case a decade earlier." This was particularly so because smoking increasingly had become "associated with certain social groups—generally those less educated and of lower socioeconomic status," and, notes Brandt, "in a culture prone to stigmatize its poor and disfavored, changing perceptions about the 'average smoker' eased the growing attribution of addiction" ([7], p. 391).

In his recent book, *The Cigarette Century*, Brandt focuses more on the dangers associated with smoking, and, consonant with his role as an expert witness for the Justice Department in its prosecution of the tobacco industry, he focuses on the health risks associated with smoking [8]. Although Brandt remains sympathetic to those who continue to smoke, others have been less scrupulous in translating the justified demonization of the tobacco industry to smokers themselves.

In sequential media conferences hosted by the American Cancer Society in 1985 and the National Cancer Institute in 1988, strategies were adopted that were aimed at portraying the tobacco industry as illegitimate, deceptive, and criminal. The American Cancer Society's *Media Handbook*, *Smoke Signals*, suggested delegitimizing the industry by referring to them as "drug pushers," "profiteers from human misery," environmental polluters, and "death and disease merchants" [3]. At the American Cancer Society meeting and its follow-up 1988 Media Advocacy Consensus Conference in Washington, DC, attendees were urged to shame the industry's allies and dependent community arts organizations into severing their ties with the tobacco industry [3, 81]. Although both conferences

warned "to be careful about blaming the victim" ([81], p. 36), inevitably these attitudes spilled over to the smokers as well. The American Cancer Society's *Media Handbook* suggested that one response to claims of smokers' rights was: "your right to smoke stops where my nose begins and my lungs are exposed." Smokers were to be confronted with the dangers that they posed to children who are "more prone to bronchitis, pneumonia, and other respiratory problems." Children, smokers were to be reminded, deserved "fresh, clean, smoke-free air" ([3], p. 23). In the last two decades, the rhetoric has ratcheted up as accusations claiming deception and criminal activity by the tobacco industry have become the subject of seemingly endless lawsuits. Those who continue to smoke often find themselves collateral victims, increasingly ostracized and demonized. "There are," writes Brandt, "powerful currents in our culture that define smokers as weak-willed and ignorant, who abuse their own health and others', while polluting the common environment" ([7], p. 398).

Despite these powerful forces and the health risks associated with smoking, many persist in the habit. Part of the reason for this persistence, according to Keane, is evident if one contrasts the immediate rewards of smoking with its long-term consequences [37]. For instance, Keane cites studies that suggest that smoking enables working-class women to cope with boring working conditions. However, as she points out, from a rhetorical perspective, smoking "is reduced to its potentially most undesirable outcomes, namely, various premature, painful, and protracted forms of death," while any potential benefits are dismissed as "illusory and excluded from the calculation of risk" ([37], pp. 102–103). Given that those who smoke are, as Brandt points out, already socially marginalized, the benefits of smoking, like those who smoke, have become increasingly unattractive.

Speaker [72] argues that the prohibition of a substance is almost always preceded by a demonization of its producers and users. If this observation is correct, we may be well along the road to prohibiting smoking in North America.

Rhetoric and Reality

In combination, these new histories make a persuasive case for the cultural construction of drug classification and addiction. They illuminate the role of rhetoric in influencing legal statutes, court decisions, and the criminal justice system. The ambiguous attitude toward smoking and nicotine addiction provides an ongoing case study of how cultural values and legal structures evolve and interact, determining where on the spectrum of legitimacy a mind-altering substance and its users are located.

Despite the growth of restrictions, heightened rhetoric, and ratcheting up of penalties for many mind-altering drugs, the use of those drugs is either persistent or increasing. However, Courtwright warns against conflating drug policy with drug use. "When doing drug *policy* history, it pays to zoom in on details: What was the mix of regulations, taxes, and penalties governing access to this drug in this society at this time? When doing drug *use* history, it pays to zoom out, looking for broader connections among drugs and across cultures." Thus, writes Courtwright, "Opium smoking would not have taken root in China had it not been for the introduction and spread of tobacco, with which opium was first smoked. Marijuana smoking would not have taken such hold among Western youth had it not been for the antecedent cigarette revolution. Fewer alcoholics would have meant fewer narcotic addicts, the relief of hangover often inspiring the use of opiates. 'Licit' and 'illicit' categories obscure the indivisibility of drug history" [18].

If substances such as caffeine, chocolate, and carbohydrates are included, not to mention addictive behaviors including gambling, sex, and shopping, we either inhabit the most addictive society that ever existed or have failed to notice retrospectively how addictive human behaviors are. Alternatively, as the logic of the histories that are reviewed here suggests, a wide range of human consumption and behaviors have been (re)constructed as addictions.

Speaker asks to what extent the "characteristic rhetoric" toward addictive substances is a

"reflection of genuine drug problems . . . and to what extent it is an expression of various social tensions—class struggles, demographic changes, racial and ethnic conflicts, etc.—or an expression of particular values and ideologies?" She also wonders "what accounts for the persistent use of these themes and images," and "to what extent . . . this popular rhetoric not only reflected but shaped public perceptions and drug policy itself during this century" ([72], p. 219). To these questions we may add what the histories of addiction reveal about the biological effects on the human brain and what these biological mechanisms reveal about the histories of addiction.

The skepticism of many addiction historians toward current scientific claims is rooted in the evidence that each successive psychiatric addiction paradigm has revealed more about the culture that enabled it than about the robustness of scientific findings. For many historians, portraying biology and the past sciences of addictions as culturally constructed appears to authorize ignoring current science altogether. However, the fact that science, like everything else, is socially constructed in no way diminishes its explanatory power any more than it limits the value of historical interpretations, such as those examined in this chapter, which—like all historical research and writing—are socially constructed and contingent [42]. In any case, an increasing number of historians of addiction have begun to engage rather than ignore current addiction science. Those historians have much to say that addiction scientists should consider.

Taking History Seriously

What does addiction history reveal about addictive behaviors? Can all this evidence be interpreted as culturally framed? According to Edwards, the answer is both yes and no. He suggests that histories of alcohol use lead to a deeper engagement with the putative organic mechanisms that have been attached to alcoholism. Such an approach opens up an alternative interpretation that brings together seemingly contradictory social constructionist and biologically reductionist claims. Alcoholism, according to Edwards, is "best approached through a framework of the dependence-syndrome concept," where "the dependent state is not a matter of all or nothing (addict or not addict), but something which can be experienced in varied and measurable degrees (more or less dependent)" ([25], p. 162). Edwards' insistence on the distinction between syndrome and disease is not trivial. Measles, polio, and Huntington's are diseases because a tentative diagnosis based on signs and symptoms is confirmed or rejected through a laboratory test indicating infection by a pathogen or the presence of a genetic mutation. In contrast, the cause of a syndrome, such as schizophrenia, Tourette's syndrome, or affective disorders (depressions), remains unknown [45, 74]. The diagnosis of syndromes depends on the identification of a list of possible combinations of signs and symptoms displayed by an individual within a certain time period. This list of signs and symptoms is tentative, and disagreement often surfaces over which signs and symptoms are crucial to authorize a diagnosis [31, 43]. As a result, identification of a syndrome often varies over time and by geographic location [86].

As with pneumonia, a variety of routes can lead to alcohol dependence. Unlike pneumonia, but like most psychiatric syndromes, these include both cultural and/or biological factors in the enabling spectrum. Those who meet the criteria (in terms of signs and symptoms) for alcohol dependence experience real illness, even if the etiology and level of distress and particular path to dependence are not the same for every alcohol-dependent person. Recognition of the many routes to an alcohol dependence syndrome sanctions researchers and clinicians to craft a variety of interventions and policies that consider a spectrum of cultural and biological triggers. Such recognition must include, no matter what the trigger, the biological and social effects on the individual. This requires engagement with the accumulating evidence from recent research that substance dependence, including alcohol

dependence, alters brain reward mechanisms, such as brain architecture and neurochemistry, sometimes permanently [9, 85]. This seems true even when the addiction, such as gambling, is not attached to a substance. The question remains whether labeling non-substance behaviors as addictions is justified because they impact and alter the same brain reward systems (i.e., the ventral tegmental area) as do cocaine and heroin [6, 56, 85]. Since most behaviors have an impact on brain chemistry, how do we decide which of these are addictions and which are not? Many of the histories of addiction discussed in this chapter agree that what is considered and not considered an addiction reflects social and cultural values as much as it tells us a truth about the mechanisms of the brain.

Saying that does not, however, excuse trivializing the importance of biology to addiction. As Edwards writes in his discussion of the history of the failed controlled drinking experiments, the "belief that the troubled drinker can recover only through abstinence" was based on "accumulated personal testimony and front-line clinical experience." Dismissing these observations and experiences "as no more than repressive moralism" is "mistaken and ungenerous" ([25], pp. 163–164). Effective treatment requires acceptance by uncontrolled drinkers and those around them that the alcoholism involves organic mechanisms. Such an admission in no way diminishes the reality that alcohol dependence includes both cultural causes and social consequences. Any understanding of the history of alcoholism requires such an integrative approach. The same claims may be made for all addictions—they are syndromes of dependence, informed and "enabled" by an interaction of culture and biology.

As with alcohol, nicotine acts differently on different hosts. It may be extremely addictive, but 50 percent of smokers have managed to cease smoking since the late 1960s. All smokers probably fit into some definition of addiction, but if we were to apply Edwards' notion of syndrome of dependence, we might develop better insights into who smokes, why some persist despite overwhelming evidence of negative health consequences, and why others are able to stop smoking.

As Tracy and Acker write, earlier scientific explanations for the mechanisms of addiction seem retrospectively quaint ([78], pp. 15–18), but there have been persistent observations of addictive predispositions, or what psychoanalysts used to label "addictive personalities." If previous theories of the mechanisms of addiction appear retrospectively tenuous, the existence of addictive personality types seems less so.

This returns us to Edwards' view that what we call addictions are actually syndromes of dependence that have multiple triggers and pathways, ranging from the cultural to organic, but are probably informed by a combination that we might label as "cultural biology." This cultural biology of substance dependence is based on centuries of observations. The science of each era has attempted to identify the mechanisms that underlay the observed behaviors. The fact that, in retrospect, these attempts reflect the dominant scientific paradigm of each era is not surprising; nor does it undercut the evidence that there are organic triggers for and biological effects from substance dependence. That these interact with cultural and social forces would not surprise any serious neuroscientist. Like Edwards, they would concede that current neurobiological hypotheses are by definition tentative, precisely because for a scientific claim to be robust, it must be testable (falsifiable) and replicable.

This interdisciplinary perspective allows us to consider the multiple meanings of the Tracy and Acker title, *Altering American Consciousness*. As Courtwright has shown in *Forces of Habit*, humans have attempted to alter their consciousness since time immemorial [17]. Evolutionary biologist Tammy Saah finds that "drug use and addiction seem to have been a part of mammalian society since ancient times." For Saah, "looking at drug addiction from an evolutionary perspective" is the best way to "understand its underlying significance and evaluate its threefold nature: biology, psychology, and social influences" [68]. Any persuasive interpretation of the history of addiction, insists Courtwright,

must consider the impact of the biological action of drugs on human hosts. However, if it ignores history and culture, the impact of that biology will be missed [17].

Western economies and culture, writes Courtwright, are built on the production, sale, and use of mind-altering drugs, including alcohol, tobacco, coffee, cocoa, tea, sugar, carbohydrates, and an array of prescription medications. This could not have happened without biological as well as cultural mechanisms. In *Dark Paradise*, Courtwright shows how addiction is exacerbated and enabled by the availability of and exposure to mind-altering substances [16]. Considering the neurobiological mechanisms of addiction, says Courtwright, can offer powerful clues for comprehending this drive to alter consciousness.

As Edwards reminds us, for much of human history, including our own era, most mind-altering substances have been initially consumed as a means of self-medication for a variety of ills, not least of all for disorders of consciousness, including major and minor psychiatric disorders [25]. That self-medication plays an important role in persistent substance use and abuse, despite awareness of potential harm, provides fertile ground for further historical research [2, 26, 54]. Self-medication, like the conditions it aims to treat, is rooted in culture and biology and cannot be understood apart from that interaction. Like all culturally mediated biological phenomena, each society responds to these human behaviors within the context and confines of larger social, political, and cultural constraints. From this perspective, addiction is one possible outcome of humans' drive to alter consciousness; what we label "addiction" might be understood as a *possible* consequence of the human desire to alter consciousness.

Taking history seriously would force addiction scientists to confront the reasons for failure of the abstinence policy. First and foremost, abstinence is a failed policy because it denies the historical evidence that humans in all societies and cultures have relied and continue to rely on substances to alter their consciousness. Addictive behaviors, rather than diminishing, have increased, spurred on in part by industries that manufacture and market consciousness-altering commodities. In the face of persistent human drives to alter consciousness and markets that cater to them, abstinence appears unattainable. Moreover, the pursuit of abstinence has led to a number of counterproductive policies. Among them is the assumption, writes Campbell, that restricting knowledge about the safe use of illicit drugs or about ways to reduce the harms associated with their use "is good because condoning drug use is bad." Yet, by denying illegal drug users information that could reduce risks, we ensure even worse outcomes. The histories of addiction indicate that abstinence is also a failed policy because, as both historians and brain researchers recognize, addiction is a chronic relapsing/remitting syndrome. From that perspective as well, any successful policy or intervention must include harm reduction. Historians of addiction, Campbell insists, "have a crucial role to play in shifting drug policy toward public health and harm reduction" ([12], p. 237). The history discussed in these pages supports that claim.

Acknowledgments The research and writing of this article were partially supported by a grant from National Institutes of Health, National Institute on Drug Abuse, entitled "Current Smokers: A Phenomenological Inquiry" (R01 DA015707–01A2) and a grant from the Engelhard Foundation, "Sophomore Year at Emory Living and Learning Experience: An Interdisciplinary Seminar Course/Internship in Addiction and Depression." Some of the material in this chapter appeared previously in Howard I. Kushner, "Taking Biology Seriously: The Next Task for Historians of Addiction?" *Bulletin of the History of Medicine* 80 (Spring 2006): 115–143. I thank Carol R. Kushner and Robert Cormier for editorial assistance.

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Diagnosis and Classification of Substance Use Disorders

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Contents

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Introduction

Diagnosis and classification are ways in which we make sense of our clinical and epidemiological observations and help communicate our findings to others. Thus, they provide an important basis for the prevention of human disorders and for the management of people who develop them. This applies as much to substance use and other addictive disorders as to other afflictions. Indeed, careful diagnosis and categorization are particularly important in the addictions given the great variety of psychoactive substances (of different pharmacological and chemical classes), the wide spectrum of use and misuse of these substances, and the innumerable complications that arise from such use. (The term "misuse" is employed in this chapter as a shorthand term to encompass a variety of types of excessive substance use; it is not used as a diagnostic term.) Precision in diagnosis is clearly vital for clinical purposes, and epidemiological researchers and health statisticians need valid and cross-culturally applicable diagnoses.

This chapter explores three distinct but overlapping areas. In the first section, there is a review of the nature of psychoactive substance use, misuse, and dependence. The alternative, indeed competing, conceptualizations are discussed, and there follows an account of how the present diagnostic and classification systems have been developed. The next section describes the main substance use diagnoses, focusing on the dependence syndrome, but also including

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_5,

non-dependent repetitive substance use and the main substance-induced mental and physical disorders. In the final part of this chapter, we examine the approach to diagnosis in research but particularly in clinical practice. This includes an account of clinical techniques, questionnaires, interview schedules, and laboratory tests.

The Nature of Substance Use Disorders

Given the many professional disciplines that have contributed to an understanding of psychoactive substances and their effects, it is not surprising that scientists and practitioners have drawn upon different traditions to explain their essential nature. There also have been many lay interpretations. In the nineteenth century, a popular conceptualization of excessive alcohol and drug use was that it represented a failure of morals or character [30]. This notion, although superseded in the professional literature of the later twentieth century, continues to influence community and political views as to the nature of substance use disorders and that of people with them.

Personality Disorder

In the first edition of the *Diagnostic and Statistical Manual of Mental Disorders*, published in 1952, substance misuse was included in the personality disorders [1]. Drug addiction was not specifically defined, but there was a statement that "Addiction is usually symptomatic of a personality disorder. The proper personality classification is to be made as an additional diagnosis." The second edition, published in 1968 [2], still had substance use disorders classified within the personality disorders. No specific definitions or criteria were provided, and there was little description of the conditions, although the text included a statement that "the best direct evidence for alcoholism is the appearance of withdrawal symptoms" and that the diagnosis of drug dependence required "evidence of habitual use or a clear sense of a need for the drug" [2].

The Disease Concept

A different tradition saw substance misuse as reflecting a disease process, which was biologically determined, resulted in the individual having some type of idiosyncratic reaction to alcohol or a drug, and had a relatively predictable natural history. This conceptualization influenced and was subsequently embraced by the self-help movements, such as Alcoholic Anonymous. Jellinek developed the concept of the disease of alcoholism in the 1940s and 1950s [25], although in his later work he increasingly recognized the role of environmental influences. During the 1960s and 1970s, the concept that substance misuse might represent a disease process was dismissed by most scientists and professionals. Likewise, the role of genetic predisposition was thought to be inconsequential, with the familial aggregation of substance misuse explained by cultural influences, role-modeling, or malfunction within families.

Epidemiological and Sociological Formulations

A third tradition may be described as the epidemiological and sociological one. Put simply, substance misuse and problems arise fundamentally because of the overall level of use of that particular substance in society. In the 1950s, Ledermann [32] proposed a relationship between the level of alcohol consumption in a community and the prevalence of alcoholism. The level of use is, in turn, influenced by the availability of alcohol, its manufacture and distribution, its price (importantly), and cultural traditions and sanctions. Inherent in these conceptualizations is that individual pathology is considered of secondary importance. The social constructionist school views substance use problems as disaggregated, with no special relationship

among them. This school of thought was concerned about the stigma attributable to diagnostic labels and the potential of treatment as a form of social control [46].

Learned Behavior

The 1970s saw the rise of social-cognitive theory [7] as an influential paradigm to explain the development and resolution of alcohol and drug problems. This school of thought teaches that the (many) influences that determined behavior in general apply to the uptake of substance use and the development of disordered use. Positive consequences encourage repeated use, negative ones the opposite. Patterns of substance use behavior could become established in this way, but, equally, repetitive substance use could be "unlearned". This led to the development of a range of cognitive behavioral therapies, some of which were aimed at moderated or "controlled" substance use [57].

Clinical Syndrome

The need for an understanding of substance misuse that spanned these various discipline-bound conceptualizations and terms was largely met by the formulation of the concept of a "substance dependence syndrome" originally proposed with regard to alcohol dependence by Edwards and Gross in 1976 [18]. The basis of the dependence syndrome was a clinical description of key clinical features in a way that was essentially atheoretical and was not based on any particular etiological understanding of the disorder, be it biological, behavioral, or sociological. Rather, certain experiences, behaviors, and symptoms related to repetitive alcohol use were identified as tending to cluster in time and to occur repeatedly. The advantage of a descriptive account of dependence is that it can accommodate etiological models but not be beholden to them.

The concept of the dependence syndrome has been very influential. It has been shown to apply to many other psychoactive substances that have the potential for reinforcement of use, including benzodiazepines, illicit and prescribed opioids, cannabis, inhalants, psychostimulants such as cocaine and the amphetamines, nicotine, caffeine, and anabolic steroids [21, 34, 40, 58]. It also may apply to repetitive behaviors that do not involve self-administration of a psychoactive substance. These include pathological gambling and compulsive shopping and exercise [33, 41].

The dependence syndrome is at the heart of the present classification systems of psychoactive substance use disorders [30, 53]. It takes center stage in the latest version of the International Classification of Diseases, published in 1992 [62], and in the most recent revisions of the *Diagnostic and Statistical Manual of Mental Disorders*, namely the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised and the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, which was published in 1994 [3] and underwent text revisions in 2000 [4].

Neurobiological Disorder

Arguably the most important development in our understanding of the nature of substance misuse in recent years has been in neurobiological processes, complemented by findings from genetic research. There is now compelling evidence that repeated use of psychoactive substances leads to powerful and enduring changes in cortico-mesolimbic reward, stress, and control systems [28]. In turn, these result in reinforcement and perpetuation of such use.

There are three key neurobiological changes that underpin dependence.

(1) Activation and then inhibition of brain reward systems, particularly involving dopaminergic transmission and opioidergic transmission. These have the effect of resetting the reward systems such that larger amounts of the substance are needed to produce the desired effect and natural rewards are not as reinforced because of the

relatively low response from these systems [60].
(2) Recruitment of brain stress systems, including those subserved by glutamate neurotransmission and corticotrophin-releasing factor [27] and suppression or uncoupling of anti-stress systems [47].
(3) Impairment of inhibitory control pathways from the prefrontal cortex to the mesolimbic systems, resulting in impaired decision-making capacity [65].

Dopamine release leads to neuronal plasticity [29], which underpins associative learning and memories that result in repetitive substance use even though the original personal triggers and environmental influences have changed [53]. Thus, dependence may be construed as an "internal driving force" [53] that results from repeated exposure to a psychoactive substance and that in turn leads to further repetitive substance use, which is now self-perpetuating and typically occurs even in the face of harmful consequences. A recent publication on the neuroscience of addiction by the World Health Organization summarizes the key developments in biomedical research over this period [63].

Investigations into possible genetic influences have accompanied this research on neural circuitry. Biometric genetic studies have shown that children born of parents with substance dependence are more likely to have substance dependence themselves [52] and that this is largely explained by genetic transmission rather than environmental factors [6, 52]. Genomic analysis in human and laboratory animals has identified several areas of the genome where mutations are associated with increased risk of substance use disorders [6].

Achieving a Synthesis

It is clear that psychoactive substance use exists as a continuum in society but equally clear that within this spectrum it is possible—and important—to define syndromes that have a distinct set of physiological and behavioral features. Substance dependence is a syndrome that occurs in response to repeated and typically high-level alcohol or other drug use, is driven by a profound resetting of key neurobiological systems, is compounded by impaired executive control, and leads to continuing and damaging substance use.

Other forms of repetitive substance use seem not to have these neurobiological changes—at least not to the extent of dependence. They appear to be influenced primarily by factors that affect many types of repetitive human behavior [7]. These include expectations of a substance's effect, responding to learned associations with substance use, the many and varied environmental influences, including peer group pressure, ethnic and workplace culture, and the influences of availability and accessibility of alcohol and various drugs.

Separate from the dependence syndrome and non-dependent forms of substance misuse are the multiple consequences of substance misuse. These may be physical, neurocognitive, mental, and social. They typically reflect the adverse effects of the substance, the mode and means of administration of the substance, and/or the implications of the dependence processes. They include disorders of the heart, lungs, gastrointestinal tract, liver, muscles, brain, and peripheral nerves. Mental health complications include mood and anxiety disorders and various psychoses. Social complications encompass interpersonal, financial, occupational, and legal difficulties.

Substance Use Diagnoses in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision

Although many different systems of diagnosis and classification have been proposed for substance use disorders over the years, two

have international recognition. They are the *Diagnostic and Statistical Manual of Mental Disorders*, currently in its fourth edition [3, 4], which covers mental and behavioral disorders, and the International Classification of Diseases, which is now in its tenth revision [62] and published by the World Health Organization. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision is a classification of all diseases, injuries, and causes of death.

Substance Dependence

The dependence syndrome is defined in both the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision as a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated drinking or substance use, and which tends to be self-perpetuating. Typically it occurs in people who use large amounts of psychoactive substances repeatedly—for example, consuming alcohol in excess of 120 g/day (men) or 80 g/day (women). However, the diagnosis of substance dependence is made primarily not on the level of consumption but on criteria based largely on the original Edwards and Gross formulation [18]. The criteria in the two systems (in summary format with comments) are listed in Table 1.

As can be seen, substance dependence in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition is defined very similarly to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision. As with all diagnostic systems, to be of optimal use in the clinic or for the needs of epidemiology and public health planning, the criteria must be both valid and straightforward, and this was foremost in the minds of those who fashioned them. The dependence syndrome applies to most psychoactive substances that have the potential for reinforcement of use (such as benzodiazepines, opioids, cannabis, psychostimulants, nicotine, caffeine, and anabolic steroids, as described earlier). However, elements of the syndrome are not necessarily applicable to all substances. For example, cannabis withdrawal is not recognized in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, although this may change in the next revision. Dependence also may apply to repetitive behaviors that do not involve self-administration of psychoactive substances, such as gambling, compulsive shopping, and compulsive exercise [33, 41], not just to impulse control disorders.

Substance Withdrawal Syndrome

The substance withdrawal syndrome refers to a state seen in individuals with the dependence syndrome when use is curtailed. It is an important manifestation of the neurobiological changes that underpin dependence. In general, the features of the withdrawal syndrome are opposite to those of the acute pharmacological effects of the substance. In contrast to dependence, the substance withdrawal syndrome varies appreciably according to the substance used. Psychostimulant withdrawal is very different from withdrawal from, say, sedative-hypnotics.

The withdrawal syndrome is defined as a group of symptoms of variable clustering and severity that occur on the absolute or relative withdrawal of a substance after repeated—and usually prolonged and/or high-dose—use of that substance. The specific criteria in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision and the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition are listed in Table 2. The onset and course of the withdrawal state are time limited and are related to the type of substance and the dose being used immediately before abstinence. Three types of withdrawal are recognized in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision and the *Diagnostic and Statistical Manual of Mental Disorders*,

Table 1 Diagnostic guidelines for dependence and sample questions [3, 4, 62]

International statistical classification of diseases and related health problems, 10th revision	Diagnostic and statistical manual of mental disorders, 4th edition	Sample questions
A strong desire or sense of compulsion to take the psychoactive substance (*craving or compulsion*).	No equivalent criterion—mentioned in text.	Have you felt a strong desire or urge to use that you could not resist?
No equivalent criterion, but text states that the subjective awareness of compulsion is most commonly seen during attempts to stop or control substance use.	There is persistent desire or unsuccessful attempts to cut down or control substance use.	Have you wanted to stop or cut down on your use but could not? Have you more than once tried unsuccessfully to stop or cut down on your use?
Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use (*loss of control*).	The substance is often taken in larger amounts or over a longer period of time than was intended.	Have you started using and found it difficult to stop (before you became intoxicated)? Have you used much more than you expected to when you began, or for a longer period of time than you intended to?
Progressive neglect of alternative pleasures because of psychoactive substance use, or increased amount of time necessary to obtain or take the substance or to recover from its effects.	Important social, occupational, or recreational activities are given up or reduced because of drinking or psychoactive substance use.	Have you given up or greatly reduced important activities in order to use, such as sports, work, or associating with friends and relatives?
Subsumed in above criterion.	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.	Is a great/er deal of time spent using a substance or getting over the effects of the substance?
Tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses.	Tolerance, as defined by either (1) a need for markedly increased amounts of the substance to achieve the desired effects or (2) markedly diminished effect with continued use of the same amount of the substance.	Have you found that you need to use much more than before to get the same effect, or that using the usual amount has less effect than before?
A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms.	Withdrawal as manifested by either (1) the characteristic withdrawal syndrome for the substance or (2) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.	Did stopping or cutting down use ever cause you problems such as (list expected withdrawal symptoms)? Have you ever used to keep from having problems or make any of these problems go away?
Persisting with substance use despite clear evidence of overtly harmful consequences.	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.	Has substance use ever caused you any physical or psychological problems? (If yes, list the problem/s.) Did you continue to use after you realized that it caused you problems? (State the problem/s.)

Table 2 Diagnostic guidelines for substance withdrawal syndrome [3, 4, 62]

International statistical classification of diseases and related health problems, 10th revision	Diagnostic and statistical manual of mental disorders, 4th edition
Clear evidence of recent cessation or reduction of substance use after repeated and usually prolonged and/or high-dose use of that substance; one of the main indicators of the dependence syndrome.	(A) The development of a substance-specific syndrome due to cessation of, or reduction in, substance use that has been heavy and prolonged.
Symptoms and signs compatible with the known features of a withdrawal state from the particular substance or substances. Physical symptoms vary according to the substance being used. Psychological disturbances (e.g., anxiety, depression, sleep disorders) also are common features of withdrawal. Typically, the client reports that withdrawal symptoms are relieved by further substance use.	(B) The substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
The features are not accounted for by a medical disorder unrelated to the substance use, and not better accounted for by another mental or behavioral disorder.	(C) The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.
Differential diagnosis: Many symptoms present in drug withdrawal state may also be caused by other psychiatric conditions—e.g., anxiety, depressive disorders.	

4th Edition criteria: simple uncomplicated withdrawal, withdrawal with convulsions, and withdrawal with delirium [3, 4, 62].

Non-Dependent Repetitive Substance Use

Repetitive substance use that does not fulfill the criteria for the dependence syndrome is still of clinical significance. It is handled differently in the two systems. In the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, the term "harmful use" applies to repetitive use of a psychoactive substance that has caused physical or mental harm to the person. In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, the term "substance abuse" refers to repetitive use of a psychoactive substance that essentially is causing social harm or problems. There is no equivalent term in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision; indeed, the International Statistical Classification of Diseases and Related Health Problems, 10th Revision eschews the notion of a disorder that is defined by social criteria. Other non-dependence conditions have been proposed and tentatively defined; they are covered later.

Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Substance Abuse

Substance abuse is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition as repeated substance use that leads to one or more social or occupational problems (Table 3). It is understood as a less severe condition than dependence. The two diagnoses cannot coexist in the same time period, as substance abuse is pre-empted by a diagnosis of dependence. Substance abuse can be envisaged as one axis of a biaxial conceptualization of substance use disorders, which separates the core syndrome of dependence from the consequences. However, there is blurring of this conceptualization because of its hierarchical relationship with dependence, i.e., as a less severe disorder. The extent to which the biaxial relationship applies—and indeed whether abuse is properly separated from dependence—remains controversial, with some studies finding that a one-factor solution that covers the spectrum of abuse and dependence criteria is optimal [19, 39, 58].

Table 3 Diagnostic guidelines for substance abuse in the *Diagnostic and Statistical Manual of Mental Disorders, 4th editio n* [4]

(A) Pattern of recurrent substance use leading to significant impairment or distress, as evidenced by one (or more) of the following criteria within a 12-month period:
1. Recurrent substance use that results in failure to fulfill major obligations at work, school, or home
2. Recurrent substance use in situations in which it is typically hazardous (e.g., drunk driving)
3. Recurrent substance-related legal problems (e.g., driving an automobile or operating a machine when impaired by substance use)
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

(B) The symptoms have never met the criteria for substance dependence for this class of substance.

International Statistical Classification of Diseases and Related Health Problems, 10th Revision Harmful Use

Harmful substance use is a repetitive pattern of substance use, at levels that result in actual physical or mental harm, but it does not fulfill the criteria for the dependence syndrome [62]. The harmful effects may be acute or chronic. Examples of acute complications include fractures and other forms of trauma, acute gastritis, and acute psychotic symptoms following substance use. Chronic medical complications encompass liver disease (e.g., alcoholic liver disease or hepatitis C-induced liver disease following injecting drug use), cardiovascular diseases, respiratory diseases, various neurological sequelae, and many others. Examples of mental complications are depressive episodes secondary to heavy alcohol intake, and substance-induced psychosis. In clear distinction from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, social complications *per se* are insufficient to justify a diagnosis of harmful use under the World Health Organization nomenclature [53, 62].

Other Diagnostic Entities

The three disorders—substance dependence, substance abuse, and harmful use—do not encompass the whole spectrum of repetitive, damaging (or potentially so) substance use and, therefore, pose limitations, especially for epidemiological purposes. In the work of a World Health Organization Expert Committee in the 1970s, several other conditions characterized by repetitive substance use were proposed to complement the dependence syndrome [19]. However, only one, "harmful use", survived to appear in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Perhaps because of the breadth of the task, there have been few attempts to develop a classification system that encompasses the broad spectrum of substance use and misuse. The terms proposed by the World Health Organization committee were "unsanctioned use", "dysfunction use", and "hazardous use".

Unsanctioned Use

This was defined as the use of a substance that is not approved by a society or by a group within that society. This term implies that this disapproval is accepted as a fact in its own right, without the need to determine or justify the basis of the disapproval.

Dysfunctional Use

This is substance use that leads to impaired psychological or social functioning—for example, loss of employment or marital problems.

Hazardous Use

This is repetitive substance use that places the person at risk of harmful consequences. In the World Health Organization formulation, this was defined as physical and mental harm, but in other definitions, harm has been taken to incorporate social and legal consequences too. Hazardous substance use is sometimes referred to as "at-risk", "risky", "medium-risk", or "high-risk" substance use.

The Need for the Term "Hazardous Use"

Hazardous ("risky") use has been operationalized for alcohol consumption in several countries. For example, in the United States, men who drink five or more standard drinks (65 g of alcohol) in a day or more than 15 standard drinks (195 g) per week, and women who drink four or more standard drinks (50 g) in a day or eight standard drinks (105 g) per week, are considered to be drinking excessively [38, 49]. Repeatedly consuming 5+ (men) or 4+ (women) United States standard drinks (65 g and 50 g of alcohol, respectively) confers a risk of alcohol use disorders, acute and chronic illnesses, and injuries [16, 48]. In Australia, hazardous or risky consumption is defined presently as repeated daily consumption of more than four Australian standard drinks (40 g of alcohol) for a man and more than two standard drinks (20 g) for a woman [10]. In other countries, it is variably defined as regular drinking of more than 29 drinks (290 g of alcohol) per week for men or more than 15 standard drinks (150 g of alcohol) per week for women, with two alcohol-free days per week recommended for both men and women. In some Asian countries, hazardous or risky drinking indicates consumption at levels that lead to intoxication twice a month or more.

The application of hazardous or "risky" use to other substances has been slower. For nicotine (tobacco), it can be argued that there is no non-hazardous level of use. Likewise, because of uncertainties as to whether there is truly a safe or low-risk level of use for other substances, the concept has not been applied widely to illicit drugs such as cannabis, the amphetamines, cocaine, or heroin, although research on quantifying and establishing the risk of low-level cannabis use is emerging.

Hazardous substance use appeared in early drafts of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision but was omitted from the published version following the results of field trials that revealed an inter-rater reliability (kappa) coefficient of only 0.4 [51]. Because of the difficulty in operationalizing it, the diagnosis was considered to be open to misuse. The decision to omit hazardous substance use from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision also was influenced by doubts as to whether it represented a disease process, which in many people's minds was a prerequisite for inclusion in a classification system of diseases. In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, one of the four criteria of substance abuse [3, 4] is recurrent substance use in situations in which it is typically hazardous. This is known by many as the "hazardous use" criterion. It is most commonly fulfilled when a person has been convicted of a drunk-driving offense. However, it differs from other definitions in that there is not a clear statement of what is being risked—namely, physical and mental consequences.

For epidemiological and public health purposes, having a term that defines various levels or patterns of substance use as conferring risk is advantageous. Indeed, recent data from the National Epidemiologic Survey of Alcohol and Related Conditions indicate that hazardous alcohol consumption (defined as the United States 5+/4+ standard drink criterion) exists within the continuum of abuse and dependence criteria [50]. As the frequency of this level of consumption increases, this experience moves along the severity continuum to overlap with abuse and dependence criteria [50].

At the same time, to examine relationships between use patterns and consequences without considering whether a diagnosable substance use disorder is present, as is usual in epidemiological studies, is limiting. The reduction in all-causes mortality among people with moderate levels of alcohol consumption is not seen in those who have had a previous diagnosis of alcohol dependence [15]. In support of including hazardous use in a diagnostic system is the evidence that it can be defined and it responds to therapy, the evidence base for the effectiveness of interventions for hazardous alcohol consumption being particularly strong [8, 26]. Thus, in a comprehensive diagnostic system, there are grounds for having a dependence category, a non-dependence disorder that is of clinical consequence, and a "sub-threshold" disorder that indicates risk to individuals and populations.

Diagnostic Orphans

Diagnostic orphans are substance users who report some symptoms of dependence but do not meet the diagnostic criteria for either *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition dependence or substance abuse. In young people, it is a common category, as common (with respect to alcohol) as dependence or abuse [20]. Alcohol diagnostic orphans have a natural history that is closest to that of alcohol abuse, though they have fewer alcohol-related problems over time. Cannabis diagnostic orphans also are similar in use patterns to those with cannabis abuse, but they do not have higher rates of mental complications than non-cannabis users [17].

Substance-Related Problems

Substance-related problems (or disabilities) were conceptualized by the World Health Organization Committee as the *consequences* of repetitive substance use [19, 53]. They include both acute (short-term) effects and chronic (long-term) ones [31]. Harmful alcohol consumption (or alcohol dependence) can affect virtually every organ system in the body, while cannabis and tobacco commonly induce respiratory complications [5]. Repetitive psychostimulant use can lead to a range of psychiatric syndromes, including mood disorder and psychotic disorder. Complications arising from repetitive substance use stem not only from the pharmacological properties of a particular substance but from unknown potency, purity, and sterility due to contaminants and adulterants with which the substance is prepared, unsafe injecting practices, and the associated lifestyle of the user. The spread of bacterial infections and viral infections, such as hepatitis C and HIV, and to a lesser extent hepatitis B, is important in this regard [5]. The disinhibiting effect of alcohol and substance use also places users at risk of sexually transmitted diseases.

Substance-Induced Mental Disorders

In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, there are several substance-related psychiatric syndromes. Here we shall discuss just three of them: delirium, psychotic disorder, and amnesic syndrome.

Delirium

Delirium (Table 4) is an uncommon feature of substance misuse, although sometimes the diagnosis is made in persons with acute intoxication. Substance intoxication with delirium is an accepted diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition [3, 4] but not in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [62]. Most commonly it is seen in those with a severe withdrawal syndrome from alcohol or

Table 4 Diagnostic criteria for delirium tremens [62]

Withdrawal state with delirium—delirium tremens
Prodromal symptoms:
• Insomnia
• Tremulousness
• Fear
Clinical features
• Clouding of consciousness and confusion
• Vivid hallucinations and illusions affecting any sensory modality
• Marked tremor
• Delusions
• Agitation
• Insomnia or sleep reversal cycle
• Autonomic overactivity

sedative-hypnotic drugs. The classical disorder is delirium tremens [56], which is a short-lived but occasionally life-threatening toxic-confusional state with accompanying somatic disturbances (Table 4). It usually is a consequence of absolute or relative cessation of alcohol in severely dependent drinkers with a long history of use. Its onset may be preceded by features of simple withdrawal and/or by withdrawal convulsions. A similar withdrawal delirium is seen after cessation of benzodiazepines and other sedative-hypnotics although with less tremor.

Psychotic Disorder

Psychosis and/or psychotic symptoms occur in many people with substance use disorders. In some, this reflects an underlying independent disorder such as schizophrenia. In others, the psychosis is a consequence of drug use. Sometimes the precise mechanism remains unclear. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision defines substance-induced psychotic disorder as a phenomenon that occurs during or immediately after psychoactive substance use (usually within 48 h) and is characterized by vivid hallucinations (typically auditory but often in more than one sensory modality), misidentifications, delusions, and/or ideas of reference (often of a paranoid or persecutory nature), psychomotor disturbances (excitement or stupor), and an abnormal affect, which may range from intense fear to ecstasy [62]. The sensorium is usually clear, but some degree of clouding of consciousness, though not severe confusion, may be present. The disorder typically resolves at least partially within 1 month and fully within 6 months. The diagnosis is excluded if the psychotic state is a manifestation of substance withdrawal syndrome. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, a substance-induced psychotic disorder is defined by: (i) prominent hallucinations or delusions developing during, or within a month of, substance intoxication or withdrawal, (ii) the phenomenon is etiologically related to the disturbance, and (iii) the disturbance is not accounted for by a psychotic disorder that is not substance induced [4].

For psychostimulants such as amphetamines and cocaine, there is a dose-response relationship, with psychosis occurring especially in those who have been using high doses and/or using the drug over a lengthy period. According to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, a diagnosis of psychotic disorder should not be made merely on the basis of perceptual distortions or hallucinatory experiences when substances having primary hallucinogenic effects (e.g., lysergic acid, mescaline, and cannabis in high doses) have been taken. In such cases, and also for confusional states, a possible diagnosis of acute intoxication should be considered. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition has no such exclusion.

Amnesic Syndrome

Amnesic (or amnestic) syndrome (Table 5) is an example of a substance-related disorder where, typically, neuronal loss has occurred. The most common form is characterized by impairment of recent memory, with relative preservation of remote memory and with normal immediate recall [3, 4, 62]. Disturbances of time sense and ordering of events are usually evident, as are

Table 5 Diagnostic criteria for the amnesic syndrome/amnestic disorder

International statistical classification of diseases and related health problems, 10th revision amnesic syndrome [62]	Diagnostic and statistical manual of mental disorders, 4th edition criteria for amnestic disorder [4]
1. Memory impairment as shown in impairment of recent memory and learning of new material; disturbance of time sense (e.g., rearrangement of chronological sequence, telescoping of repeated events into one, etc.) 2. Absence of defect in immediate recall, impairment of consciousness, and of generalized cognitive impairment 3. History of objective evidence of chronic (and particularly high-dose) use of alcohol or drugs Includes Korsakoff's psychosis or syndrome, induced by alcohol or other psychoactive substance	(A) The development of memory impairment as manifested by impairment in ability to learn new information or the inability to recall previously learned information (B) The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning. (C) The memory disturbance does not occur exclusively during the course of a delirium or dementia and persists beyond the usual duration of substance intoxication or withdrawal. (D) There is evidence from history, physical examination, or laboratory finding that the memory disturbance is etiologically related to the persisting effects of substance use.

difficulties in learning new material. Confabulation may be marked but is not invariably present and should not be regarded as a prerequisite for diagnosis. Importantly, other cognitive functions are usually relatively well preserved; the amnesic defects are, therefore, out of proportion to other disturbances. Personality changes, often with apparent apathy and loss of initiative, and tendency toward self-neglect may be present but are not regarded as necessary for diagnosis.

Practical Approaches to Diagnosis

The Distinction Between Research and Practice

The way diagnoses are made varies considerably. For the research scientist, there are several well-validated diagnostic interview schedules, which allow diagnoses to be made from a systematic structured interview of the respondent. They include the Diagnostic Interview Schedule [43, 44], the Composite International Diagnostic Interview [45], the Schedules for Clinical Assessment in Neuropsychiatry [61], and the Alcohol Use Disorder and Associated Disabilities Interview Schedule [9, 22, 23]. The constituent questions represent the individual diagnostic criteria of the particular condition. Algorithms are employed to establish whether the combination of responses fulfills these criteria and then to determine the number and combination of criteria that are required to fulfill the diagnosis. These questionnaires have sound psychometric properties; they have been subjected to rigorous testing of their reliability and validity [14, 42], and there is much information available on their cross-cultural applicability [59]. In addition to their use in research studies, the structured interview schedules have an important role in the training of psychiatrists, psychologists, and other health practitioners.

Making a diagnosis in clinical practice is usually much less systematic than this. It requires that the practitioner has a clinical qualification, typically in medicine or psychology, and has had a lengthy period of specific supervised experience. In most cases, the clinician will take a narrative history and there will be an assessment of the person's mental state and, in the case of medical practitioners, his/her physical state. The information amassed is set against the known features and diagnostic criteria of the various disorders, and a decision is made as to whether the individual has a particular condition or not. Following completion of training, clinicians tend not to employ diagnostic schedules. However, some clinical services

require completion of such a schedule or an alternative, such as the Addiction Severity Index [36, 37], to ensure consistency in the assessment of clients. Shorter screening and brief assessment questionnaires, such as the Alcohol Use Disorders Identification Test [55] and the Alcohol, Smoking and Substance Involvement Screening Test [64], also are employed in many services to facilitate assessment.

Much of the information obtained in clinical work is designed to identify experiences and problems that the person has had and that lead not only to a diagnosis but to a comprehensive understanding of the person's background, symptoms, problems, and difficulties [43]. Thus, the information obtained in a clinical assessment is broad-ranging and has multiple purposes, of which only one, albeit a crucial one, is to make the diagnosis. In this final part of the chapter, we shall summarize the information that is relevant to collect in clinical practice and the extent to which this points to a diagnosis or is important ancillary information.

Approaches to the History

The great majority of diagnostic information relevant to substance use disorders is obtained from a careful history. The accuracy of the information is highly dependent on the setting and context of the interview and the interactional style of the clinician. With an empathic approach and in a clinical (as opposed to a custodial) setting, a high level of accuracy can be obtained. Inter-rater and test-retest assessment indicates reliability coefficients of 0.8–0.9 for average daily alcohol consumption and the experience of dependence symptoms and problems [13, 54]. Validity, as assessed by comparison with information provided and by a collateral source or from official statistical data, also is high, with intraclass coefficients of approximately 0.65–0.85 [35, 54].

Among the approaches that enhance the quality and accuracy of the history are to:

(1) show empathy and understanding;
(2) establish a good therapeutic rapport with the client;
(3) be non-judgmental, and
(4) be sensitive to the client's cultural background.

Experienced practitioners sometimes employ what are termed "enhancement techniques", such as:

(1) placing the onus of denial of substance use on the client;
(2) suggesting high levels of intake, the "top high technique" [54], and
(3) being aware of diversionary tactics and not being diverted from the line of questioning.

These techniques should be employed only by experienced clinicians as their use may rebound on the practitioner and lead to termination of the interview.

In addition, collaborative information should be sought from family members, the family physician, and the client's medical records, with due care paid to ethical and privacy issues.

Quantification

Quantification of the amount of a substance used is a key aspect of the history. This is relatively easy with legal substances such as alcohol, tobacco, and prescribed medication but still is feasible with illicit drugs (Table 6).

Amongst the information that should be obtained is the following:

- quantity
- frequency
- cost
- duration
- pattern or variability
- mode of administration
- time of last use
- periods of abstinence.

The reliability and validity of such information obtained on illicit drug use is generally good, provided that there are no negative implications of supplying the information [24, 35].

Table 6 Quantification of substance use

Alcohol	Grams Standard drinks Standard units
Tobacco	Number of cigarettes Ounces of tobacco
Sedative-hypnotics	Dose (per tablet) Number of tablets per day
Cannabis	Number of joints Number of cones Number of bongs
Heroin	Weights "Street" grams Cost (e.g., dollars)
Amphetamines/ methamphetamine	Points (0.1 g) Grams Cost (e.g., dollars)
3,4-Methylenedioxy-methamphetamine	Number of tablets
Cocaine	Grams Cost (e.g., dollars)

Experiences Indicating Dependence

Establishing whether an individual has a dependence syndrome is the next step. Although this is typically suggested by the quantity and frequency of substance use, these measures are not diagnostic criteria in and of themselves. The experienced practitioner will, however, assess whether the history of substance use points to dependence from information provided about the circumstances and intensity of use, whether this has continued despite harm, and the extent to which the person's life is shaped around the substance. Questions reflecting the individual diagnostic criteria for dependence then are asked. Sample questions and the criteria from which they derive are presented in Table 1.

Problems or Consequences

The adverse consequences of a substance use disorder are legion. At this stage in the interview, the practitioner will have identified several that are uppermost in the client's (or relative's) mind. Enquiry should continue on problems typically associated with the substance in question. These can be grouped conveniently with the following domains:

- relationships
- interpersonal difficulties
- financial
- work related/unemployment/prostitution
- legal/forensic—drunk driving, assault, criminal charges.

Key Factors on Physical Examination

Physical examination is an integral part of a comprehensive medical assessment, but it often is omitted, in which case important diagnostic information can be missed. Signs on physical examination can on occasion point almost instantaneously to diagnoses, and a wealth of corroborative information is potentially available. In general, physical examination abnormalities are more apparent in individuals with alcohol use disorders, particularly in those with alcohol dependence. Specific physical abnormalities also are evident in many individuals who are injecting drugs; these may reflect local complications at the site of injection or systemic infections. Significant respiratory abnormalities also may be apparent in people who are tobacco or cannabis smokers.

Physical examination is undertaken routinely by internal medicine physicians and most addiction physicians. A focused examination is undertaken typically by family physicians and some psychiatrists. Physical examination is considered by many psychiatrists to interfere with the development of a therapeutic relationship, and there are readily apparent requirements for chaperoning, particularly when examining individuals of the opposite sex. These compose significant hurdles in a busy practice. Psychiatrists often refer patients to their general medical practitioner for physical examination. Attempts have been made to establish a minimum physical examination that is appropriate for psychiatric practice [54], but there is no

consistency nationally or internationally as to what is an accepted minimum.

Table 7 depicts some of the findings on physical examination that are commonly seen in substance use disorders in relation to the primary substance used. There are many more that stem from alcohol use disorders than any other substance class, reflecting the widespread tissue toxicity caused by alcohol misuse [16, 31].

Neurological and Mental State Examination

Emphasis should be placed on identifying the common mental comorbidities and neurocognitive impairments. The mental state examination is a vital component of the overall assessment when undertaken by a medical practitioner or psychologist. Key components are the client's general appearance, his/her reaction to the interview, speech, mood, affect, thought form, thought content, perception, presence of hallucinations, cognitive function, attention, concentration, orientation, memory (immediate recall, short-term memory, and long-term memory), intelligence, insight, and judgment [31].

The degree of rapport between the client and clinician provides clues about the client's relationships with others. The clinician's reaction to the client also may provide clues on the disorder from which the client is suffering. Suicide risk assessment is particularly important.

Laboratory Tests

The assessment of the client is complemented by undertaking relevant laboratory tests. These can include blood tests, urine assays (typically for drugs or metabolites), saliva analysis, breath analysis, and, less commonly, analysis of hair. Such samples can be examined for the presence of alcohol, nicotine, prescribed and illicit drugs, and their metabolites. In addition, for alcohol there are numerous tests that reflect its pathophysiological effects on blood, the liver, and other organs.

Considerable effort has been devoted to the development of laboratory tests of substance use disorders. There are several reasons for this. There remains a lingering concern by many researchers and clinicians about the validity of self-report despite the evidence for its accuracy in most circumstances. There is a desire for corroboration of self-report information, particularly in forensic settings or where there are significant implications for the individual for being diagnosed with a substance use problem. In addition, there is a desire for tests to simplify or speed the diagnostic process. More substantively, a test that reflects the biological processes of dependence or other pathology would be a valuable addition to diagnostic capability.

At present, no diagnostic test or procedures such as imaging directly point to specific substance use disorders. The nearest example perhaps is the finding of a high blood alcohol or drug level in a person who shows no signs of intoxication (or any substance effect). This is presumptive evidence of tolerance and points to the likely presence of a substance dependence syndrome. The biological markers of alcohol reflect a range of physiological processes [11], including liver enzyme induction and liver cell damage, suppression of hematopoiesis, and metabolic disturbances, such as hyperuricemia. None of these abnormalities is specific to alcohol. However, abnormalities can be used to support a diagnosis in conjunction with primary evidence of the substance use disorder. The most specific test reflecting the biological effects of alcohol is the presence of abnormal isoforms of transferrin, collectively known as carbohydrate-deficient transferrin [11]. An elevated blood carbohydrate-deficient transferrin is found in 40–70% of persons with alcohol dependence or harmful alcohol consumption. It is highly specific for these diagnoses (a specificity of 98% has been reported), with only a few uncommon inherited metabolic disorders and occasionally primary biliary cirrhosis and pregnancy resulting in abnormal levels. Table 8

Table 7 Findings on physical examination

Alcohol	Alcohol on breath Features of intoxication or of withdrawal Facial/periorbital puffiness Facial flushing/telangiectasia Old scars Conjunctival injection Scleral jaundice Signs of: • trauma • chronic liver disease • gastritis/duodenitis/gastric bleeding • pancreatitis • hypertension • atrial fibrillation • rib fractures • nystagmus • peripheral neuropathy • head injury • cognitive impairment
Tobacco	Nicotine-stained fingers Chronic airways disease Cardiovascular disease
Cannabis	Smell of marijuana Conjunctival injection Features of intoxication
Sedative-hypnotics	Drowsy, slurred speech (overdose) Anxious agitated (withdrawal)
Injecting drug users in general (unsafe injecting practices, associated lifestyle)	Malnutrition Poor self-care Needle track marks (fresh or old) Tattoos Jaundice (viral hepatitis C and B) Thrombophlebitis Cellulitis Lymphedema Skin abscesses Indurated skin Caries Mouth ulcers Pneumonia Septic arthritis HIV/AIDS and sexually transmitted infections
Heroin	Overdose or withdrawal Pupillary size: • pinpoint (overdose) • dilated (withdrawal) Low blood pressure Low respiratory rate Non-cardiogenic pulmonary edema
Psychostimulants	Underweight and emaciated Pupil size—dilated Excoriations (formication) Clenched jaws (bruxism) Caries/broken teeth Repetitive stereotypic movements Nasal septal necrosis (cocaine)

Table 8 Biological markers of alcohol misuse

Laboratory tests	Indicates excess alcohol intake
Urine or blood alcohol concentration >0.05%	Does not distinguish between acute and chronic consumption of excess alcohol
Full blood count: • Macrocytosis	Detects heavy drinkers: 20–30% in the community and 50–70% in hospital inpatients
Liver function tests • Elevated gamma-glutamyl transferase	Detects heavy drinkers: 30–50% in the community and 50–80% in hospital inpatients
Carbohydrate-deficient transferrin $t^1/_2$	Carbohydrate-deficient transferrin >2.6% reflects heavy alcohol use in the past 2 weeks
Newer biological markers not yet in common use	
Ratio of urinary 5-hydroxytryptophol/5-hydroxyindoleacetic acid	Increased ratio of 5-hydroxytryptophol/5-hydroxyindoleacetic acid
Ethanol metabolites in the urine: • ethyl glucuronide • ethyl sulfate	Helps to detect excess alcohol use when blood alcohol concentration is zero in the emergency department
Ethanol metabolites in hair samples • ethyl glucuronide • fatty acid ethyl esters	Evidence of excessive drinking when: • >25 pg/mg • >1 ng/mg

summarizes some of the most commonly employed laboratory markers of alcohol (see also [12]).

Neuroimaging techniques such as functional magnetic resonance imaging, positron emission tomography, and single photon emission computerized tomography scanning currently are illuminating some of the central neurobiological mechanisms of dependence. As yet, they are not part of routine clinical assessment, but this may well change with greater experience using these techniques over the next decade.

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Part II
Behavioral Theories for Addiction

Drug Reinforcement in Animals

Wendy J. Lynch and Scott E. Hemby

Contents

Introduction

Early demonstrations that drugs could serve as reinforcers maintaining operant behavior in laboratory animals led to the development of a model of human drug abuse (see Box 1). The traditional self-administration model was developed within a behavior analysis conceptual framework that views drugs as reinforcers similar to other "natural" reinforcers such as food and sex. The fundamental principle underlying behavioral analysis is that certain aspects of behavior are controlled by their consequences [54]. A drug is said to be functioning as a reinforcer if responding for it is maintained above responding for saline or other control conditions. The traditional model entails training an animal to self-administer a drug during a short daily session, typically 1–3 h. A low ratio requirement is typically used, such as a fixed ratio 1 where each response produces a drug delivery. Under these conditions, intake is incredibly stable, which allows for the determination of the effects of pharmacological and environmental manipulations on the stable baseline level of intake.

Although the rat is most often used in these studies, this model has been implemented with a variety of species including non-human primates, mice, dogs, cats, and baboons. A variety of operant responses have also been used, and typically they depend on the species studied. For example, a lever press or a nose poke response is typically used for rats, whereas a panel press response is typically used for non-human primates. The most common routes of administration are intravenous and oral, but intracerebroventricular, intracranial, inhalation, intragastric, and intramuscular routes have also been used. Generally, these studies use the route of administration that is most similar to the route used in humans for that particular drug, so, for example, animal studies with alcohol typically use an oral route of administration, whereas an intravenous route is used for drugs that have a rapid onset in humans, such as cocaine, heroin, and nicotine.

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_6,

Box 1 Definitions and terms

This glossary of some of the terms used in studying drug reinforcement, drawn primarily from Iversen and Lattal [46], is provided to aid in the reading of this chapter.

Addiction – a disease that is characterized by impaired control over use of the substance, preoccupation with the substance, use of the substance despite adverse consequences, and distortions in thinking [66].

Acquisition – the process by which a new behavior, such as lever pressing for drug deliveries, is added to the organism's behavioral repertoire.

Choice procedure – the allocation of one of two or more alternative, usually incompatible, responses.

Fixed-ratio schedule – a schedule in which a response is reinforced only after the animal has responded a specified number of times. For example, with a fixed-ratio 5 schedule of reinforcement, responding is reinforced after every 5 responses.

Progressive-ratio schedule – a higher-order schedule that requires the animal to emit an increasing number of responses for each successive reinforcer. For example, at the start of the session, the animal may be required to lever press once to receive a drug delivery, twice for the second drug delivery, four times for the third, eight times for the fourth, etc.

Operant behavior – emitted behavior that can be modified by its consequences (also termed instrumental behavior). This class of behavior is often referred to as purposeful or voluntary.

Reinforcer – a stimulus event that strengthens the behavior that follows it.

Reinforcement – the *process* whereby a behavior is strengthened by the event that follows the behavior, and a *procedure* by which the contingencies between the reinforcers and behavior are arranged within a paradigm.

Reinforcing efficacy – the likelihood that a drug will serve as a reinforcer under various experimental conditions (also termed reinforcing strength). For example, a drug that is only self-administered when the work requirement to obtain a delivery is low (i.e., fixed-ratio 1) would be considered a weak reinforcer, whereas a drug that is self-administered under a variety of different experimental conditions and when the work requirement is high would be considered a strong reinforcer.

Reinstatement paradigm – a model of relapse whereby the animal is tested on responding on a lever that was formerly associated with the drug following re-exposure to a small priming dose of the drug or the environmental stimuli associated with the drug. Stress also is often used as a trigger for drug-seeking behavior during reinstatement testing.

Self-administration – operant responding that directly produces administration of the drug.

Second-order schedule (higher-order schedule) – a schedule requiring the completion of an individual component of the schedule that produces availability to the terminal event. A second schedule of reinforcement must then be completed to produce the terminal event. For example, under a second-order fixed-ratio 10 (i.e., fixed interval of 10 s) schedule of reinforcement, 10 successive fixed-interval schedules would have to be completed before a response is reinforced.

Results from animal drug self-administration studies have revealed good correspondence between humans and animals; drugs abused by humans generally maintain responding in animals, whereas drugs that do not maintain responding in animals are typically not abused by humans, indicating this paradigm's utility for determining abuse liability [22, 42, 47]. Additionally, similar patterns of drug intake have been reported in humans and animals for ethanol, opioids, nicotine, and cocaine self-administration (for a review, see [43]). These parallel results between the human and animal drug literature validate the animal model of drug abuse and suggest that the use of this model may lead to a better understanding of human drug-taking behavior.

In addition to screening drugs for abuse liability, the traditional self-administration procedure has been used to study, through biochemical and pharmacological manipulation, the neurobiological processes underlying the drug reinforcement process. For example, by demonstrating that lesions in some areas of the brain decrease or abolish self-administration behavior, we have developed an understanding of the neuroanatomical substrates for drug reinforcement (e.g., [88]).

Assessing Reinforcing Efficacy

Despite the advances in our understanding of drug reinforcement in animals, reinforcing efficacy, or a drug's reinforcing strength, has been more difficult to measure. The ability of a drug to support self-administration in laboratory animals under different experimental conditions is a measure of the drug's strength as a reinforcer. Thus, a highly efficacious drug will be self-administered under a variety of experimental conditions such as low dose conditions, conditions that require a large work effort, or enriched environmental conditions where other reinforcers are available as choices. In contrast, a weakly efficacious drug will be self-administered only under limited conditions such as food-restricted conditions, moderate-to-high dose conditions, conditions that require a low work effort, or impoverished environmental conditions where there are few or no other reinforcers available as choices.

Although it is generally believed that the reinforcing strength of a drug is related to its abuse liability, actually measuring reinforcing strength is not as straightforward because factors other than the drug's reinforcing effects can directly and indirectly influence responding (i.e., satiating effects, direct effects on responding, and aversive effects). As mentioned above, the fixed-ratio schedule is typically used in studies investigating drug reinforcement in animals (e.g., 1- to 3-h sessions), and under these conditions, an inverted U-shaped relationship has been described between drug dose and rate of responding [16, 39, 72, 73]. That is, as dose increases, responding initially increases (ascending limb) and then decreases (descending limb). At low doses, responding decreases and these doses may not maintain responding. However, doses on the descending limb, which would be presumed to be more efficacious than doses on the ascending limb, maintain quantitatively similar levels or even lower levels of responding than those maintained by doses on the ascending limb. This issue is particularly problematic for the interpretation of changes in reinforcing efficacy in that it is difficult to determine the direction of the change. A number of approaches have been taken to address this issue, including the use of rate-independent approaches such as the progressive-ratio schedule, second-order schedules, and the choice paradigm.

Progressive-Ratio Schedule

The progressive-ratio schedule has been used to evaluate the reinforcing strength of self-administered drugs. With this schedule, the ratio requirement to obtain a delivery progressively increases within a session, and the final ratio completed, or breakpoint, is believed to be a sensitive measure of motivation to obtain the

drug (for a review, see [5]). In contrast to the fixed-ratio schedule, the dose-effect curve under the progressive-ratio schedule is linear, whereby responding is directly related to reinforcer magnitude; an increase in the unit dose of the self-administered drug corresponds to an increase in breakpoint. This linear relationship allows for a more straightforward determination of direction of change in reinforcing efficacy than is allowed by more traditional self-administration procedures. Other strengths are that responding for a particular dose of drug can be incredibly stable from day to day within subjects and that there are considerable individual differences in levels of responding between subjects. Sensitivity to individual differences is thus a strength of the progressive-ratio schedule. Sex differences and hormonal influences on drug self-administration behavior are good examples of this strength in that under simple fixed-ratio schedules, sex differences and hormonal influences are generally not revealed, whereas, under the progressive-ratio schedule, these factors influence breakpoints robustly (for a review, see [56]). Another advantage with this schedule is that it can be used reliably across different pharmacological classes of drugs. However, as with the more traditional self-administration paradigms, the satiating and behavioral disruptive effects of drugs can also impact responding under a progressive-ratio schedule, particularly during earlier parts of the sessions and under low or slowly increasing progressive-ratio schedules.

Second-Order Schedules

Second-order schedules have been developed and have been useful for minimizing issues of satiety and other rate-limiting effects of drugs on responding. Much of the early work using second-order schedules was conducted with non-human primates and focused on conditioned or secondary reinforcement (for a review, see [77]). With this type of schedule, a non-drug stimulus, usually a light or a tone, takes on the characteristics of a reinforcer by its association with the drug delivery. Second-order schedules of drug delivery allow the study of more complex behavioral sequences than do traditional self-administration procedures. The use of second-order schedules has recently been extended to self-administration in rats, and these studies have been useful for the investigation of drug-seeking behavior (i.e., responding for drug that occurs prior to drug availability or when the drug is no longer available) and its neurobiological mechanisms (e.g., [31]).

Like the progressive-ratio schedule, second-order schedules minimize the descending limb of the dose-effect curve, allowing for determination of changes in reinforcing efficacy as a result of a pharmacological or environmental manipulation. Another advantage is that high rates of behavior can be maintained by the conditioned reinforcer with relatively few actual primary reinforcers delivered. Nicotine is a good example of a drug that is robustly self-administered under second-order schedules, whereas, under simple fixed-ratio schedules, it has been historically difficult to establish that it functions as a reinforcer [40]. In fact, even under more traditional self-administration paradigms, nicotine maintains more robust levels of responding when the drug deliveries are paired with a stimulus cue, such as a light [13]. However, one disadvantage of this approach is that it is often difficult to separate the reinforcing strength of the secondary reinforcer from that of the primary reinforcer.

Choice Procedures

Choice procedures are an increasingly popular tool for examining the reinforcing efficacy of drugs of abuse (for a review, see [8]). Early studies employing choice procedures showed that laboratory monkeys chose to self-administer a reinforcing drug over its vehicle [48]. The procedures used in choice experiments typically involve one of three types of experimental schedules: discrete trial schedules,

concurrent schedules, and concurrent chain schedules. With each of these schedules, animals choose among two or more options by responding on one of two or more levers. With choice procedures, the session typically begins with a sampling period during which the subject can respond to obtain each of the available reinforcer options (i.e., a low versus high dose of drug, drug versus saline, or drug versus some other reinforcer, such as food). The sampling period is then followed by a series of discrete trials or concurrent schedules during which the animals must complete the schedule requirement in order to obtain a drug delivery. Response allocation, rather than response frequency, provides a measure of the drug's reinforcing strength. This feature allows for the determination of reinforcing strength relative to behavior allocated toward an alternative reinforcer. As such, choice procedures are believed to mirror more directly the real-world situation where drug users allocate resources to obtain drugs rather than other non-drug reinforcers such as food and extracurricular activities. Indeed, most self-administration studies using drug-dependent humans have used choice procedures where subjects choose between drug deliveries and a non-drug alternative such as money (for a review, see [24]).

Studies have shown that laboratory animals not only choose drug over saline deliveries, but also prefer higher doses of drugs. For example, Carroll [17] conducted a study in which monkeys chose between a standard dose of phencyclidine (0.25 mg/kg) or one of several other doses that were concurrently available (0.06, 0.12, 0.50, or 1.00 mg/kg). Carroll found that subjects chose the large concentrations more often than the smaller ones. Similar results have been shown for a variety of other drugs including cocaine, remifentanil, methylphenidate, and pentobarbital [4, 45, 48, 52, 64]. Importantly, larger doses have been shown to be preferred over lower doses even under conditions where the behavioral disruptive effects of the drug are apparent (i.e., conditions that allow for access to the moderate-to-high drug doses with relatively short inter-dose intervals; [45]). One disadvantage with the choice procedure is that preference for high doses over lower ones has been more difficult to show in rats [58, 59].

Modeling Aspects of Addiction

The majority of the preclinical studies on addiction have used the traditional self-administration paradigm or other conditions that limit drug intake—that is, maintenance conditions that produce stable and relatively low levels of self-administration. As such, the behavioral and neurobiological principles defined by these studies may be restricted to drug reinforcement and not necessarily be characteristic of "addiction". Specifically, while the positive reinforcing effects of drugs are involved in addiction, particularly during initiation of drug use, other characteristics, such as loss of control over drug use and the resulting excessive use of the drug, as well as the negative reinforcing effects of drugs (i.e., use to alleviate withdrawal or craving), also appear to be critically involved. Newer methods have attempted to incorporate features of human drug addiction that are not represented in more traditional procedures. These methods have focused on addressing critical questions regarding addiction, such as: "Why do some individuals become addicted but not others?"; "What are the factors that influence the transition from controlled or causal use to compulsive use or addiction?", and "What are the factors that influence relapse or reinstatement to drug use?" The models that have been developed to address these questions are discussed below.

Individual Differences in Vulnerability to Addiction

The majority of people in the United States have used drugs, and if alcohol is included, users comprise over 90% of the population [82]. Although a substantial number of people do become addicted, addicts make up only a small

percentage of the total number of users. Thus, mere drug use does not inevitably lead to addiction. The reinforcing effects of a drug appear to be a primary determinant during initiation of drug self-administration. Clinical data suggest that a strong predictor of the development of drug addiction is the individual's "vulnerability" to the reinforcing effects of drugs. Retrospective reports from drug users reveal that the response to initial drug exposure varies from highly positive to negative [35], and some evidence suggests that individual differences in sensitivity to drug reinforcement are predictive of later use [25].

Consistent with the clinical findings, there is considerable variability in laboratory animals in their propensity to self-administer drugs. Animal models of the initiation or acquisition phase have been developed to identify biological and behavioral factors underlying individual differences in vulnerability to the reinforcing effects of drugs of abuse that may apply to prevention efforts in humans (for a review, see [15]). However, the acquisition phase is difficult to study because it is typically brief and is characterized by a sudden shift from low to high levels of intake. Thus, methods that slow the acquisition process and decrease intersubject variability are necessary to observe this transitory period. For example, acquisition of drug self-administration is optimally investigated in drug-naive and experimentally naive animals that are maintained under food-satiated conditions (e.g., food restriction serves as a stressor that can greatly accelerate the acquisition process and obscure individual differences) and tested under low dose conditions (e.g., high doses are associated with not only reinforcing effects but also direct effects and aversive effects that may interfere with responding). Under these conditions, individual differences are maximized, and some rats will acquire self-administration whereas others will not; the question that is addressed is: "Which animals can detect the reinforcing effects of this low drug dose?"

A simple method of evaluating acquisition is to give an animal access to a drug during a daily experimental session, with deliveries available contingent upon an operant response (i.e., lever press; e.g., [26]). Another method that has been used to investigate individual differences in acquisition of drug self-administration is an autoshaping procedure. This procedure was adapted to the study of the acquisition of drug self-administration [18] from methods used to study the acquisition of food-reinforced responding [12]. Daily sessions consist of six 1-h autoshaping components followed by a 6-h self-administration component. During each 1-h autoshaping component, rats receive computer-automated, response-noncontingent infusions delivered on a random interval schedule that are paired with light cues and lever retraction. During each 6-h self-administration component, the lever remains extended and each response will result in a drug infusion. With both procedures, acquisition of drug self-administration is measured as the number of sessions needed to reach a criterion level of intake, which can be standardized and adjusted for dose and drug availability. The ratio of active to inactive lever-press responses is often used in conjunction with the intake criteria. All of the animals are included in the analyses, whether or not they acquire self-administration, and the focus is on how rapidly this process takes place and what percentage of each group of animals acquires drug-reinforced responding.

These acquisition methods have revealed a number of organismic and physiological factors that predict vulnerability to drug self-administration, such as genetic strain [81, 86], impulsivity [70], exploratory behavior in a novel environment [26, 67], corticosterone levels [71], innate saccharin preference [41, 68], dopamine release in brain regions associated with drug reward [37, 38, 44], behavioral reactivity to stressors and to acute injections of drugs [27, 61], age [79], and sex [56]. For example, we used an autoshaping procedure to train male and female rats to lever press for either cocaine infusions (0.2 mg/kg) or heroin infusion (0.015 mg/kg) under a fixed-ratio 1 schedule (i.e., one response per infusion). Under these conditions, female rats acquired cocaine and

heroin self-administration at a faster rate than male rats, and a greater percentage of female rats acquired cocaine self-administration than did male rats [57].

Environmental factors, such as feeding condition, the presence of an alternative non-drug reinforcer, and drug history, can also greatly impact acquisition [20, 21]. For example, Childs et al. [21] examined the effects of chronic cocaine exposure on subsequent rates of acquisition of cocaine, using rats with a history of cocaine discrimination. They found that rates of acquisition of cocaine self-administration were more rapid in cocaine-exposed rats compared with non-cocaine-exposed rats. Rates of acquisition also vary widely as a function of drug dose, type of drug, and route of administration. Under high dose conditions with a drug such as cocaine that rapidly enters the brain after an intravenous infusion, most if not all animals will acquire self-administration rapidly. However, when lower doses of cocaine are used, or an oral route of administration is used, fewer animals will acquire and the rates of acquisition become much slower. Similarly, when drugs such as caffeine or alcohol that are considered to have a less intense or less rapid onset of action are used, the acquisition process is slowed. With oral administration, the taste of the drug can also influence the probability and rates of acquisition (e.g., the acquisition of oral alcohol self-administration is relatively slow because animals typically have an aversion to the taste of unsweetened alcohol).

Animal Models of "Addiction"

Two of the defining features of addiction in humans, loss of control over drug use and the resulting excessive use of the drug, have been modeled in animals using several different methods (for a review, see [75]). Early studies with monkeys and rats used unlimited access conditions (e.g., each response is reinforced under a fixed-ratio 1 schedule of reinforcement during 24-h sessions) and showed that, as in humans, patterns of self-administration in laboratory animals were characterized by dysregulated and binge patterns of use. For example, animals self-administering psychomotor stimulants such as cocaine, d-amphetamine, and methamphetamine demonstrated periods of erratic and rapid drug intake interspersed with periods of self-imposed abstinence [9, 28]. Excessive drug self-administration develops rapidly under these conditions, leading to severe toxicity and, in some cases, death. Toxicity appears to be particularly problematic for psychostimulant drugs and opiates, thus necessitating the use of procedures that limit access to these drugs in some way.

Recent studies have attempted to capture these features, excessive and dysregulated patterns of consumption, but without the serious signs of toxicity. For example, excessive drug intake with limited signs of toxicity has been observed under 24-h access conditions with low unit doses of drug [19] under continuous-access fixed-ratio self-administration conditions that limit the number of hours of access each day (i.e., 6–12 h daily; [1]) or each period of continuous access (i.e., 72 h; [85]). Another method that allows for extended access to cocaine with limited toxicity is a discrete trial procedure wherein animals are given 24-h access to cocaine infusions that are available in discrete 10-min trials [34]. With this method, excessive cocaine use is observed as access conditions increase. For example, under short-access conditions (1–2 discrete trials/h, 1.5 mg/kg/infusion), rats consumed low levels of cocaine and intake was relatively stable over time [74]. However, under extended access conditions (i.e., 4 discrete trials/h, 1.5 mg/kg/infusion), rats self-administered high levels of cocaine in "binge/abstinent" patterns, taking nearly every infusion available for the first 1–2 days, followed by periods of self-imposed drug abstinence that were interspersed with periods of active drug use. Importantly, increased motivation for cocaine [65], as well as increased cocaine-primed and cue-induced cocaine-seeking [50, 63, 76], other critical

features of cocaine addiction (as discussed below), are observed following extended-access self-administration when examined after an abstinence period. For example, in our previous work with rats, we found that 10 days of access to cocaine under the discrete trial procedure (4 trials/h) produced a sustained increase from baseline levels of progressive-ratio responding for cocaine when assessed following a 7-day abstinence period [65]. Similar results have recently been reported following extended access to self-administered heroin and methamphetamine using similar procedures [2, 76, 87].

Other drugs, such as nicotine and ethanol, typically can be available under unlimited-access conditions with limited toxicity, and results from studies with these types of drugs have also revealed "addiction-like" behavioral profiles. For example, Wolffgramm and Heyne [89] developed an animal model of this transitional phase for oral alcohol self-administration in rats. Their procedure entails long-term ad libitum self-administration (1–2 months) followed by an extended drug abstinence period (4–9 months). Subsequently, rats were retested on self-administration behavior, and those animals that developed escalating patterns of intake prior to abstinence self-administered higher levels of intake compared with rats that did not show escalation.

As discussed above, access conditions, drug dose, and the drug being self-administered are crucial factors for the observation of excessive and dysregulated patterns of consumption [1, 51, 58, 75]. Individual differences during this transition phase also have been reported. For example, females appear to require less drug exposure than males to display increased motivation for cocaine, due to levels of circulating ovarian hormones [53, 56]. Sweet preference and level of reactivity to novelty also appear to influence the appearance of drug escalation/dysregulation as well as motivational changes following extended-access self-administration [62, 69]. Notably, the underlying neurobiology associated with extended-access drug self-administration appears to be different from the neurobiology associated with short-access drug self-administration (e.g., [6, 7, 11, 33, 36, 84]).

Animal Models of Relapse

Relapse, or recurrent resumption of drug use after detoxification and abstinence, is one of the most challenging problems in the treatment of addiction [3]. Various types of stimuli can precipitate relapse, including internal cues such as re-exposure to small "priming" doses of the drug and external cues such as specific people and places that were associated with drug use. Often, external stimuli lead to drug use, and then the internal stimuli associated with drug use sustain relapse [10]. Animal models of relapse have been developed and have provided critical information on the neurobiological mechanisms underlying the vulnerability to relapse to drug abuse [55, 80].

One model that has been used to investigate mechanisms underlying relapse is the reinstatement paradigm [49]. With this procedure, animals are trained to self-administer a drug and, once stable, responding is extinguished by discontinuing drug delivery. After responding reaches come criterion of unresponsiveness, the ability of various stimuli to reinstate drug seeking is determined under conditions of non-reinforcement (i.e., responses are no longer reinforced by the drug). A stimulus is said to reinstate responding if it causes an increase in responding that was formerly reinforced by the drug. This sequence of events can occur once a day (e.g., [29, 30]) or several times per day [78]. The results from preclinical studies have revealed that the conditions that reinstate drug seeking in laboratory animals are similar to those that trigger relapse in humans, including small doses of the drug itself, cues associated with the drug, and exposure to stressors (for a review, see [49]), thereby demonstrating the predictive validity of this model. As such, the reinstatement paradigm can be useful for screening potential medications for relapse prevention in humans as

well as for studying factors influencing relapse to drug use.

In general, reinstatement studies have shown that drugs from the same pharmacological class as the self-administered drug, or drugs that share discriminative stimulus effects with the self-administered drug, act as effective priming agents to reinstate extinguished responding [29, 30]. Examination of environmental manipulations under conditions of maintenance and reinstatement in the same animals reveals a dissociation between these two states of behavior. For example, Comer et al. [23] examined the effect of food restriction on the maintenance and reinstatement of extinguished cocaine-reinforced responding using the relapse model in rats. They found that food restriction potentiated the effects of priming injections of cocaine. One interpretation of these results is that food restriction produces an increased motivational state that generalizes to drug-seeking behavior (reinforcer-interaction hypothesis; [23]). In contrast, food restriction did not affect responding for cocaine during the 2-h self-administration session. A dissociation of treatment effectiveness in the maintenance versus reinstatement phases also has been reported (e.g., [14]).

Results from reinstatement studies also have revealed a number of factors that predict a vulnerability during this phase, including responsiveness to the acute and chronic locomotor activating effects of psychostimulants (e.g., [32]), locomotor responses to novelty [83], pattern of drug intake prior to reinstatement testing [83], and sex [56]. Notably, there appear to be important interactions of cues used to trigger reinstatement responding and vulnerability factors. For example, while females show enhanced reinstatement responding compared with males following exposure to priming injections of a drug, males have been reported to respond at similar or higher levels following exposure to drug-associated cues [56]. Similar results have been reported in laboratory studies with drug-dependent men and women (for a review, see [60]), suggesting that vulnerability to relapse may be due to a complex interplay of environmental and biological factors.

Conclusions

Traditional self-administration procedures have firmly established that drugs of abuse function as reinforcers in animals. While the reinforcing effects of drugs are certainly important in the acquisition and maintenance of the addiction process, it is becoming increasingly apparent that other factors are involved. The shift to focusing on vulnerability factors for addiction and the use of models that mimic more closely characteristics of addiction in humans is likely to advance our ability to understand the key factors involved in addiction and, ultimately, identify potential pharmacological and environmental treatments.

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Role of the Human Laboratory in the Development of Medications for Alcohol and Drug Dependence

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Contents

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Introduction

According to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition—Text Revision* [7], drug dependence involves "…a pattern of repeated self-administration that can result in tolerance, withdrawal, and compulsive drug-taking behavior". The development of medications useful for the treatment of alcohol or drug dependence requires the clinical and preclinical testing of existing and novel compounds in various experimental models useful to evaluate the mechanism, safety, and possible efficacy of the putative treatment [113, 132, 178, 233]. Medication development research

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_7,

has sought to evaluate both existing medications already on the market for other indications as well as new, novel compounds never yet tested in humans. Regardless of the stage of development for any particular medication, experimental studies of human subjects in controlled laboratory environments (i.e., "human laboratory" studies) will be required at some step of the process for one of three possible reasons.

a) *Phase I Safety Testing of Novel Compounds*: For novel compounds not yet approved by the United States Food and Drug Administration, Phase I clinical trials will be required to evaluate the safety and abuse liability of the new medications. Basic safety testing in healthy subjects is normally required for first-in-man studies but basic Phase I safety testing approaches will be required in the drug-using target population as well before the Food and Drug Administration will allow Phase II and III treatment trials to proceed.
b) *Phase I, II Safety Testing in the Target Population*: If the medication is already approved by the Food and Drug Administration for another indication, development of that medication for addictions treatment still will require testing its safety in drug-using or addicted populations. Safety evaluation includes both the biomedical safety of treatment in a drug-using population but also an assessment of the abuse liability of the medication in a population likely to misuse substances. Additionally, the Food and Drug Administration likely will require these studies to address the safety of the drug interaction between the treatment medication and the drug of abuse.
c) *Evaluation of Pharmacokinetic and Pharmacodynamic Mechanisms*: Though Phase III treatment trials will be required to demonstrate efficacy, human laboratory studies also can be helpful to evaluate the clinical pharmacology (both kinetics and dynamics) of the medication. These studies can evaluate the possible behavioral or neurochemical mechanism(s) of action or use human laboratory models to estimate the possible efficacy of new medications.

For many human laboratory studies, subjects are research volunteers not engaged in treatment. However, individuals who are "in treatment" also may be tested under controlled human laboratory conditions. The purpose of this review is to identify and highlight the role of and contributions made by human laboratory studies in the development of new medication treatments for alcohol and drug dependence.

Pioneering studies conducted in the 1950s, 1960s, and 1970s at the Addiction Research Center of the Public Health Service Hospital in Lexington, Kentucky developed the basic experimental approaches useful to understand the clinical pharmacology of alcohol and drug dependence, and their treatment [59–61, 153]. Because studies of addiction require an understanding of the clinical effects of drugs of abuse and how these drugs promote or maintain drug-taking behaviors, even the earliest of studies involved the administration of drugs of abuse to subjects with histories of drug abuse and dependence. The National Advisory Council on Drug Abuse has recommended guidelines for the ethical and safe study of drugs given to human subjects (http://www.drugabuse.gov/Funding/HSGuide.html) [50, 51, 161] and human laboratory methods and approaches for these studies have been well established. Broadly speaking, pharmacological approaches to the study of the behavioral effects of drug abuse and its treatment are characterized under the umbrella of abuse liability assessment [10, 11, 69]. Abuse liability assessment involves estimation of the *likelihood* that a substance will be used or self-administered and/or the *liability or harmfulness* of that use [193, 198]. Thus, abuse liability assessment approaches to human laboratory studies encompass all aspects necessary to evaluate both the safety (i.e., *abuse liability* of the treatment agent and the *harmfulness* of the drug interaction) and possible efficacy (i.e., does it reduce the *likelihood* of using the drug of abuse) of medications useful to treat alcohol and drug dependence. The current chapter

is designed to highlight how human laboratory studies have or have not contributed towards understanding and developing medication treatments for addiction. We will focus on studies done with opiate, alcohol, and stimulant dependence where the bulk of this work has been done.

Role of the Human Laboratory to Evaluate the Abuse Liability of New Medications

When medications are developed for human use, the Food and Drug Administration or Drug Enforcement Administration may require an assessment of the abuse potential of the new agent and this generally will require human laboratory studies [10, 69, 149]. Typically, abuse liability assessment will be required when the medication under development shares pharmacological characteristics or planned indications with other drugs of known abuse potential. Broadly speaking, the abuse liability of a potential medication can be characterized in the human laboratory using one or more of three different behavioral approaches as described below.

To Characterize Adverse or Harmful Effects

Characterizing the effects of a new drug on various dimensions of physiological function and performance or other behavioral impairment, can be valuable to understand how the drug might alter or impair important biobehavioral functions [193]. For example, drugs could be examined for how they alter cognitive, psychomotor, or other behavioral performance [33, 34, 96] or physiological functioning [104, 105, 153]. Characterization of drug effects on each of these dimensions provides valuable information to assess the potential *liability* or *harm* that can occur with drug use. For the development of any new medication, awareness of these potential effects is important to assess the safety of the medication. In the context of drug abuse, it also is important to know about the safety of the drug interaction should the new medication be combined with the drug of abuse. For this reason, many studies have been devoted to assessing the potential interactions between the new medication and alcohol—the most common drug for which potentially dangerous interactions might occur [4, 5]. The safety of drug interactions also is very important for Food and Drug Administration approval of potential treatments for alcohol or drug addiction since it is very likely that drug-dependent populations undergoing treatment with a medication will at some point at least sample their primary drug of dependence. In many National Institute on Drug Abuse-sponsored Phase I clinical trials for stimulant dependence, the safety of the drug interaction on cardiovascular toxicity has been a primary concern to be addressed in these studies. Furthermore, the characterization of the drug interaction in the experimental laboratory may provide insight into the mechanism and possible effectiveness of that medication.

To Characterize Its Comparative Pharmacological Profile

The most common approach of abuse liability assessment is the pharmacological bioassay, which is a standard evaluation of the clinical and pharmacological profile of the new drug in comparison with another known drug from the same or similar pharmacological class [10, 69, 198, 209]. Necessarily, pharmacological profiling means evaluating the pharmacodynamic effects of the drug on a variety of dimensions which could include assessment of performance or physiological effects, but for abuse liability also includes assessment of subjective effects or euphoria. An adequate evaluation of pharmacological profile requires the testing of a range of doses to construct a dose-response curve because the testing of a single dose loses an understanding of the dose-responsiveness of observed effects and is fraught with the potential for

false negative findings. Because drug abusers are likely to consume supra-therapeutic doses of a marketed medication, its true potential for abuse cannot be known without testing doses that are at the higher end of the dose-response curve. Comparison of the new drug with a standard drug of known abuse potential is an essential element in the pharmacological comparison approach for at least three reasons. First, use of the standard drug establishes the positive control level of response to drugs of abuse under the standard conditions employed by the experiment. This is particularly important given that false positive or negative results may occur due to variations in the assessments, population, or other study conditions. Second, relative potency or relative effect size comparisons between the novel drug and the standard drug of abuse provide the basis for the most meaningful interpretation of data. Thus, the new drug may differ in the dose-response slope, the maximum effect size, or the relative potency on different dimensions of effect. Each of these variables has a different implication for abuse liability. Third, for clinical advantage estimation purposes, the Food and Drug Administration and medical prescribers would like to know about the differential efficacy contrast of the new drug in comparison with a known drug, which may be a standard drug of abuse or a scheduled prescription medication that has known abuse potential.

To Evaluate Its Reinforcing Effects or Potential for Self-Administration

Numerous animal models of addiction, studied across a wide variety of drugs and species have shown that drug taking is a drug-reinforced behavior controlled by operant contingencies and schedules of reinforcement [70, 201]. The same also has been shown in humans where several human laboratory models of drug reinforcement and self-administration have been established [28, 70, 91, 92, 219]. Ultimately, the behavior we are interested to understand, predict, and treat, is the likelihood that a drug/substance will be used or consumed in a pattern consistent with abuse or dependence. For a medication to be used in a substance-abusing population, we need to identify whether or not the medication has any potential for abuse in and of itself. A yes/no decision whether or not the drug is self-administered by the subject population may not be sufficient here because the environment and the availability of alternatives influence choice behavior. For example, the likelihood that a sedative or stimulant drug will be self-administered is influenced by how stimulating the experimental environment is [213, 221]. This phenomenon likely explains how even the sedating atypical antipsychotic quetiapine, with little apparent abuse liability, may become a highly preferred drug of abuse in a prison or psychiatric hospital environment where access to other drugs is limited [131, 227]. Therefore, an all-or-none conclusion of whether or not a drug is self-administered under one set of conditions doesn't indicate much about its potential for self-administration under a different set of circumstances. Thus, studies of the potential for reinforcement or self-administration are limited by the range of conditions (dose, circumstance, population, etc.) under which they are tested [69, 198, 209].

Issues in Human Laboratory Studies of Abuse Liability

There are several issues which need to be considered by any human laboratory study of abuse liability. Information below summarizes the issues that generally exist in the field and potentially limit any conclusions coming from human laboratory studies of medication effects on drugs of abuse.

Role of Subjective Effects

Ever since the earliest studies at the addiction research unit at the United States Public Health Service Hospital at Lexington, Kentucky,

it has been observed that drugs of abuse as diverse as alcohol, barbiturates, opiates, and psychomotor stimulants all share a profile of psychoactive effects characterized as euphoria [49, 188, 191]. It is generally accepted that euphoria is at least a partial explanation of why these drugs are abused. Because of the subjective and unobservable nature of this psychoactivity, self-report questionnaires are used to assess these subjective effects. One of the early questionnaires developed to measure the subjective effects of drugs of abuse was the Addiction Research Center Inventory. The Addiction Research Center Inventory is a multi-item questionnaire completed by human subjects during drug intoxication [76]. Factor analysis was used to empirically derive subscales of items responsive to characteristic drugs of abuse including amphetamine, benzedrine, morphine, pentobarbital, alcohol, chlorpromazine, and lysergic acid diethylamide. Subsequently [59], the morphine-benzedrine groups were combined to represent an opiate or stimulant-type of "euphoria" scale, the pentobarbital-chlorpromazine-alcohol group a distinctly "sedative" scale, and the lysergic acid diethylamide scale as a "dysphoria" or unpleasantness scale. It is important to recognize that these scales actually were derived to measure subjective mood changes induced by pharmacologically distinct drugs of intoxication and not euphoria *per se*. Therefore, while the morphine-benzedrine scale is called a "euphoria" scale, it really measures morphine and benzedrine intoxication, and is not sensitive to sedative euphoria [59, 69, 198]. The Profile of Mood States [158] is a multi-item questionnaire derived in the measurement of mood in normal healthy college students. Nonetheless, it has been used commonly to measure changes in depression-dejection, tension-anxiety, vigor, arousal, and other mood states by various populations under the influence of drugs [35, 48, 49, 247]. Generalized mood measures are valuable to assess the pharmacological profile of a drug and are sometimes presumed to predict abuse potential under the assumption that positive mood states could reflect an increased potential while negative mood states could reflect a decreased potential. In alcoholism research, the biphasic alcohol effects scale [151] was derived to measure the positive and disinhibiting arousal that may occur during the ascending limb of the blood-alcohol curve and the sedative-inhibition that occurs on the descending limb of the curve. Actually, there are many other factor-analyzed and single item rating scales that have been used to evaluate the subjective effects of psychoactive drugs and enumerating them is beyond the scope of this review.

The psychoactive effects of psychotropic drugs are studied in animal subjects using discriminative stimulus procedures where subjects are trained to discriminate the differences between drugs. Discriminative stimulus procedures also have been developed to train human subjects to discriminate the interoceptive stimulus effects of drugs [43, 107, 187, 191, 222]. While subjective rating scales take advantage of the verbal capacity of human subjects to quantitatively report the qualitative characteristics of their subjective experience, the discriminative stimulus approach uses a qualitative analysis of same/different comparisons between drugs. There is reasonable correspondence between conclusions drawn from subjective effects and those from discriminative stimulus studies in humans [43, 191, 222]. Because of differential reinforcement of behavior during discriminative training, it is likely possible to gain a tighter level of discriminative control with this paradigm than with standard subjective questionnaires. However, the specificity and sensitivity of this procedure very much depends upon the discrimination training conditions [108] and are achieved only through lengthy training procedures. Nonetheless, the ability to compare the human study results with the preclinical data using discriminative stimulus analyses is a distinct advantage of this procedure [43, 107].

Clearly, a description of subjective mood states induced by drugs is part of a thorough characterization of pharmacological effects in humans [10, 69, 198]. The question of some debate is whether or not treatment-related changes in discriminative or subjective effects predict a change in the likelihood of

drug taking [28, 52, 53]. Although there is a good correspondence been "positive" subjective effects and the likelihood of drug self-administration, it is certainly not true that either positive or negative subjective effects alone explain the cause or the reason why drugs are or are not self-administered.

Role of Subjective Euphoria

The cardinal subjective effect commonly assumed to be important to abuse potential is the experience of psychoactive drug effects which are pleasant, preferred, or "euphoric". A number of reviews of human abuse liability have discussed issues of drug-induced subjective euphoria and its measurement [49, 52, 53, 69, 188, 191, 198]. Actually, most drug users do not refer to "euphoria" but rather describe the drug intoxication as a "high". Though cocaine intoxication has been described as "intensely stimulating and pleasurable", or "orgasmic", it is clear that not all drugs of abuse produce such intense pleasurable sensations. For many drugs including alcohol, the intoxication is more often described as a "buzz", or "drunk", or "high" that has "good" features and that people report "liking". Consequently, most studies employ individual item rating scales for subjects to rate the extent of "high" and "good" subjective effects and the extent to which subjects "like" the effect. There is no standard euphoria scale used by a majority of studies. Though the Addiction Research Center Inventory-morphine-benzedrine scale has been described as a general euphoria scale it really is only validated for opiate and stimulant drugs and usually is not responsive to sedative drugs of abuse. Likewise, the Profile of Mood States "elation" scale has been used as a general euphoric mood scale, but its sensitivity as a general measure of drug-induced euphoria has not been established. In fact, it is likely that the soporific and disinhibited state of sedative euphoria is inherently different than the exhilarated and aroused state of stimulant-induced euphoria.

Importance of Measuring Self-Administration Behavior

There have been controversies over the definitions and value of terms such as use, misuse, abuse, addiction, tolerance, withdrawal, craving, etc., and their importance as "explanations" of alcoholism or drug dependence. Current conceptions of the disease condition recognize that the core feature of substance abuse or dependence is the pattern of drug self-administration that is considered by society as harmful or compulsive [7, 178]. Consequently, most studies of abuse liability seek primarily to predict the *likelihood* of drug self-use for non-medical purposes. Though studies of subjective euphoria may have some predictive correlation with drug-taking behavior, it is important to directly study the self-administration of drugs as the cardinal symptom of substance abuse or dependence. Ample previous research clearly has demonstrated that drugs of abuse maintain the self-administration behavior of both humans and animals through the process of operant reinforcement. Ever since the earliest studies at the Addiction Research Center observing heroin self-administration in a heroin addict [248], a variety of different procedures have been developed to study self-administration behavior in human laboratory environments and these have been described in previous reviews [28, 70, 83, 90, 92, 201, 219]. These reviews describe the effects of variations in self-administration procedures such as:

a) the specific drug reinforcer, its route of administration, and whether or not dose was varied (higher doses and more rapid increases in blood level are more reinforcing);
b) whether the drug reinforcer was administered immediately or after a time delay (immediate drug delivery is more reinforcing);
c) whether the self-administered dose was a high bolus dose or multiple smaller doses (multiple smaller doses result in more sensitive measures of reinforcement);
d) whether or not the drug reinforcer was "blinded" and placebo controls were

employed (blinded procedures have greater validity);
e) whether the self-administration behavior was a verbal request or responses on a response instrument (responses on a manipulanda provide quantitative measures of behavior);
f) the extent to which behavioral "cost" was varied in the operant contingency (increasing "cost" decreases the probability of self-administration);
g) whether the self-administration procedure included choices among alternative reinforcers (choice between alternatives provides a better quantitative assessment of relative reinforcement); and
h) whether drug taking was quantified by measuring amount consumed vs. the proportion of subjects responding (amount measures are more sensitive measures).

Thus validated operant models of drug reinforcement have been established for human laboratory studies, and these have become increasingly used over the last two decades. Although pleasant subjective effects generally are correlated with the tendency of subjects to self-administer drugs in the human laboratory [25, 35, 70, 109, 110, 191, 198] drug-taking behavior does occur in the absence of measurable subjective effects [141, 197]. At times, the needs to examine complete dose-response functions in making between-drug pharmacological comparisons [69] may preclude self-administration studies [198]. Nonetheless, direct observations of drug-taking behavior generally are preferred over measures of subjective effects alone [28].

Role of Environment and Cost in Controlling Self-Administration

Although this review will not discuss specific advantages and disadvantages of different self-administration procedures, variations in the procedure are likely to alter the sensitivity to change of the drug-taking measure [219]. In fact these procedural variables are likely to be important both in determining whether or not the drug is self-administered, as well as the sensitivity to change to show increases or decreases in drug-taking behavior. One of the variables that importantly influences drug-taking behavior is the role of the internal or external stimulus environment and how that can increase or decrease the likelihood of self-use. For example, diazepam is not normally preferred by healthy controls [109] but preference increases under environmental conditions which increase anxiety [90]. Also, sedative drugs are preferred over stimulants in sedentary environments while stimulants are preferred over sedatives when task performance contingencies require alertness [213, 221]. The reason that a stimulating environment may decrease the reinforcing effects of a sedative but enhance the reinforcing effects of a stimulant probably is related to behavioral cost and alternative reinforcement [201, 219]. Understanding this phenomenon involves recognition of the behavioral economics of drug taking [14, 15]. In behavioral economics, choice of the drug involves a behavioral cost and may occur at the expense of access to alternative reinforcers. In human laboratory studies, it is common to make monetary choices available as an alternative to drug taking [30, 94, 160, 219] wherein choices between increasing amounts of money vs. drug result in reductions of drug self-administration. Griffiths and colleagues [72, 73] exploited this phenomenon in creating the "Multiple Choice Procedure", which is a questionnaire wherein across a series of single-item questions, subjects choose between receiving the drug or a gradually increasing amount of money. In order to establish the questionnaire responses as a true measure of choice/preference for drug, one of the many item questions is selected at random and the subjects actually receive as a consequence, the drug or the money amount they selected for that item.

Role of Subject Population Variables

One of the issues associated with subjective effects assessment, is that the extent to which

subjective psychoactivity is considered pleasurable or "euphoric" varies across different populations and is shaped and influenced by experience. For example, early studies by Beecher [12] showed that normal healthy volunteers reported unpleasant experiences when given opiates or barbiturates while drug-experienced users reported those drug effects to be pleasant or euphoric. Balanced placebo research designs controlling subject expectations with 2 × 2 factorial experiments where subjects were either told or not told they are receiving drug under conditions where they actually did or did not receive drug have shown that the subjective reports of drug effects in normal populations are substantially influenced by expectation [157]. Of course expectations occur in drug-dependent populations as well. Compared with normal drinkers, heavy alcohol drinkers report greater expectations of euphoric responses and other positive or beneficial effects of alcohol [21, 31]. It is likely that some of the differences between drug-experienced and naive populations are due to learned or acquired factors altering attribution or expectation. For example, the itching, flushing, and nauseating effects of opiate analgesics is unpleasant to most people, but narcotic addicts call these signs a "pleasant sickness" associated with "good stuff". Thus, associative experience may condition drug users to "like" the effects of drugs of abuse and report euphoric "highs" in response. Generally, normal subject populations, who do not abuse drugs, do not report higher levels of liking drug effects or do not experience euphoric mood changes, or self-administer most drugs of abuse [69, 109, 110, 198, 209]. Strong evidence for the importance of drug abuse history and experience is seen in patient-controlled analgesia studies where opiate analgesics with known addiction potential can be given for medically ill populations to self-administer and yet those without a substance abuse history do not become drug abusers or addicts [95, 246]. Therefore, valid assessment of abuse liability must employ drug-experienced abuser populations in order to gauge what drug abusers will do with a drug of abuse [69, 198, 209]. This is not to say that certain drugs may not have some abuse liability even for normal healthy populations. In fact, studies of stimulant abuse liability [52, 53] among normal college populations observe that amphetamines tend to be preferred over placebo while sedative benzodiazepines are not preferred [35, 109, 110]. Of course, caffeine clearly has reinforcing properties in healthy human populations worldwide [71]. For these reasons, valid inferences about relative changes in abuse liability have to include experimental controls showing base response rates of the study population and study procedures as a point of comparison [69, 198, 209]. For pharmacological studies comparing across drugs, the comparison drug may show greater or less abuse liability than a standard reference drug in the designated population under standard study conditions.

Population-related differences in drug response could be due in part, to genetically controlled individual differences in innate sensitivity [154]. An example of this is found in Asians populations who commonly have the ALDH2*2 allele for aldehyde dehydrogenase which increases levels of the ethanol metabolite acetylaldehyde, resulting in an unpleasant flushing response which reduces the risks of experiencing alcohol-induced euphoria [236, 238]. Another example of this may be found in studies of the children of alcoholic parents where young adult children of alcoholic parents may report greater euphoric response and lesser negative, sedative effects of alcohol than do children without a family history of alcoholism [212].

Role of Craving

Many addicted individuals report that stimulus cues in the environment elicit powerful "cravings" and impulses to use drugs [40, 176, 177]. However, there has been much debate about the meaning of the term "craving" and what role it plays in the risk of drug use [186, 229]. Early pioneering work in the human

laboratory considered craving as a conditioned-withdrawal-like motivational state [249, 250]. With the operant model of drug dependence, it has been argued that "craving" primarily refers to the urge or impulse to use [137]. Still others suggest that craving involves at least three dimensions: (1) withdrawal and negative affect-related escape motivation, (2) reward-related conditioned impulses/urges, and (3) obsessive thoughts and/or cognitive-control mechanisms [41, 229]. Many human laboratory studies have studied cue-induced craving in addicted populations (cf. [24, 41, 176, 177]). These studies provide visual, olfactory, auditory, and/or tactile stimuli historically associated with drug use; though tactile cue procedures of handling drug paraphernalia have been among the most effective stimulus cues [8, 203]. Idiosyncratic script-driven mental imagery techniques also can be used to guide the cue exposure session [215, 216]. Cue responses can be physiological (of which heart rate is the most reliable) or subjective (of which craving is the most reliable) though there often is not a good correlation between the physiological and subjective craving measures [202]. A meta-analysis of the literature [24] concluded that subject ratings of craving were the most reliable and selective reaction to drug cues and showed the largest effect size across studies. Multi-item factor scales have been used in the human laboratory to measure craving for alcohol [17, 210], marijuana [89], or cocaine [78] but many studies commonly use only graded analog scales of single item ratings such as "crave" [103], "desire" [37], "urge", or "want" [52, 53, 244]. Craving ratings sometimes have been correlated with drug use in outpatient studies [88]. However, dissociation between craving ratings and drug-taking behavior have been demonstrated clearly in laboratory studies [42, 81, 142, 186] and the extent of cue-craving observed in the laboratory has not correlated with relapse to alcohol drinking among alcoholics [205]. Thus, craving is neither a necessary nor sufficient precursor to drug use or relapse. Rather, it appears to reflect a parallel cognitive process as proposed by Tiffany [228, 229] or a subjective state experienced as urge or impulse that is associated with drug-related environmental stimuli as suggested by a consensus panel [186]. In either case, "craving" is not a proxy for drug self-administration and may not always predict or be correlated with drug-taking behavior.

Human Laboratory Studies of Pharmacological Agonists and Antagonist Treatments

Human laboratory studies have been useful to help us understand the potential value of various pharmacological approaches to treatment. The potential of using pharmacological agonists or antagonists in the treatment of substance abuse is best illustrated through studies of opiate dependence as described below.

Utility to Evaluate Pharmacological Antagonist Treatments

Early studies of opiate antagonists at the Addiction Research Center showed that they could completely block the subjective and physiological effects of morphine [60, 105, 152] and precipitate withdrawal in dependent individuals [104, 105]. Subsequent studies showed that oral naltrexone [2, 160] blocked heroin self-administration and subjective effects in human laboratory models of drug taking. The robustness of the observed pharmacological antagonism and the nearly complete blockade of any behavioral effects or abuse liability of heroin observed in these studies strongly suggested efficacy for the antagonist approach. However, as we now know, outpatient treatment effectiveness with antagonists like naltrexone is poor [134] because of poor medication compliance among heroin addicts who find it too easy to discontinue antagonist therapy so as to recover the heroin effect they seek. These findings suggest a significant weakness of human laboratory procedures to predict efficacy with antagonist approaches.

Specifically, even perfect blockade of abuse potential does not predict treatment efficacy because medication non-compliance will nullify even complete pharmacological blockade. More recently, human laboratory studies again have evaluated the depot formulation of naltrexone [29, 224] and shown that it will block heroin self-administration and subjective effects. Although there is reason to hope that depot formulations of naltrexone could improve the effectiveness of antagonist treatments, especially in conjunction with court-ordered treatment [183], the outcome data do not yet exist to support it [145]. Notably, because of the diffuse mechanisms of action for alcohol, cocaine, and methamphetamine, direct, receptor-medicated pharmacological antagonists are unlikely to exist for those drugs. For nicotine dependence, human laboratory studies of the nicotinic antagonist mecamylamine have shown increased smoking [169] or increased intravenous nicotine self-administration [207] which is consistent with a surmountable pharmacological blockade. However, another human laboratory study found no effect of mecamylamine [245], and clinically, there is no evidence for treatment efficacy with nicotinic antagonists [22] in outpatient treatment. No efficacy trial has examined the use of the cannabinoid-1 antagonist, anandimide (rimonabant), for cannabis dependence, but early human laboratory studies have shown only partial or inconsistent blockade of the effects of smoked cannabis [98].

Utility to Evaluate Pharmacological Agonist Replacement Approaches

A study at the Addiction Research Center [128] was the first human laboratory study showing that oral methadone produced dose-related decreases in the subjective effects, liking, and self-administration of hydromorphone. Thirty years later, a human laboratory study showed that short-term treatment with methadone doses of 50, 100, and 150 mg showed dose-related blockade of the subjective effects and self-administration of heroin [38]. The authors of this later study used their human laboratory data to argue that clinical tendencies to use lower methadone doses for maintenance are counterproductive. Importantly, these findings exactly parallel the dose equivalence and clinical experience with methadone maintenance treatment [223]. Previous reviews [16, 104, 188] have described human abuse liability testing with a variety of opiate agonists, partial agonists, and mixed agonists/antagonists which demonstrated unequivocally that agonist effects at the mu opiate receptor are responsible for the abuse potential of opiates. In the course of this work, human laboratory studies were critical to the ultimate development of buprenorphine as a partial agonist pharmacotherapy, with a reduced abuse potential [28, 106, 240]. Human laboratory studies were particularly important to demonstrate buprenorphine reduced the reinforcing effects heroin [159] and to demonstrate that small doses of naloxone could be added to buprenorphine to further reduce its abuse potential without precipitating withdrawal in morphine-dependent subjects [162]. These studies illustrate very clearly, a strong concordance between the human laboratory studies and clinical experience with buprenorphine. Furthermore, when compared with the studies and clinical experience with antagonist medications, they suggest that human laboratory studies seeking to antagonize the reinforcing effects of a drug of abuse might look for medications that have at least a partial agonist-like activity. Of course, nicotine replacement strategies for tobacco dependence have been very successful [22] to reduce smoking behavior. Human laboratory studies have shown that smoking [185] and nicotine gum [170] pretreatments each decreased cigarette smoking. Also, transdermal nicotine patches decreased cue-induced craving [230], the discriminative stimulus and reinforcing effects of nicotine spray [184], and reinforcing effects of intravenous nicotine [217]. The partial nicotinic agonist, varenicline, is the first non-nicotine treatment for tobacco dependence approved by the Food and Drug Administration [232], though human laboratory studies evaluating its ability to decrease nicotine reinforcement have not been conducted.

Role of Human Laboratory Studies in Developing Medications for Alcohol Dependence

A brief review of medications which have been or are being developed for alcoholism treatment will be used to illustrate how pharmacological mechanisms other than agonist replacement or direct pharmacological antagonism of the drug of abuse can be exploited in medications development. Currently, there are three medications approved by the Food and Drug Administration for the treatment of alcohol dependence. Additionally, we will discuss human laboratory studies conducted with three other medications which have shown promise in clinical treatment trials.

Disulfiram

Disulfiram (Antabuse®) was the first medication approved by the United States Food and Drug Administration for the treatment of addiction. Human laboratory studies as well as preclinical studies of biochemistry and toxicology were included in the first report of the disulfiram-ethanol reaction which ensues upon alcohol exposure [77]. Over a period of more than 40 years, human laboratory studies have been important to characterize the nature, the safety, and the mechanism of the Antabuse®-alcohol reaction [26, 111, 192, 208]. These studies were instrumental in showing that inhibition of aldehyde dehydrogenase and the subsequent accumulation of the acetylaldehyde metabolite is responsible for the unpleasant effects of the Antabuse® reaction and that a hypotensive crisis is a serious medical risk. Either because of the way the disulfiram makes alcohol effects so unpleasant or because of the direct side effects of disulfiram itself, compliance with this medication is a serious problem limiting its utility and effectiveness for the treatment of alcohol dependence [20, 140]. Consequently, there is little ongoing research in further development of disulfiram as a treatment for alcohol dependence.

Naltrexone

The opiate antagonist, naltrexone was the second medication approved by the Food and Drug Administration for the treatment of alcohol dependence. Based largely upon preclinical studies showing that naltrexone reduced alcohol drinking in rodents, the first clinical trials [180, 235] were Phase III outpatient efficacy trials of a medication that had already been approved for narcotic addiction. Subsequently, human laboratory studies have been useful to demonstrate that naltrexone can reduce alcohol self-administration in some paradigms [40, 181] but not others [39] and has a mixed profile to reduce some of alcohol's positive subjective effects [133, 226] and cue-reactive craving [33, 164, 181, 204]. Naltrexone also has been shown to reduce the behavioral activating effects of alcohol as measured by heart rate increases, subjective liking, and ACTH/Cortisol elevations [156]. This latter finding is interesting given that other studies have shown that parental family histories of alcoholism are associated with greater activation of the hypothalamic-pituitary-adrenal axis at baseline and in response to mu-opioid receptor blockade by naloxone [93] and that these differences may predict naltrexone response [133, 181]. Recently, a study administered naltrexone vs. placebo to 92 non-treatment-seeking, alcohol-dependent subjects for 6 outpatient days before bringing them into the human laboratory for a drink self-administration session [139]. Study findings showed that naltrexone reduced alcohol self-administration in subjects with a positive family history of alcoholism and may actually have increased drinking in subjects without a family history. Though the genes associated with family history are not known, an earlier laboratory study identified a single nucleotide polymorphism of the mu-receptor conferring naloxone-reactive hypothalamic-pituitary-adrenal activation [243] and this same polymorphism recently was shown to predict naltrexone treatment response in Project COMBINE [6]. Overall, these human laboratory studies have shown results consistent

with the outpatient treatment trials concluding that naltrexone is modestly effective to reduce some of the reinforcing but not the subjective effects of alcohol and that this action may block the alcohol-seeking or craving that is primed or cued by the initial doses of alcohol consumed during a binge. Intriguingly, human laboratory studies of the functioning of the hypothalamic-pituitary-adrenal axis may lead to a better understanding of the inherited biologic risk of alcohol dependence and treatment responsiveness with medications such as naltrexone.

Acamprosate

Based largely upon three European treatment trials [138], the Food and Drug Administration approved the glutamate antagonist acamprosate, as the third medication for the treatment of alcohol dependence. Prior to that approval, a human laboratory study examined the safety of the combination of acamprosate with naltrexone in alcohol-dependent subjects [119] as a prelude to the larger outpatient treatment trial known as Project COMBINE which tested the efficacy of acamprosate and naltrexone alone and in combination [6]. Although meta-analyses of several clinical trials have supported the efficacy of acamprosate at preventing relapse in alcohol-dependent individuals [138, 148], Project COMBINE did not demonstrate efficacy at reducing drinking in alcohol-dependent outpatients. Despite a large preclinical literature examining acamprosate's actions and mechanisms [36], only two human laboratory studies have been reported. One study found that acamprosate reduced the heart rate response, but not the subjective craving induced by alcohol cues [182]. Another study administered repeated doses of acamprosate to non-treatment-seeking heavy drinkers in an outpatient setting and brought the subjects into a human laboratory where acamprosate was without effect to alter the subjective or behavioral responses to challenge doses of alcohol [18].

Other Possible Medications for Alcohol Dependence

Two other medications have been reported to have efficacy in the outpatient treatment of alcohol dependence and to be examined in human laboratory studies evaluating possible mechanisms. The serotonin-3 antagonist ondansetron was initially reported to reduce the subjective effects of ethanol in social drinkers [117, 225]. Subsequently, a large clinical trial showed efficacy of ondansetron to reduce alcoholic drinking, at least in Early Onset Alcoholics, but not Late Onset Alcoholics [125]. Serotonergic abnormalities in "biologically predisposed" individuals have been suggested as the mechanism of this differential efficacy [112]. A subsequent human laboratory study reported that the alcohol cue-induced craving of early onset alcoholics may differ as a function of genetic polymorphisms in the serotonin transporter [1]. Topiramate, an anticonvulsant with gamma-aminobutyric acid agonist and glutamate antagonist activity, has been shown to have efficacy to reduce drinking in alcohol-dependent outpatients in two randomized controlled trials [114, 126]. After the initial treatment study evidenced efficacy, a large sample ($n = 61$) human laboratory study was designed to evaluate whether or not these effects of topiramate were due to reductions in craving induced by alcohol cues [163]. In order to reduce some of the adverse cognitive side effects of topiramate, the study included a gradual dose-escalation period of more than 5 weeks where of subjects received placebo, 200, or 300 mg per day during outpatient treatment before they were brought into the laboratory. Interestingly, there was no evidence for topiramate to reduce cue-induced craving in the laboratory. However, investigators did observe that these non-treatment seeking heavy drinkers reported topiramate-related reductions in their drinking during the outpatient dose-run up phase. Though it may be true that topiramate does not block craving in response to alcohol cues, the findings of drinking reductions during the outpatient dose loading procedure are

consistent with the treatment trials. This finding further supports the idea that cue-reactive craving is not well correlated with self-administration behavior.

Hutchinson and colleagues have been studying olanzapine in the human laboratory and in the clinic as a medication having a mixed profile of actions as an antagonist at the D_2, D_4, and serotonin-2 receptors. An initial laboratory study of heavy social drinkers reported that 5 mg olanzapine reduced the urge to drink after exposure to alcohol cues and a priming dose of alcohol [100]. However, a treatment trial in alcohol-dependent outpatients failed to show efficacy of 10–15 mg olanzapine [74]. Subsequently, another laboratory study [99] showed that a functional polymorphism in the dopamine D_4 receptor (DRD4) gene mediates the cue-reactive effects of alcohol and that olanzapine really was only effective to reduce cue-reactivity [102] in the subgroup of subjects having the long (L) form of the variable number tandem repeat for the DRD4 gene. Finally, this investigative group studied a group of alcohol-dependent subjects given 2.5–5 mg olanzapine vs. placebo during a 12-week treatment trial [101]. These subjects were brought into the human laboratory before and after 2 weeks of double-blind treatment and were tested in the cue-reactivity paradigm. The study showed that olanzapine was effective only in the L-carriers where it reduced cue-reactive craving observed in the laboratory and also was effective to reduce alcohol drinking in the outpatient treatment component of the study.

Role of the Human Laboratory to Evaluate Medications for Cocaine Dependence

At least partly because of lack of interest from major pharmaceutical manufacturers, the National Institute on Drug Abuse has maintained an active Medications Development Program [45, 233, 234] which has included Phase I, II, and III clinical trials directed to evaluate and possibly develop medications to treat cocaine and methamphetamine dependence. Through research funded mostly by the National Institute on Drug Abuse, many different potential medications with a variety of different pharmacological mechanisms have been tested in Phase II and III efficacy trials looking for a medication to treatment cocaine dependence. Several recent reviews have described the different medications that have been evaluated for the treatment of cocaine dependence and so the reader is referred to those articles for further information [62, 65, 218, 234]. Although there have been some promising developments from these studies, no medications have yet been proven effective or approved by the Food and Drug Administration. Cocaine acts to inhibit monoamine transporters although the mechanism of action related to addiction is believed to be primarily through actions on the dopamine transporter to enhance dopamine activity in brain reward neurocircuitry. Consequently, many pharmacological studies have targeted dopamine synthesis, receptors, and the reuptake transporter. Additionally, other medications targeting other neurochemical modulators of the brain reward pathways also have been studied.

Evaluation of Dopamine Agonists and Antagonists for Cocaine Treatment

Several human laboratory studies have examined the ability of dopamine antagonists to reduce cocaine-induced subjective effects or self-administration. In cocaine-dependent individuals, haloperidol antagonized cue-elicited craving [13]. In subjects with cocaine abuse or dependence, risperidone [172] reduced the subjective effects of cocaine, but flupenthixol [47] had no effect on cocaine subjective effects or self-administration. Again, in subjects with cocaine abuse or dependence, the $D_{1/5}$ antagonist ecopipam reduced cocaine's subjective effects acutely [206]; however, these effects were not replicated in a study employing repeated ecopipam dosing [167] or in a study of smoked cocaine where ecopipam actually increased the subjective and reinforcing effects of cocaine [84]. These results suggest that at

best, dopamine antagonists produce variable and inconsistent reductions in positive subjective effects of cocaine. The overall conclusion from these and other studies do not support the utility of dopamine antagonist treatments [28, 65, 67, 234]. Furthermore, they suggest that direct and potentially unpleasant side effects of treatment with dopamine antagonists could actually enhance the reinforcing effects of cocaine which could explain the increase in cocaine use observed in an outpatient treatment study using olanzapine [130].

Human laboratory studies also have examined the effects of direct acting dopamine agonists. The D2 agonist, bromocriptine was shown to reduce the blood pressure elevations but enhance the heart rate effects of cocaine and it caused undesirable "fainting" without changing cocaine's subjective effects [190]. Another D2 agonist, pergolide [81] reduced the subjective effects but did not alter cocaine self-administration. The D1 agonist ABT-431 was reported also to reduce the subjective effects and blood pressure but enhance the heart rate effects of cocaine without altering cocaine self-administration [80]. Two dopamine partial agonists also have been examined. Amantidine had no effect on the cardiovascular or subjective effects of cocaine or on cocaine self-administration [27] and aripiprazole was actually reported to increase cocaine subjective effects [144] and self-administration [82]. Though not acting directly upon the dopamine receptor, but rather indirectly upon the dopamine transporter, bupropion was found only to produce slight alterations in cocaine-related subjective effects [179]. The general lack of positive results in these human laboratory studies is consistent with the lack of efficacy of dopamine agonists, partial agonists, and bupropion in the outpatient treatment of cocaine dependence [65, 237].

Evaluation of Stimulant Replacement Strategies for Cocaine

In contrast to the disappointment with dopamine agonists and antagonist approaches, studies examining the use of psychomotor stimulants in a stimulant "replacement"-type of reproach [65, 67, 200] have been more encouraging. The basis for stimulant use is related to the clinical experience with opiate and tobacco dependence where harm-reducing pharmacological-replacement treatments have demonstrated efficacy. An intriguing 5-week inpatient human laboratory study showed that gradually increasing oral doses of cocaine (25–100 mg/kg 4 times daily) produced modest reductions in the subjective effects of intravenous challenge doses of cocaine without potentiating the cardiovascular effects of cocaine [241]. Previous human laboratory studies have shown that cocaine binges are associated with substantial "acute" tolerance where most of the subjective and cardiovascular effects of cocaine are seen with the initial dose and subsequent doses only serve to maintain the initial effect without adding additional effect [3, 54, 57, 58]. When combined with data that speed of onset is an important determinant of euphoria [168], the efficacy of the oral cocaine pretreatment is likely due to the lesser euphoria resulting from the oral pretreatment dose of cocaine coupled with cross-tolerance to the acute effects of the additional cocaine challenge doses. This is exactly analogous to what is believed to occur with methadone maintenance and is similar to that observed in a human laboratory study where experimenter-administered doses of heroin given on top of methadone pretreatment show diminished responses [38]. Nonetheless, concerns about the ethics or social acceptance of cocaine-replacement approaches for cocaine addiction are likely to limit consideration of this approach. Thus, most studies of the agonist-like replacement approach [65, 67, 200] have examined dopamine reuptake inhibitors and stimulant drugs other than cocaine. Although human laboratory studies with cocaine have reported substantial tolerance to the cardiovascular acceleration that occurs within a cocaine binge [54, 57, 58], there still are substantial cardiovascular safety concerns regarding the possible drug-drug interactions between cocaine and other stimulant drugs. Thus, human laboratory studies evaluating medications with possible

stimulant profiles must address the safety of this drug interaction. Actually, for any medication to be approved by the Food and Drug Administration for use in humans, Phase I and early Phase II safety testing including drug-drug interaction studies are required and human laboratory studies are required to achieve this end.

A double-blind, placebo-controlled efficacy trial examined the effects of placebo and two doses of oral dextroamphetamine as a treatment for cocaine-dependent outpatients [64]. That study included a human laboratory component which gave the outpatients their initial double-blind dose in a controlled environment as part of a safety assessment [200]. In the laboratory assessment component, dextroamphetamine showed characteristic stimulant effects including mild elevations of subjective effects and euphoria, and there were no limiting adverse events observed. Coupled with treatment findings showing dose-related increases in treatment retention and reduced cocaine use without evidence of abuse or diversion of dextroamphetamine, these data suggest stimulant therapy for cocaine dependence may be a reasonable approach. In another study taking the same approach with methylphenidate, the human laboratory component found that methylphenidate produced adverse stimulant effects but not subjective euphoria in the cocaine-dependent population [196]. Interestingly, methylphenidate also was not efficacious in the main outpatient treatment trial either [66]. Thus, these two studies, conducted in treatment-seeking individuals, show a good correspondence between the human laboratory findings and treatment outcome and further suggest that the positive subjective effects of dextroamphetamine may be an essential component of efficacy in the stimulant-replacement approach to treatment of cocaine dependence [65, 67, 200].

Still the question remains about the safety of the cocaine + stimulant drug interaction in cocaine-dependent populations. Several human laboratory studies have evaluated the cardiovascular safety and abuse liability of giving combinations of cocaine plus other stimulants. In one such study [189], acute dosing with mazindol did not substantially alter the acute subjective effects of cocaine, but it significantly enhanced the blood pressure and heart rate elevations produced by intravenous cocaine leading the authors to suggest that mazindol would not be a desirable treatment. A follow-up clinical treatment trial in cocaine-dependent methadone maintenance participants did not find mazindol vs. placebo differences in outcome [150] although, importantly, there was no evidence for harmful or counter-therapeutic effects of mazindol either. Another study gave up to 30 mg oral dextroamphetamine in combination with up to 96 mg intranasal cocaine to non-treatment seeking cocaine abusers and reported that there were no significant potentiating effects on cardiovascular measures [194, 195, 200]—a finding that generally was supported in the outpatient trial of dextroamphetamine for cocaine dependence [64]. In yet another study [32], modafinil blunted several subjective effects and even the systolic blood pressure increases produced by intravenous cocaine infusion. This human laboratory study was followed up by the National Institute on Drug Abuse in clinical treatment trial which found that modafinil was superior to placebo to reduce cocaine use among the subgroup of individuals without a comorbid alcohol use disorder, but it was not effective amongst the subgroup of individuals who had a comorbid alcohol use disorder [44]. Overall, these human laboratory data clearly predicted that stimulant medications with lesser abuse potential than cocaine could be given safely to cocaine-dependent populations with a reasonable expectation that individuals would benefit from a stimulant-replacement approach to treatment.

Evaluation of Cocaine Treatments Affecting Other Neurochemical Systems

A number of other pharmacological approaches to treatment for cocaine dependence also

have been evaluated in the human laboratory. Aside from dopamine, several studies have attempted to alter other monoamine neurotransmitter levels (i.e., norepineprine and serotonin). Catecholamine depletion by means of consuming a tyrosine-depleting amino acid beverage was shown to reduce cue and low dose cocaine-induced craving for more cocaine, but did not alter cocaine-induced euphoria or self-administration [142]. The monoamine oxidase-B inhibitor selegiline, which should increase catecholamine levels including dopamine, was reported to have no effect [75] or to reduce [97, 171] the subjective effects of cocaine. Two studies [50, 135] reported that the catecholamine reuptake inhibitor desipramine increased baseline blood pressures, decreased cocaine craving, and altered the positive subjective effects of cocaine without altering the high or self-administration of cocaine. Blockade of the serotonin transporter with fluoxetine was reported to reduce the subjective euphoria of cocaine in one study [242] but not another study [85]. These human laboratory studies indicate that at best, medications which alter serotonin or norepinephrine activity in general do not have robust effects to alter cocaine euphoria or reinforcement and so it is no surprise that outpatient treatment trials with these medications have not been positive either [65, 234]. In cocaine using research volunteers, the gamma-aminobutyric acid reuptake inhibitor tiagabine, had no effect on the subjective or reinforcing effects of oral cocaine [143] and the gamma-aminobutyric acid agonist gabapentin reduced the subjective effects but not self-administration in cocaine-dependent subjects [87]. Each of these pharmacological approaches has been evaluated in clinical trials and none have been found to efficacious [65, 234].

Several human laboratory studies have examined the effects of antihypertensive calcium channel blockers in cocaine dependence. As cerebrovascular vasodilators, they have been suggested as possible treatments of vascular stroke and cognitive impairment related to cocaine dependence [63, 118]. In this regard, isradipine was shown to reduce the ischemic effects of cocaine infusion [116]. In other laboratory studies in cocaine-dependent subjects, nifedipine [166], nimodipine [136], and isradipine [121] were shown to block the blood pressure elevating effects of cocaine in subjects but not the stimulant or euphoric subjective responses. Following both acute [121] and repeated dosing [127] with isradipine, the reduction in cocaine-related pressor effects was also associated with an exacerbation of cocaine-related heart rate increases. Additionally, repeated dosing with isradipine was shown to produce headaches and other unpleasant effects and to increase the positive and reinforcing effects of intravenous cocaine infusion [199]. Given these laboratory results as noted above, it is no wonder that a 12-week trial of amlodipine for the treatment of cocaine-dependent outpatients was plagued by high drop-out rates, and failed to reduce cocaine craving or cocaine use more than was seen with placebo treatment [146].

Two other medications have shown efficacy in human laboratory and outpatient treatment studies, but are not likely to be pursued as treatments for primary cocaine dependence for safety reasons. The mu-receptor partial agonist, buprenorphine, was shown in two studies to reduce cocaine self-administration. One study in intravenous heroin and cocaine users reported that buprenorphine decreased intravenous cocaine self-administration, but it also potentiated several subjective effects including euphoria and sedation [55]. Another study in cocaine-dependent methadone maintenance participants found that substitution to buprenorphine was superior to continued methadone maintenance to decrease desire ("I want") for cocaine and self-administration behavior without altering other subjective effects [56]. Despite these positive results, the abuse potential of buprenorphine coupled with its potential for physiological dependence, make its use for primary cocaine dependence unlikely. Nonetheless, it still may be useful to decrease cocaine use in buprenorphine-maintenance therapy for opioid dependence [165]. A second medication, shown

to have efficacy in the outpatient treatment of cocaine dependence [23], is the alcoholism treatment agent disulfiram. Several human laboratory studies have shown that disulfiram inhibits cocaine metabolism and increases cocaine blood levels and its cardiovascular effects [79, 155]. Although those initial studies reported no significant alteration of cocaine's subjective effects, a more recent study [9] reported that disulfiram decreased cocaine-induced subjective high. The putative mechanism for efficacy of disulfiram in the treatment of cocaine dependence is presumed to be due to its inhibition of dopamine beta-hydroxylase [218]. However, because of disulfiram's inhibition of cocaine metabolism and its side effect profile, there are concerns about its safety as a treatment for primary cocaine dependence. Because alcohol may be consumed by a cocaine-intoxicated individual treated with disulfiram, the safety of an Antabuse®-alcohol reaction was evaluated in subjects with cocaine abuse or dependence in a 3-way drug interaction study (Roache JD. An early initial report of this study was presented at CPDD [239], but now the study data are complete and being analyzed for final publication, "unpublished observations"). That study found that alcohol administration was associated with clinically significant hypotension and increased heart rate in subjects given 5–7 days of disulfiram (250–500 mg) pretreatment. Intravenous infusion of 30 mg cocaine under these conditions counteracted the hypotension but tended to potentiate the heart rate effects. However, safety stop-point criteria prevented the administration of cocaine in two of three subjects who were hypotensive due to an Antabuse®-alcohol reaction in subjects treated with 500 mg disulfiram. This human laboratory study illustrates the safety concerns of using disulfiram in the treatment of cocaine dependence. Nonetheless, a review of the safety data from a number of published studies administering disulfiram to cocaine-dependent outpatients and to patents with dual cocaine-alcohol dependence has concluded that it can be safely used for cocaine treatment [147].

Human Laboratory Studies of Medications for Amphetamine or Methamphetamine

Evaluation of Dopaminergic Treatments for Methamphetamine

In normal healthy volunteers, acute doses of pimozide failed to reduce the subjective effects of amphetamine [19] and neither haloperidol nor risperidone reduced the euphoric effects of methamphetamine [237]. In subjects with histories of amphetamine abuse or dependence, acute doses of haloperidol did reduce positive subjective effects of amphetamine [211], as did repeated doses of chlorpromazine and to a lesser extent pimozide [129]. However, these mixed findings focusing on subjective effects are similar to those seen using dopamine antagonists for cocaine dependence. There is no reason to believe that dopamine antagonists will be any more successful for amphetamine or methamphetamine dependence than they have been for cocaine [67]. The partial D2 receptor agonist, aripiprazole, has been evaluated in two human laboratory studies and in one outpatient treatment trial. In normal healthy subjects, acute doses of aripiprazole produced dose-related reductions in the discriminative stimulus, subjective effects, and cardiovascular increases produced by d-amphetamine [220]. In methamphetamine-dependent volunteers, two weeks of treatment with aripiprazole did not increase cue-induced craving for methamphetamine, but did increase methamphetamine-induced stimulant and euphoric subjective effects, and increased baseline levels of desire for methamphetamine [175]. These data in non-treatment seeking methamphetamine-dependent subjects clearly suggest that aripiprazole would be counter-therapeutic as a treatment for methamphetamine. In an clinical treatment trial of amphetamine-dependent outpatients, a three-arm comparison study was stopped early in the trial, because an interim analysis showed that aripiprazole increased amphetamine use

relative to placebo, while methylphenidate was significantly better than placebo [231]. These data clearly indicate that dopamine agonist treatments may be counter-therapeutic for the treatment of amphetamine/methamphetamine dependence. However, the one study with methylphenidate, and several with bupropion suggest that dopamine reuptake inhibitors may be beneficial for the treatment of amphetamine/methamphetamine dependence. In methamphetamine-dependent research volunteers, a Phase I safety study showed that repeated oral doses of bupropion reduced both the cardiovascular pressor effects of methamphetamine as well as the subjective high and liking produced by intravenous infusion of moderate doses of methamphetamine [173, 174]. Subsequent to this human laboratory study, a multisite treatment trial [46] found that bupropion was superior to placebo to reduce methamphetamine use in outpatients who used less frequently than daily, but not in frequent daily users (Elkashef A, "personal communication", reported that a reanalysis of these data showed that bupropion was superior to placebo in all subjects using methamphetamine less frequently than daily.

Evaluation of Methamphetamine Treatments Affecting Other Neurochemical Systems

In two human laboratory studies conducted in healthy volunteers, ondansetron, was reported to produce modest reductions of positive subjective effects of amphetamine [68] or to reduce the amphetamine-induced decrease in hunger [214]. However, a treatment trial using varying doses of ondansetron in methamphetamine-dependent outpatients did not show evidence of efficacy [115]. The *N*-methyl-*D*-aspartate antagonist memantine was reported to alter the discriminative stimulus effects of methamphetamine in healthy subjects with limited histories of cocaine or amphetamine use [86]. Importantly, memantine also produced positive stimulant-like subjective effects of its own and did not reduce those produced by methamphetamine. In methamphetamine-dependent volunteers given intravenous methamphetamine, acute doses of the anticonvulsant topiramate produced sedative and undesirable side effects by itself and enhanced the positive subjective effects [122] and reduced the perceptual-motor facilitating effects [123] of methamphetamine. These human laboratory studies are consistent with the findings of a pilot outpatient treatment study where topiramate was not helpful to reduce methamphetamine use (Johnson BA, A NIDA-sponsored, multisite trial using topiramate treatment for methamphetamine dependence failed to show evidence of efficacy vs. placebo "personal communication"). In healthy volunteers, acute doses of isradipine reduced some of the positive subjective effects produced by methamphetamine and increased ratings of "I could refuse" [124]. In subjects with methamphetamine dependence, a within-subject crossover design found that repeated doses of isradipine reduced euphoria and positive subjective effects of methamphetamine but only when placebo treatment occurred first and not when isradipine treatment occurred first [120]. Although isradipine did reduce blood pressure elevations produced methamphetamine, it also enhanced the heart rate effects [127]. Though no treatment study has been attempted to our knowledge, the potential for tachycardic interactions between isradipine and methamphetamine are considered a sufficient concern to preclude further development.

General Conclusions Regarding Human Laboratory Studies

Methods to assess the abuse liability of multiple classes of drugs of abuse in human subjects tested in experimental laboratory environments are well established and validated. Increasingly, over the past decade, the human abuse liability assessment model has been used to examine

the drug interaction of candidate medication treatments with opiates, alcohol, cocaine, and methamphetamine. This review illustrated the: (1) results with the agonist/antagonist approaches that have been the basis for the treatment of opiate and nicotine dependence; (2) mechanistic evaluation of approved and potential medications for alcohol dependence, and (3) numerous medications that have been evaluated as possible treatments for cocaine and methamphetamine dependence. Useful and important information from these studies has helped to advance our understanding of the safety, mechanism, and possible efficacy of different pharmacological approaches to treatment and has contributed to the development of specific agents for treatment. Several general conclusions are possible from this review.

Human laboratory studies of direct pharmacological agonist or antagonist therapy mostly have been possible only in the study of opiate and nicotine dependence where opiates and nicotine act directly and selectively upon specific neurotransmitter systems. Here it is notable, that human laboratory studies of the effects of agonist replacement therapy with nicotine replacement, methadone, and buprenorphine have played an important role to verify possible efficacy and understand the mechanism(s) involved in such drug-drug interactions. Conclusions from the human laboratory studies showing that agonist replacement produces cross-tolerance with commensurate reductions in euphoria and reinforcing effects are consistent with outpatient treatment trials showing efficacy with agonist replacement strategies for nicotine and opiate dependence. However, human laboratory studies with antagonist treatments generally have produced false positive results because, though a pharmacological antagonist shows perfect efficacy in the human laboratory, clinical experience reveals poor effectiveness of antagonist treatment due to poor medication compliance. Though behavioral/legal contingencies may be useful to enhance compliance and efficacy of antagonist therapy, this is not a strategy that is generally available in community practice.

Although human laboratories are increasingly being used in studies of medications for alcohol dependence, disulfiram, naltrexone, and acamprosate were developed without the benefit of those studies. Nonetheless, newer putative treatments are increasingly being studied in the human laboratory and even the existing treatments are being studied using human abuse liability methods to better understand the possible biobehavioral mechanism(s) for the actions of these medications. Notably, the laboratory study results showing that disulfiram and naltrexone can reduce the euphoric and reinforcing effects of alcohol are generally consistent with the outpatient treatment literature. Again, though human laboratory studies did reveal the aversive and unpleasant effects of the Antabuse®-alcohol reaction, it took clinical experience to recognize that this would be a limitation on effectiveness due to poor compliance.

Many different pharmaceutical approaches have been tried for cocaine and methamphetamine dependence treatment. Since none have proven generally useful or effective, it is difficult to gauge exactly the extent to which the human laboratory results have been helpful towards this objective. Nonetheless, this review has suggested that in general, the results from the human laboratory studies have been consistent in the following ways. First, direct acting dopamine agonists and antagonists generally have not been effective in either the human laboratory or in the outpatient clinical setting and there is some evidence from both the laboratory and clinic that dopamine agonists may actually be countertherapeutic. Second, human laboratory experiments with agonist-like replacement strategies using stimulant medications have been valuable to show possible efficacy and the safety of this approach. These findings are consistent with the results of outpatient treatment trials showing efficacy with D-amphetamine, modafinil, or bupropion. Third, though there are some false positive results from human laboratory studies showing treatment-related reductions in cocaine or methamphetamine effects, we conclude that many of these suffer from limitations related to studying healthy volunteers rather than

drug-dependent populations and/or because of a focus on craving/subjective effects rather than self-administration. Fourth, the human laboratory plays an indispensible role to enable Phase I, II safety evaluations of medication effects in the target population both with and without the addition of the drug interaction between the treatment and cocaine/methamphetamine.

Finally, this review shows that when one recognizes the strengths and limitations of human laboratory methods in the medication development process, it is clear that these kinds of studies are valuable and will play an increasingly important role in the evaluation of the mechanism, safety, and possible efficacy of putative treatment agents for alcohol, cocaine, and methamphetamine. Though it has not been discussed specifically, it is reasonable to suggest that human laboratory methodological approaches are useful to evaluate medication treatments for other drug dependencies as well.

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Conditioning of Addiction

M. Foster Olive and Peter W. Kalivas

Contents

Introduction

It is widely held that drug use is initiated because of the ability of these substances to produce feelings of pleasure and well-being (i.e., euphoria). Over time, however, tolerance develops to the euphorigenic properties of many drugs of abuse, which perpetuates drug-seeking behavior by leading the user to increase the dose and/or frequency of drug use in order to obtain the euphoria that was previously experienced (so-called "chasing the dragon"). With repeated drug use, the user begins to form associations between the subjective effects of the drug and environmental stimuli that are associated with the drug. These associations are formed by classical (Pavlovian) conditioning processes, and the types of stimuli or "cues" that become paired with drug use can be spatial, visual, auditory, tactile, olfactory, temporal, or interoceptive in nature. Examples of such stimuli include drug paraphernalia, the location in which the drug is repeatedly taken, the smell of alcohol or tobacco smoke, or the time of day. Since drug addicts do not typically live under conditions in which they are isolated from drug-associated cues (a possible exception being an addict who has been incarcerated or placed in a residential treatment program), active drug addicts typically encounter these drug-associated environmental stimuli on a daily basis. This repeated exposure to drug-associated stimuli can elicit expectation of drug availability or memories of previous euphoric experiences under the influence of a particular drug, which may in turn result in drug craving and drug-seeking behavior, leading ultimately to the perpetuation of drug self-administration and the addiction cycle [21, 43, 48, 51, 99, 121, 137, 140].

Most drugs of abuse are ingested in cyclic patterns consisting of active drug self-administration followed by abstinence. During the abstinence phase, the repeated emergence

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_8,

of withdrawal symptoms may result in conditioned associations between environmental stimuli and the negative affective state (i.e., depression, anxiety, irritability, etc.) that typically manifest during withdrawal. As a result, withdrawal-associated environmental stimuli may also trigger drug-seeking behavior to alleviate the evoked negative affect via negative reinforcement processes (i.e., removal of withdrawal-induced dysphoria).

The neurobiological basis of conditioning of drug addiction has been significantly advanced by 1) the development of various animal models of drug-environment conditioning and 2) human imaging studies in which brain activity is monitored during exposure of an addict to drug-associated stimuli. In this chapter, we will discuss four of the most widely used animal models of drug conditioning: the conditioned place preference paradigm, cue-induced enhancement of drug-self administration, second-order schedules of reinforcement, and cue-induced reinstatement of drug-seeking behavior. We will then summarize key findings from studies using these paradigms on the neural substrates of drug conditioning. Next, we will discuss the findings from human brain imaging studies that have revealed specific neuroanatomical loci that are involved in processing information regarding drug-associated stimuli. Finally, from a treatment perspective, we will discuss recent progress in using behavioral and pharmacological therapies to facilitate the extinction of drug-environment associations, as well as to attenuate cue-evoked drug craving and relapse.

Methods for Assessing the Conditioned Effects of Drugs of Abuse in Laboratory Animals

Like human beings, laboratory animals including rats, mice, dogs, and non-human primates are able to form associations between environmental stimuli and appetitive rewards such as food, sweetened substances such as sucrose, and euphorigenic drugs of abuse. These species are also able to form similar associations between environmental stimuli and aversive events such as the presentation of an electric shock or the experience of drug withdrawal symptoms. The most notable experimental studies on this type of "conditioning" were conducted in the late nineteenth and early twentieth centuries by noted Russian physiologist Ivan Pavlov [107]. Pavlov noted that experimental dogs began to salivate in anticipation of the presentation of food. Eventually, Pavlov was able to elicit salivation in these dogs by presentation of a discrete environmental stimulus (the sounding of a bell) immediately prior to the presentation of food. These landmark studies, for which Pavlov was awarded the Nobel Prize in Physiology and Medicine, were the first to describe the phenomenon of "classical" or "Pavlovian" conditioning, where a previous neutral stimulus (i.e., the sound of a bell, serving as the "conditioned" stimulus) becomes associated with a naturally appetitive stimulus (i.e., food, the "unconditioned" stimulus). Eventually, with repeated conditioning, the organism learns to predict the availability of the unconditioned stimulus upon presentation of the conditioned stimulus, and thus the conditioned stimulus becomes motivationally salient.

In the context of drug addiction, classical conditioning is a widely prevalent phenomenon, such that during the course of repeated drug-taking behavior, environmental stimuli associated with the drug (i.e., the conditioned stimulus, such as the smell of tobacco smoke or the sight of a hypodermic syringe) become associated with and eventually predict the availability of the drug (i.e., the unconditioned stimulus). The chronic nature of drug addiction allows for numerous pairings of the conditioned stimulus and unconditioned stimulus, to the point that the conditioned stimulus becomes motivationally salient to the addict. In the case of an addict attempting to abstain from drug use, encountering a conditioned stimulus can provoke intense drug craving, which leads to drug-seeking behavior and greatly increases the propensity for relapse.

The neural basis of classical conditioning has been studied for decades at the cellular and molecular levels from *in vitro* preparations to the behavioral analysis of animals and humans. Here, we will briefly summarize four of the most commonly used behavioral paradigms in laboratory rodents that are designed to investigate the phenomenon of conditioning factors in drug addiction. These include the conditioned place preference paradigm, cue-induced enhancement of drug-self administration, second-order schedules of reinforcement, and cue-induced reinstatement of drug-seeking behavior.

Conditioned Place Preference

In the *conditioned place preference paradigm*, an animal learns to associate the effects of a passively administered substance with the environment in which the drug was received. A typical conditioned place preference apparatus is shown in Fig. 1, and consists of two compartments with unique tactile and visual characteristics (i.e., striped walls and mesh flooring in one compartment vs. transparent or solid walls and metal bar flooring in the other). Occasionally, distinct

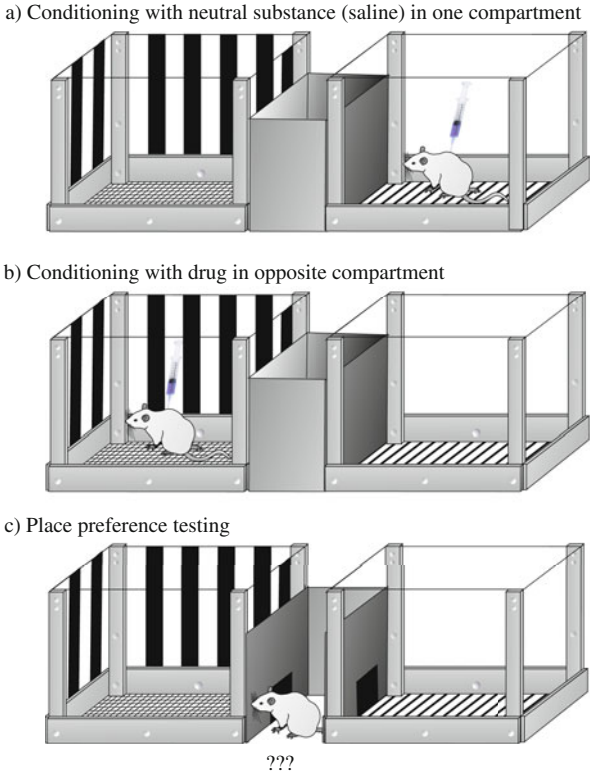

Fig. 1 The conditioned place preference paradigm. (**a**) Following a pre-conditioning test to habituate the animal to the conditioned place preference apparatus and to detect any innate bias toward one of the conditioning compartments, the animal is injected with a neutral substance, such as saline, and confined to one of the two contextually distinct conditioning compartments for a fixed amount of time. (**b**) After a period of several hours or on the following day, the animal is injected with a drug of abuse, such as cocaine, and confined to the other compartment for the same amount of time. (**c**) Following several days of conditioning, the animal is then placed in the center "start" compartment and is given the opportunity to enter either compartment at will (as indicated by *question marks* in the figure). Most abused drugs reliably produce a preference for the drug-paired environment over the saline-paired environment. The front wall of the start compartment in panel c is removed to show the location of the animal

olfactory cues are used in each compartment. These two "conditioning" compartments are connected by a neutral center "start" compartment. Each compartment is typically equipped with photobeams located just above the floor that can detect the presence of the animal and concurrent locomotor activity and record them via an interfaced computer.

In a typical conditioned place preference experiment, an animal undergoes baseline preference testing and habituation, whereby it is placed in the center start compartment and allowed free access to both conditioning chambers for a set amount of time (i.e., 30 min). This allows for the animal to habituate to the testing environment as well as for the experimenter to determine whether the animal exhibits any innate bias toward one of the two conditioning compartments. (An ideal conditioned place preference apparatus would produce no innate preferences for either compartment.) This first period of access to the conditioning compartment also serves as a preconditioning test, and the time spent in either compartment can later be compared against the same variable after conditioning with the drug. Following this habituation and preconditioning test, the animal is injected with a neutral substance (i.e., saline) and is then confined to one of the two conditioning compartments (using automated or manual guillotine-type doors) for a fixed period of time. On the following day, the animal is injected with the conditioning drug (e.g., morphine, cocaine, amphetamine, etc.) and confined to the other conditioning compartment for the same amount of time. These conditioning trials are repeated in an alternating fashion (i.e., saline-drug-saline-drug-. . .) a number of times so the animal learns to associate the unique physical characteristics of the drug-paired compartment with the subjective effects of the conditioning drug. Finally, on the test day, the animal is placed back in the center compartment in a drug-free state and is allowed free access to both conditioning compartments for the same amount of time as during the preconditioning test. If the animal spends significantly more time in the drug-paired compartment than in the saline-paired compartment, conditioned place preference has been established, reflecting the animal's association of the drug compartment with the subjective (presumably pleasurable or "rewarding") effects of the drug. Conditioned place preference has been demonstrated in rodents for all drugs of abuse [9, 115, 129, 130], although the experimental procedures may vary by the drug and its individual pharmacokinetic properties. Conditioned place aversion is observed if the animal spends significantly less time in the drug-paired compartment than in the saline-paired compartment. Withdrawal from chronic drug exposure reliably produces conditioned place aversion. In addition, some drugs such as ethanol can also produce conditioned place aversion if the peak positive subjective effects of the drug are not timed and paired correctly with the drug-conditioned compartment [31, 32, 112].

One advantage of the conditioned place preference paradigm is that the experiments are relatively simple, inexpensive, and less time-consuming to conduct than more involved procedures such as intravenous drug self-administration. In addition, conditioned place preference paradigms can be used to simulate various aspects of relapse. This is accomplished in one of two ways: (1) extinguishing an established conditioned place preference by repeatedly pairing the previously drug-paired compartment with saline, or (2) allowing the conditioned place preference to dissipate over a period of several weeks by repeated testing of place preference. Then, drug priming or stress can be introduced to the animal to reinstate the original conditioned place preference, a phenomenon that has been hypothesized to model drug-seeking behavior [75, 97, 138].

Despite its simplicity and ease of use, there are several disadvantages of the conditioned place preference paradigm. First and foremost, the animals do not actively self-administer the drug; it is passively administered as a bolus injection by the experimenter. In addition to potential pharmacokinetic differences in plasma and brain levels of the drug between passive and active self-administration, a substantial

amount of evidence has accumulated showing that active versus passive drug administration produces significant differences in neurochemical, endocrine, and other responses to drugs of abuse [42, 66, 76, 77, 123, 124]. These differences may underlie some of the discordant findings between studies using pharmacological or other experimental manipulations in the conditioned place preference paradigm and those utilizing active self-administration. In addition, the primary dependent variable measured in the conditioned place preference paradigm does not directly measure drug-seeking behavior but, rather, the motivation for drug-associated environments. Despite these limitations, the conditioned place preference paradigm undoubtedly has provided useful information on the neural substrates that underlie drug-environment conditioning and their contribution to addictive behaviors, as will be discussed later in this chapter.

Cue-Induced Enhancement of Drug Self-Administration

One of the most widely used paradigms to study drug addiction in animals is the intravenous self-administration paradigm (Fig. 2). In the case of rodents, a rat or mouse is surgically implanted with an indwelling intravenous catheter into the jugular or femoral vein, which exits the skin on the dorsal side of the animal and is connected to a vascular access port. Following recovery from surgery, the animal is placed in a self-administration apparatus chamber equipped with one or two levers that are interfaced to a computer and a syringe pump. In lieu of levers, some investigators utilize a nose-poke hole on the wall of the self-administration apparatus, whereby a nose-poke into the correct hole triggers the delivery of a reinforcer. A positive reinforcer is defined as a stimulus that increases the likelihood the response will occur again in the future

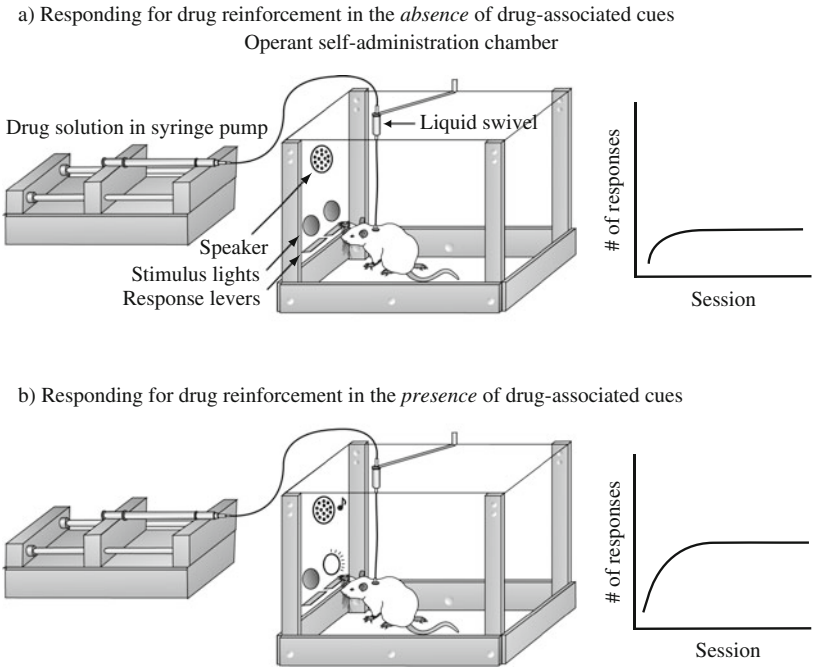

Fig. 2 Cue-induced enhancement of drug self-administration. (**a**) Animals trained to perform an operant task (such as a lever-press or nose-poke) in the absence of simultaneous presentation of any discrete cues (i.e., light, tone, or olfactory stimulus) show relatively low levels of responding for the drug alone. (**b**) In animals trained to self-administer the drug with concomitant presentation of discrete cues, responding for drug reinforcement is increased

(e.g., an addictive drug), while a negative reinforcer is defined as a stimulus that decreases the likelihood the response will occur again (e.g., an aversive stimulus such as an electric shock). In order to learn the operant task (i.e., lever-press or nose-poke), the animal is often initially trained to perform the task in order to receive a natural reinforcer such as a food or sucrose pellet. (The animal is mildly food-restricted to increase its motivation to seek food during initial training.) However, not all investigators use this initial food restriction and training, since it changes the nutritional and metabolic state of the animal. Instead, some investigators may choose to capitalize on the intrinsic exploratory nature of rodents, since over time the animal will eventually exert the correct operant response, receive an intravenous drug infusion, and, with repeated training sessions, learn that this correct response results consistently in the delivery of the drug solution.

The drug solution is delivered by a computer-controlled syringe pump located outside the self-administration apparatus. The pump contains a drug solution that is connected to a single-channel liquid swivel, which allows free rotation of the animal while maintaining a continuous flow of fluid. Plastic tubing is then housed in a stainless steel spring tether and is attached to the animal via a vascular access port implanted on the dorsal side of the animal, which is connected to the indwelling venous catheter.

In the case of alcohol, intravenous self-administration procedures are used less frequently since this method lacks the face validity and pharmacokinetics of human oral alcohol consumption, and the ability of intravenous ethanol to function as a reinforcer is less reliable. Thus, most animal models of alcohol self-administration utilize an experimental apparatus by which—instead of a syringe pump delivering the drug solution intravenously—a dilute ethanol solution (usually 8–12% v/v) is delivered into a receptacle located near the lever or nose-poke orifice, where the animal can consume it orally. However, because of the aversive orosensory nature of ethanol, many researchers often initially train animals to consume alcohol solutions sweetened with sucrose or saccharin to increase its palatability. Then, slowly over a period of weeks, the concentration of the sweetener is gradually reduced until eventually the animal performs the operant task to consume an unsweetened ethanol solution.

There are many advantages of the operant self-administration paradigm as a model for human drug-taking behavior, including: (1) the drug is administered voluntarily by the animal (as opposed to passive administration by an experimenter); (2) the drug-taking behavior can be temporally examined within and between self-administration sessions; (3) candidate therapeutic pharmacological compounds or other experimental manipulations can be administered to determine their effects on drug self-administration; (4) the number of responses that must be exerted by the animal in order to receive the drug can be gradually increased (called a "progressive ratio") until the animal "gives up" and no longer performs the operant task (called the "breakpoint")—this method is used to measure the level of motivation to self-administer the drug as well as the efficacy of the reinforcer, and, finally, (5) the procedure is amenable to the study of relapse-like behavior (see Section "Cue- and Context-Induced Reinstatement of Drug-Seeking Behavior").

One additional advantage of operant self-administration procedures is their amenability to the study of the role of conditioned cues in the reinforcing effects of drugs of abuse. In addition to delivery of the drug, many researchers also use environmental cues such as the presentation of stimulus light, auditory tone, olfactory cue, or combinations thereof that are simultaneously paired with the intravenous delivery of the drug solution. Over successive self-administration sessions, the animal learns to associate these cues with availability of the drug and its pharmacological effects. Studies have shown that, for most drugs of abuse, the presence of drug-associated cues greatly increases the number of operant responses exerted per

test session, compared with when the drug is self-administered in the absence of such cues (Fig. 2) [22–24, 34, 49, 50, 58, 59, 72, 87, 102–105, 111, 122, 141]. These findings suggest that in addition to the primary reinforcing effects of the drug itself, drug-associated stimuli (also termed secondary reinforcers or conditioned stimuli) regulate drug self-administration behavior, a phenomenon referred to by experimental psychologists as "stimulus control" of behavior. This stimulus control has also been demonstrated in human cocaine users in a laboratory setting [106]. In the case of psychostimulants, this enhancement of drug reinforcement by drug-associated cues has been hypothesized to be a result of the augmentation of the impact of sensory information caused by this class of drugs [48].

Second-Order Schedules of Reinforcement

Another experimental paradigm that exemplifies the ability of drug-associated cues to exert stimulus control over behavior is the *second-order schedule of reinforcement* [47, 116]. In this paradigm, animals are initially trained to self-administer a drug of abuse intravenously (or orally, in the case of alcohol) as described in the previous section; each operant response results in drug delivery and the simultaneous presentation of a discrete cue (i.e., a light, tone, and/or olfactory stimulus). After successful training of the animal under this "primary" schedule reinforcement, the contingency of drug delivery upon completion of the operant task is removed, such that only the drug-associated stimulus is presented following each operant response. Thus, each lever press or nose-poke results in presentation of the drug-associated cue stimulus (secondary reinforcer) but no drug delivery (primary reinforcer). The primary advantage of this paradigm is that it allows the investigator to examine "drug-seeking" behavior in the absence of drug delivery, similar to the cue- and context-induced reinstatement discussed in the next section. Thus, the effect of pharmacological or neurobiological manipulations on responding for the secondary reinforcer can be performed without the potential confound of the psychoactive effects of the primary reinforcer. Acquisition of responding on a second-order schedule can be enhanced by non-response-contingent exposure to a sensitizing regimen of the drug (i.e., cocaine) following the primary reinforcement phase [36] (Fig. 3).

However, in order to avoid the extinction of drug-seeking behavior due to the absence of primary reinforcement, a response-contingent delivery of the drug solution must be given at a fixed time interval (i.e., every 30 or 60 min), after the completion of a certain number of operant responses, or at the end of the test session. This allows the animal to receive the primary reinforcer and thus maintain the associations between the drug and responding for drug-associated cues.

Further evidence for the motivational salience of drug-associated cues lies in the fact that when animals are subject to extinction procedures (i.e., when the primary drug reinforcer is withheld in subsequent test sessions following responding under a second-order schedule of reinforcement), response-contingent presentation of the light/tone/olfactory stimulus during extinction trials results in enhanced responding and a slowing of the rate of extinction in rats trained to self-administer cocaine [6], suggesting that the drug-associated cues maintain their motivational salience despite the fact that the primary drug reinforcer is no longer available. This phenomenon has also been demonstrated during extinction following primary drug reinforcement [117, 118]. However, slowing of the rates of the extinction following second-order heroin reinforcement by response-contingent presentation of the drug-associated cues during extinction trials has not been observed [3], suggesting that discrete heroin-associated cues exert a lesser degree of stimulus control over behavior than those associated with cocaine.

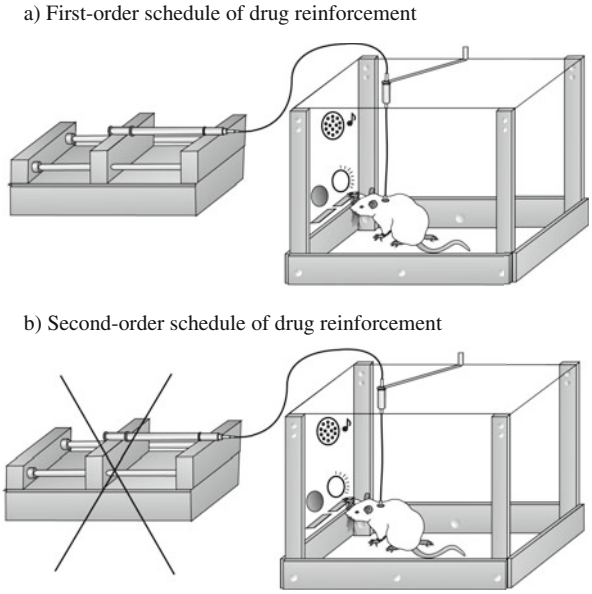

Fig. 3 First- and second-order schedules of reinforcement. (**a**) In a first-order schedule of reinforcement, each correct operant response (i.e., lever-press or nose-poke) results in the delivery of the drug solution as well as simultaneous presentation of discrete drug-associated stimuli. (**b**) Following sufficient training on a first-order schedule of reinforcement, a second-order schedule of reinforcement can be initiated whereby each correct lever response results in the presentation of the drug-associated cue, but infusion of the drug solution is withheld until a fixed time point or the end of the test session

Cue- and Context-Induced Reinstatement of Drug-Seeking Behavior

Relapse is one of the most problematic aspects in the treatment of drug addiction, as it can occur months or years following the last episode of drug intake. Fortunately, animal models have been developed that appear to mimic the phenomenon of relapse in humans. The most widely used animal model of relapse is the *reinstatement paradigm* [44, 45, 79, 100, 101, 115]. In this paradigm, animals are trained to self-administer a particular drug of abuse as described in the Section "Cue-Induced Enhancement of Drug Self-Administration". Following stabilization of patterns of self-administration, animals are then subject to extinction training, where the operant response that previously resulted in drug delivery either has no consequences or results in the delivery of a non-reinforcing substance such as saline. During extinction training, the animal learns that the operant response no longer results in drug delivery and subsequently decreases the number of operant responses exerted. Once specific extinction criteria have been reached (for example, the number of operant responses performed during an extinction trial is less than 20% of those that were observed prior to the commencement of extinction training), the animal is then exposed to one of three types of stimuli that are known to trigger relapse in human addicts: brief exposure to the drug (drug priming), exposure to drug-associated cues, or stressors. The animal then exhibits a significant increase in the number of operant responses that previously resulted in drug delivery; in other words, drug-seeking behavior has been *reinstated*. It should be noted, however, that in the reinstatement model, performing the operant task does not actually result in drug delivery; the behavior is not reinforced by the drug, and, therefore, the reinstatement of drug seeking is relatively

short-lived. Herein lies one of the fundamental (and often criticized) aspects of the reinstatement paradigm where it diverges from the human condition of relapse, since in humans drug-seeking behavior is usually followed by drug self-administration [44]. In the reinstatement paradigm, execution of the operant response does not result in drug availability and self-administration. Nevertheless, the reinstatement paradigm offers a particularly unique method for studying the neural basis of relapse, since *drug-seeking* behavior is inherently parsed out from actual *drug-self-administration* behavior, and the behavior of the animal can be observed and recorded in the absence of psychomotor-altering effects of the drug itself.

With regard to the study of the influence of conditioned cues on drug-seeking behavior, the reinstatement paradigm offers the possibility of studying two distinct phenomena. First, if the discrete cues (i.e., a tone, light, or olfactory stimuli) that were presented to the animal during each drug delivery prior to extinction procedures are re-introduced to the animal in a response-contingent manner, presumably the animal expects that the drug is now available and exerts a significant increase in the number of operant responses that previously resulted in drug delivery. Alternatively, some investigators present the drug-associated cues in a non-response-contingent manner. Regardless, this phenomenon is known as *cue-induced reinstatement*, and has been used extensively to study the role of discrete drug-associated cues in the control over drug-seeking behavior (see Fig. 4).

During the phase of the experiment where animals are actively self-administering the drug, the animal makes associations not only between the drug and the discrete cues presented upon its delivery but also between the drug and the physical environment in which the drug is self-administered. This is particularly relevant to drug addiction in humans since drug-taking behavior is usually performed ritualistically in distinct physical locations (i.e., in the addict's bedroom, local crack house, etc.). The role of the physical environment in controlling drug-seeking behavior can be modeled in animals through what is known as *context-induced* or *contextual reinstatement* [5, 19, 30, 82, 128, 149]. In this paradigm, animals are trained to self-administer the drug in a particular self-administration apparatus. However, subsequent extinction training is conducted in an apparatus that is contextually distinct from that where the active drug self-administration phase occurs (i.e., with different colored walls, different textured flooring, the presence of a different odor, etc.). After extinction criteria have been met, the animal is placed back in the original apparatus where the initial drug self-administration was performed. As a consequence of the drug-environment associations formed during active drug self-administration, the animal then displays a significant increase in the number of operant responses that previously resulted in drug delivery. (This phenomenon is sometimes referred to as a *renewal* effect.) As with cue-induced reinstatement procedures, during context-induced reinstatement, no drug is actually delivered as a result of the operant response, so as to provide a model of contextual influences over drug-seeking rather than drug self-administration behavior.

Neural Substrates of Drug Conditioning: Results from Animal Studies

Studies utilizing the aforementioned animal models of drug conditioning have yielded a wealth of information regarding the neural mechanisms underlying the ability of drug-associated stimuli to control drug-seeking behavior in the absence of primary drug reinforcement. The results of these studies have identified several brain regions that subserve stimulus control over drug-seeking behavior, namely the amygdala, nucleus accumbens, dorsal striatum, hippocampus, frontal cortex, and ventral tegmental area, with both glutamatergic and dopaminergic transmission in many of these regions being implicated (see Fig. 5).

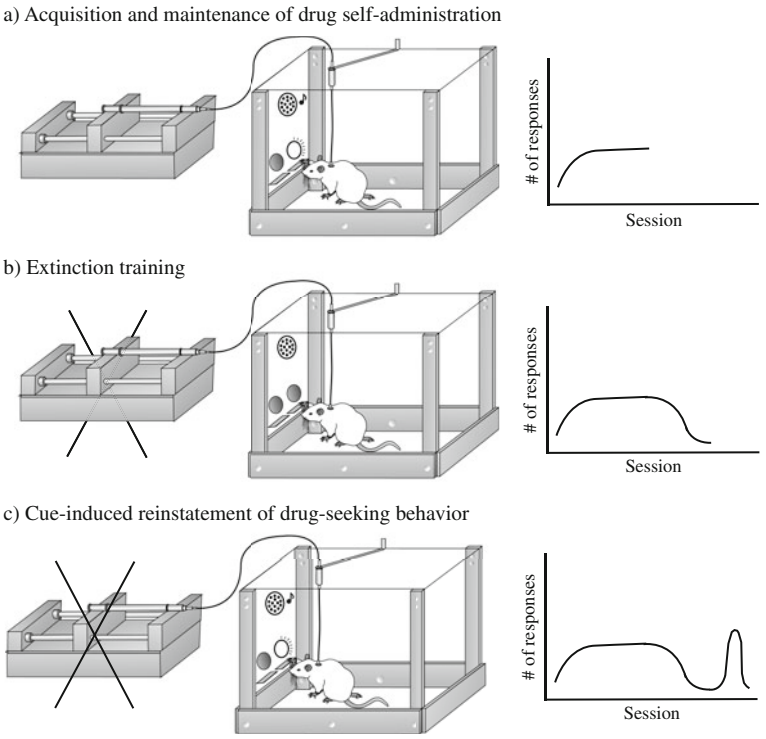

Fig. 4 Cue-induced reinstatement of drug-seeking behavior. (**a**) The animal is first trained to self-administer the drug solution under a standard first-order schedule of reinforcement in the presence of discrete drug-associated cues during drug delivery. This schedule of reinforcement is maintained until response patterns stabilize. (**b**) During extinction training, each correct operant response that previously resulted in drug delivery either results in infusion of saline or has no programmed consequences. Extinction training is performed until predefined extinction criteria have been met. (**c**) During cue-induced reinstatement testing, discrete cues that were previously paired with drug delivery are presented to the animal in a response-contingent or non-contingent manner. Most investigators conduct reinstatement testing in the absence of actual drug delivery so as to separate drug-seeking behavior from actual drug-self-administration behavior, as well as to avoid the potential confounds of psychomotor effects of the drug on operant performance

The amygdala, or amygdaloid complex, is a small set of nuclei found in the temporal lobe that receives a considerable amount of input from cortical regions involved in sensory processing as well as other cortical, subcortical, and limbic structures. In turn, the amygdala provides efferent output to many of these same regions. Everitt and colleagues were among the first to show that the basolateral portion of the amygdala is important for stimulus-reward associations when they demonstrated that lesions of the basolateral amygdala abolished the expression of a conditioned place preference for sucrose [46]. These investigators subsequently expanded their investigation into the role of the amygdala in processing stimulus-reward associations to drug rewards by demonstrating that lesions of the basolateral amygdala reduced the ability of rats to respond for cocaine under second-order reinforcement [144]. In this latter study, rats were still able to acquire cocaine self-administration, suggesting that this region is not involved in the acquisition of primary cocaine reinforcement. However, another study by this group showed that lesions of the basolateral amygdala did not alter second-order heroin reinforcement [2], suggesting that drug class may determine whether the basolateral amygdala mediates the acquisition of second-order drug reinforcement. Thus, the basolateral amygdala appears to mediate

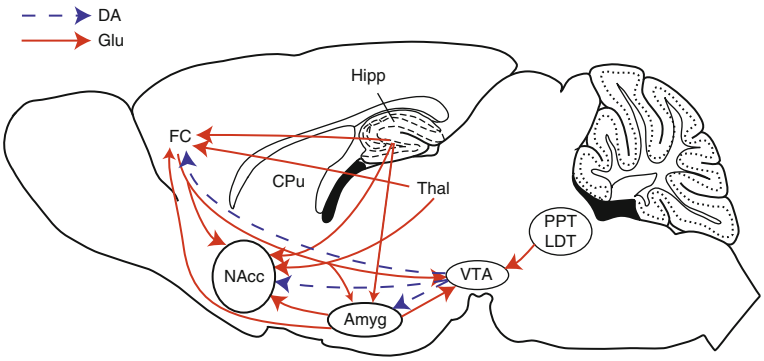

Fig. 5 Sagittal section of the rat brain showing the neural circuitry underlying conditioning processes in drug addiction. The ventral tegmental area (VTA) sends dopaminergic (DA) projections (*blue dashed lines*) to the nucleus accumbens (NAcc), frontal cortex (FC), and amygdala (Amyg), and this pathway is believed to mediate the primary reinforcing effects of most drugs of abuse. These structures also receive substantial glutamatergic (Glu) input (*red solid lines*). For example, the hippocampus (Hipp) and FC send glutamatergic projections to the FC, NAcc, and Amyg, while the thalamus (Thal) also innervates the NAcc and FC with glutamatergic input. Finally, the VTA receives glutamatergic input from many of the aforementioned regions as well as the pedunculopontine tegmentum (PPT) and laterodorsal tegmentum (LDT) in the brainstem. CPu = caudate putamen (for color figures see online version)

the motivational salience of cocaine-associated cues. In agreement with this, numerous other studies have shown that lesions or inactivation of the basolateral amygdala also attenuate cue- and/or context-induced reinstatement of cocaine-seeking behavior [53, 63, 81, 85, 89, 90, 109, 145].

Cocaine-associated stimuli increase the expression of neuronal activation markers such as the immediate early gene c-fos in the basolateral amygdala [28, 64, 92, 93, 98]. Cocaine- and amphetamine-conditioned stimuli also elicit the release of dopamine in the basolateral amygdala [65, 127, 141], and microinjection studies have shown that dopamine acting on D_1-like receptors [4, 119] or $D_{2/3}$-like receptors [35, 67] in the basolateral amygdala mediates the encoding of stimulus control over drug-seeking behavior. Studies using the conditioned place preference paradigm have shown that *de novo* protein synthesis in the basolateral amygdala is required for long-term maintenance of morphine conditioned place preference [91] and that activity in this nucleus is necessary for reinstatement of heroin conditioned place preference [113]. On the other hand, ionotropic glutamate receptors in the basolateral amygdala do not appear to be involved in cue-induced reinstatement of cocaine-seeking behavior [119]. Thus, the basolateral amygdala appears to play a critical role in the ability of conditioned cues to exert control of drug-seeking behavior and drug reward, and these effects appear to be mediated primarily by dopaminergic transmission in this region.

Another brain region known to be involved in the neural coding of drug-associated cues is the nucleus accumbens, located within the ventral striatum of the rostral forebrain. The nucleus accumbens receives dense dopaminergic projections from the ventral tegmental area of the midbrain as well as glutamatergic projections from the prefrontal cortex, hippocampus, amygdala, and thalamus. Neurons in the nucleus accumbens are primarily of the medium spiny type that utilize the inhibitory amino acid gamma-aminobutyric acid—as well as various neuropeptides—as transmitters in its outputs to the ventral pallidum and ventral tegmental area. Lesions of the nucleus accumbens core, but not the shell subregion, selectively impair acquisition of second-order heroin reinforcement [1, 71, 74] while having no effect on maintenance of responding. Likewise, inactivation of the nucleus accumbens core, but not the

shell, attenuates cue-induced or contextual reinstatement of cocaine-seeking behavior [40, 54, 109]. Despite the fact that response-independent presentation of cocaine-associated cues elevates extracellular levels of both dopamine and glutamate in the nucleus accumbens core [11, 69, 73] and increases nucleus accumbens core neuronal firing [20, 68], glutamatergic signaling in the nucleus accumbens may be more important than dopamine signaling in drug-conditioned stimulus control of behavior. Evidence for this comes from studies showing that blockade of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainic acid-type glutamate receptors in the nucleus accumbens core reduces second-order responding for cocaine [37], whereas blockade of D_3 receptors in the nucleus accumbens shell has no effect on second-order cocaine reinforcement [35].

Drug-associated stimuli and environments also increase the expression of various transcriptional regulators including Fos, ets-like gene 1, extracellular signal-related kinase, and cyclic adenosine monophosphate-responsive element binding protein [92–94, 98], and some of these molecular signaling intermediates as well as de novo protein synthesis in the nucleus accumbens appear to be necessary for retrieval of drug-associated contextual memories [91, 94]. More recently, some investigators have determined that in addition to the nucleus accumbens, the dorsal striatum (particularly the dorsolateral region) plays a role in cue-controlled cocaine seeking [40, 52], with both dopamine and glutamatergic transmission being involved [10, 131].

An elegant study by Di Ciano and Everitt demonstrated a functional interaction between the basolateral amygdala and the nucleus accumbens core in mediating drug seeking under a second-order schedule of reinforcement [39]. In this study, bilateral antagonism of dopamine but not AMPA receptors in the basolateral amygdala impaired second-order cocaine reinforcement, whereas the reverse was true when these manipulations were performed in the nucleus accumbens core. When unilateral injections on opposite sides of the brain were performed in a disconnection procedure, dopamine receptor blockade in the basolateral amygdala combined with blockade of AMPA receptors in the contralateral nucleus accumbens core produced the same effect as the bilateral injections. A similar disconnection procedure recently showed that unilateral dopamine receptor antagonism in the dorsal striatum combined with a unilateral lesion of the nucleus accumbens core impairs second-order cocaine responding [10].

The prefrontal cortex and many of its subregions also play a significant role in drug conditioning and stimulus control of behavior. Lesions of the orbitofrontal cortex impair second-order responding for cocaine [108], whereas lesions of the medial prefrontal cortex actually increase responding for cocaine under a second-order schedule of reinforcement [142]. In this latter study, however, omission of the conditioned stimulus did not reduce these elevated patterns of responding, suggesting that the medial prefrontal cortex may not encode the motivational salience of drug-associated cues but rather control behavioral inhibition. Discrete drug- and alcohol-associated stimuli increase c-fos expression in frontal cortical regions such as the medial prefrontal/prelimbic cortex [28, 33, 92, 93, 146], infralimbic cortex [64, 93], and anterior cingulate cortex [98, 146], and it has been shown that dopamine D_1-like receptors play a role in increasing cue-evoked immediate early gene expression [28]. Inactivation of the dorsomedial/prelimbic, ventral prefrontal, and lateral orbitofrontal cortices attenuates cue- or context-induced reinstatement of drug-seeking behavior [41, 53, 55, 89] and drug priming-induced reinstatement of cocaine conditioned place preference [147], and retards the extinction of amphetamine conditioned place preference [70].

Another region involved in drug conditioning is the hippocampal formation, which is involved not only in episodic memory storage but also in spatial navigation and the influence of environmental contexts on behavior. Inactivation of the dorsomedial hippocampus attenuates contextual reinstatement of cocaine-seeking behavior [53], whereas inactivation of slightly more ventral portions of the hippocampus reduces

cue-induced reinstatement [114]. However, conflicting evidence exists over whether inactivation of ventral output regions of the hippocampal formation (i.e., the subiculum) mediates cue-induced reinstatement evoked by discrete drug-associated cues [12, 125]. Given the relatively large size of various regions of the hippocampus, it is likely that differences in anatomical localization of microinjection guide cannulae contributed to these disparate results. Certain regions of the hippocampus, such as the CA1 region and dentate gyrus, show elevated expression of c-fos expression when animals are exposed to an environment previously associated with cocaine self-administration [98]. Similar to the basolateral amygdala, *de novo* protein synthesis in the hippocampus is required for long-term maintenance of morphine conditioned place preference [91]. Thus, the hippocampus appears to play a role in the ability of drug-associated contexts to influence drug-seeking behavior.

One final brain region involved in drug conditioning is the ventral tegmental area, which receives glutamatergic afferents from various cortical and subcortical regions and sends dense dopaminergic projections to the nucleus accumbens and prefrontal cortex and less dense projections to the basolateral amygdala and ventral pallidum. While the ventral tegmental area-nucleus accumbens dopamine projections have long been considered to be a part of the "reward circuit" of the brain [140], there are several recent studies to suggest that glutamatergic input to the ventral tegmental area modulates the ability of drug-associated cues to influence drug-seeking behavior. For example, suppression of glutamate transmission in the ventral tegmental area by local infusion of a type 2/3 metabotropic glutamate receptor agonist, which suppresses glutamate release by stimulating presynaptic metabotropic glutamate receptor 2/3 autoreceptors, attenuates contextual reinstatement of heroin-seeking behavior [14]. Likewise, temporary inactivation of the ventral tegmental area attenuates second-order responding for cocaine [38]. Thus, there is evidence to suggest that the ventral tegmental area controls both primary and secondary drug reinforcement.

Neural Substrates of Drug Conditioning: Results from Human Imaging Studies

Advances in imaging of the living human brain have greatly added to our understanding of the neural basis of reactivity to drug-associated cues [61, 133]. Such imaging studies have shown repeatedly that cues associated with drug intake activate forebrain regions such as the anterior cingulate, dorsolateral prefrontal, and orbitofrontal cortices, the insular cortex, and striatal and limbic regions such as the amygdala and nucleus accumbens [13, 18, 27, 56, 60, 62, 83, 84, 88, 95, 134–136, 139, 143]. Activation of these brain regions is highly correlated with drug craving. These findings correlate well with the animal studies reviewed in the previous section, and suggest that cortical, striatal, and limbic structures are highly involved in processing drug cue-related information. A recent study showed that when drug-associated stimuli were presented to subjects for a period of time too brief to be processed at a conscious level (33 ms), similar regions of the brain were activated [25]. However, additional increased activity was observed in a transition zone between the amygdala and ventral pallidum, suggesting that some regions of the brain are activated by drug-associated visual stimuli even when "unseen" at the conscious level. Clearly, further research in this area is needed to identify an anatomical rodent correlate of this amygdalar/ventral pallidal transition zone and its potential role in mediating stimulus control of drug-seeking behavior (Fig. 6).

Strategies for Extinguishing Drug Conditioning and Reducing Cue-Elicited Drug Craving: Focus on Glutamate

Reactivity to drug-associated cues is an important determinant of propensity to relapse among drug addicts [21, 26]. However, exposure

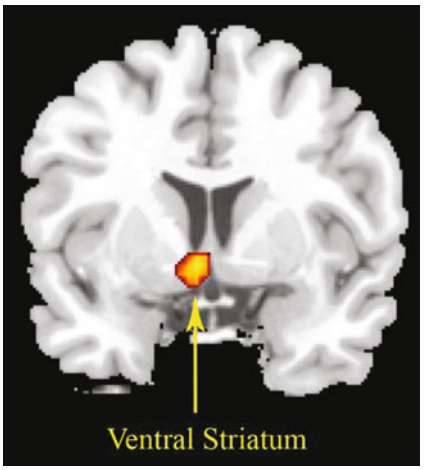

Fig. 6 Coronal section of the human brain showing activation of the ventral striatum by drug-associated cues. Alcohol-dependent individuals were exposed to images of either alcohol-related cues (e.g., a glass of wine) or a neutral image (e.g., a light switch) while undergoing functional magnetic resonance imaging of the brain. A significant increase in activity in the ventral striatum (which contains the nucleus accumbens) was observed following exposure to an alcohol-related cue. Image courtesy of Dr. Hugh Myrick and Mr. Scott Henderson, Center for Drug and Alcohol Programs, Medical University of South Carolina

therapy, whereby the addict is desensitized to the craving evoked by drug-associated cues by repeated exposure to the cues—and is taught coping skills on how to curb drug craving if he or she encounters a drug cue—has been shown to be only moderately effective in reducing rates of relapse [29]. The unsuccessful outcomes of exposure therapy are most likely due to the high degree of context specificity of extinction, whereby extinction of craving evoked by drug-associated cues in one context (i.e., the therapist's office) fails to generalize to the "real world" where such cues are encountered more frequently and in different contexts [16, 17].

Extinction of the motivational salience of drug-associated cues is a process of active learning and involves many of the neurobiological signaling mechanisms underlying normal learning and memory processes, including neuroadaptations in glutamatergic neurotransmission [120, 126]. Thus, one potential pharmacological mechanism by which to enhance extinction processes is via mild stimulation of glutamatergic neurotransmission, since excessive augmentation of glutamate transmission would likely produce central nervous system hyperexcitability and excitotoxic effects. Recently, studies in both animals and humans have shown that the *N*-methyl-*D*-aspartate receptor partial agonist *D*-cycloserine is effective at facilitating the extinction of conditioned fear [132]. Similarly, it has been shown in animals that *D*-cycloserine accelerates the extinction of cocaine conditioned place preference [15]. Stimulation of type 5 metabotropic glutamate receptors, which are positively coupled to *N*-methyl-*D*-aspartate receptor function, also facilitates the extinction of cocaine conditioned place preference [57].

An alternative method by which to stimulate glutamatergic transmission and thus enhance extinction learning is by administration of the cystine pro-drug *N*-acetylcysteine. Once *N*-acetylcysteine enters the body, it is converted to cystine, where it acts as a substrate for the cystine-glutamate exchanger. This exchanger is an antiport protein localized to glial cells in the brain that exchanges extracellular cystine molecules for intracellular glutamate. Withdrawal from repeated exposure to cocaine is accompanied by reduced basal extracellular levels of glutamate in the nucleus accumbens [110], and it has been shown that administration of *N*-acetylcysteine to cocaine-withdrawn rats reduces the ability of cocaine priming injections to increase extracellular glutamate in the nucleus accumbens and, as a consequence, reduces cocaine-primed reinstatement of cocaine-seeking behavior [7, 8, 96]. *N*-acetylcysteine also reduces extinction responding following heroin self-administration and produces long-lasting reductions in the ability of drug-associated cues to reinstate heroin-seeking behavior [148]. Translating these basic research findings to the clinic, LaRowe and colleagues recently demonstrated that *N*-acetylcysteine reduces drug craving and cue reactivity in cocaine addicts [86]. Thus, normalization of extracellular levels of glutamate in the nucleus accumbens during drug withdrawal

may be a novel avenue by which to facilitate extinction of the motivational salience of drug-associated cues and, therefore, reduce the incidence of relapse in human addicts.

Conclusions

Although drug addiction is a chronic and multifaceted disease that has numerous genetic, socioeconomic and behavioral causes, one of its key features is an increased incentive salience of drug-associated stimuli and impaired executive inhibitory control of drug craving elicited by these cues [78, 80]. These manifestations of the addictive state are mediated by dysfunction of limbic and prefrontal-accumbens circuitry. Therefore, it is of clinical interest to restore the normal functioning of these circuits during the course of treatment of the addict so as to allow him or her to extinguish the motivational salience of drug-associated cues and regain inhibitory control of drug-seeking and drug self-administration behaviors. Clearly, more research is needed to parse out the neurobiological substrates of drug conditioning at the molecular, cellular, and systems levels, and how this conditioning can be "reversed" in the addicted state. In addition, increased attention needs to be given to novel methodology—both behavioral and pharmacological—that is designed to facilitate the extinction of drug conditioning, particularly with regard to the generalization of extinction to "real world" situations.

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Part III
Genetic and Other Biological Theories for Addiction

Mouse Models: Knockouts/Knockins

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Introduction

Vulnerability to addictions is a complex trait with strong genetic influences from family, adoption, and especially twin studies. These genetic factors underlying addiction-related phenotypes can be identified with linkage and association approaches in humans and animal models. This traditional tracing of the defects to particular altered genes is commonly referred to as forward genetics. Many loci with nominally significant linkage to addiction phenotypes have been identified for most common addictions in linkage-based genome-wide scans, typically with genetic markers approximately every 1/300–400th of the genome. The genetic regions identified by linkage analysis are relatively large, at which a gene or genes implicated in addictions may reside in the proximity of the genetic marker. Further effort can be made to refine gene mapping to a single gene or a single genetic variant by the association analysis approach, which employs an increased density of genetic markers such as single-nucleotide polymorphisms

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_9,

(SNPs), the most common form of genetic variation between individuals occurring once several hundred bases or so. Until now, many candidate genes containing allelic variants have been identified as being associated with different addiction phenotypes. Recently, with the aid of the Human Genome Project, International HapMap Project, and chip technology, genome-wide association studies have revealed previously unsuspected genetic components that predispose to substance abuses [9, 55, 78, 79]. Despite these advances, the final proof that a candidate gene association study has truly captured the relevant gene(s) requires a collection of converging evidence drawn from a wide range of genetic and non-genetic analyses. As such, the number and identity of genes that are susceptible to drugs of abuse remain largely unknown.

The expense and limitations inherent in human genetic research have led to an increase in the use of genetic animal models to elucidate the pathways from gene to addiction behavior. Particularly, the mouse is one of the most favorite models because of its smaller size, its relatively low cost of maintenance, a generation time that measures only 9 weeks from being born to giving birth, and a large amount of inbred strains available. [Please refer to the Mouse Genome Informatics at the Jackson Laboratory (http://www.informatics.jax.org) for the inbred strains and their phenotypes.] Genome projects have revealed that mouse and human genome sequences are quite similar. Both mice and humans have approximately 30,000 genes. About 99% of the genes are shared by both species, and only about 300 genes are unique for each species. Moreover, 90% of the genes associated with diseases are identical in the human and mouse. Exploiting synteny between mouse and human disease loci has thus been proposed as a cost-effective method for the identification of human susceptibility genes. Much effort has been undertaken to map genes associated with addictive behaviors (especially alcohol dependence) in mice, using the quantitative trait locus (QTL) mapping approach. Because the addictive behavioral traits in mice are continuous and determined by multiple genetic and environmental factors, each of the genetic factors responsible for such quantitative traits is defined as a QTL. Many QTLs have been identified for drug response phenotypes in mice [7, 59, 77], and a significant convergence between these QTLs in mice and those from human genome-wide association studies of dependence on various addictive substances has also been revealed [77], further indicating that the genetic discovery in mice can be extended to human population studies for confirmation, and vice versa.

Classic forward genetic analyses are performed by observing a phenotype, designing the necessary cross-matings, and using the resulting population to perform statistically significant experiments to find the mutation and to understand the function of the altered gene. This method has been successfully applied for identifying genes that function in a particular biological process. Recombinant DNA technology and the explosion in genome sequencing have made possible a different type of genetic approach, reverse genetics. Starting with a particular gene with interesting properties, one can proceed to make mutations and create mutant organisms so as to analyze the gene's function in the development or behavior of the organism. Using reverse genetics, one can examine the hypothesis proposed or prove the conclusion drawn from forward genetics. In addition, one can investigate the function of all genes of interest, something not easily done with forward genetics. Thus, reverse genetics is an important complement to forward genetics. However, due to ethical problems, most reverse genetics can only be done in animal models.

A normal gene can be altered in several ways in a genetically engineered organism. (1) In the transgenic approach, the normal gene or its mutant is simply added to the genome. The overexpression of the introduced normal gene or mutant gene overriding the function of the endogenous normal gene may provide useful information about the gene function. (2) In the knockout approach, the normal gene can be disrupted completely, for example, by making a

large deletion within it. The resulting phenotypes in development or behavior of the organism may thus be studied. (3) In the knockin approach, the normal gene can be replaced by a mutant copy of the gene, which may provide information on the activity of the mutant gene without interference from the normal gene. The effects of small and subtle mutations may thus be determined. (4) In the knockdown approach, the engineered genes introduced into the organism can produce antisense RNA, small interfering RNA, short hairpin RNA, or microRNA, which is completely or partially complementary in sequence to the normal gene and can reduce expression of the normal gene. The effects of gene expression reduction may thus be investigated. These powerful approaches of manipulating genes in intact organisms can be combined to examine gene function in the context of the intact organism, such as addictive behaviors.

In this chapter, we provide a brief description of gene targeting technology, including strategies for knockout, knockin, and conditional gene modification. We also provide an overview with some examples of gene targeting applications in reverse genetic studies of drug addictions, demonstrating the power of gene targeting technology in advancing our knowledge of gene functions.

Basics of Gene Targeting

A fragment of genomic DNA introduced into a mammalian cell can locate and recombine with the endogenous homologous genomic sequences but not integrate in any other loci in the genome. This type of homologous recombination is known as gene targeting. The technique was developed in the late 1980s by Mario R. Capecchi [73], Martin J. Evans [41], and Oliver Smithies [21], who shared the 2007 Noble Prize in Physiology or Medicine for their pioneering works. Now, gene targeting has been widely used, particularly in the mouse model, to make a variety of mutations in many different loci so that the phenotypic consequences of specific genetic modifications can be assessed in the organism. In theory, any deletion, point mutation, inversion, or translocation can now be modeled in mice.

The process of gene targeting includes three major steps: (1) generation of a DNA targeting construct; (2) homologous recombination in embryonic stem cells, and (3) production of genetically engineered mice. A simplified schematic illustration of the gene targeting procedure is demonstrated in Fig. 1.

Targeting Construct

A targeting construct is designed to recombine with and mutate a specific target chromosome locus. Typically, a targeting construct contains three components: (1) bacteria plasmid backbone for DNA manipulation; (2) genomic DNA sequences that are homologous to the desired chromosomal site for DNA integration, and (3) positive and negative selection markers for strong recombination selection in embryonic stem cell clone screening.

When a targeting construct is transfected into mammalian cells, it can be integrated either specifically into its target locus or randomly into chromosomal sites. The relative ratio of gene targeting to random integration events depends on a number of factors that cannot be experimentally controlled, such as the location of the target gene in the genome. In most cases, the frequency of random integration is far greater than that of gene targeting, which is only about one in every 10^5–10^6 treated cells. Increasing the efficiency of homologous recombination will thus determine the ease with which targeted embryonic stem clones can be identified in the following screening step and is one of the major concerns in the targeting construct design.

One aspect to affect the targeting frequency is the length and sequence of the homologous sequences in the targeting construct. As a general rule, the greater the length of the homolog, the higher is the recombination frequency; on the other hand, the more difficult

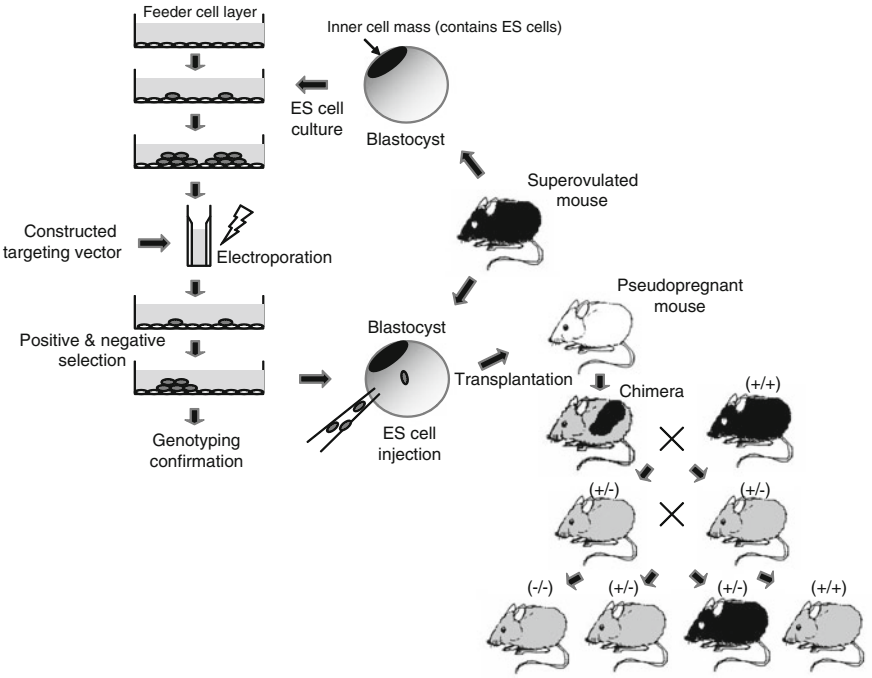

Fig. 1 Schematic illustration of gene targeting procedure. Embryonic stem (ES) cells are isolated from the blastocyst and cultured on the feeder cell layer. The constructed targeting vector is introduced in the embryonic stem cells by electroporation. Embryonic stem cell colonies resistant against positive-negative selection are screened and verified by genotyping. Targeted embryonic stem cells are then injected into the blastocyst, which is then implanted in the uterus of a pseudopregnant mouse. Coat color strategy is often used as an early marker of a successful lineage contribution of the targeted embryonic stem cells. The resulting chimeric mice are mated with wild-type mice to confirm germline transmission. Homozygous mice are finally produced with further breeding of heterozygous mice

are the DNA cloning and manipulation. An ideal length of homolog is recommended in a range of 5–10 kilobases. Additionally, the homologous sequences should be derived from genomic libraries isogenic with the specific line of embryonic stem cells used in the targeting experiment. The existence of sequence mismatches between the homolog in the vector and the target locus will reduce the targeting frequency.

Another aspect to enrich the representation of targeted clones within a transfected population is to apply the positive-negative selection technique, which can significantly reduce the number of embryonic stem clones with random integration. In this selection scheme, the positive marker serves to isolate rare transfected cells that have stably integrated the construct DNA, irrespective of the targeted or random incorporation, whereas the negative marker serves to kill transfected cells that have incorporated the construct DNA at a random location (Fig. 2). Both positive and negative selection cassettes contain a promoter to drive expression of an antibiotic-resistance gene and a polyadenylation signal to terminate efficiently the antibiotic-resistance gene transcription. The commonly used antibiotic-resistance genes for positive selection include the neomycin resistance gene *neo*, puromycin resistance gene *pur*, and hygromycin resistance gene *hyg*. Those for negative selection are the thymidine kinase gene *TK* and diphtheria toxin A gene *DTa*. Since the most common gene targeting is to ablate the function of a target gene, the positive selection marker can also serve as a mutagen, for instance, if it is inserted into the coding exon of a target gene or replaces the coding exon(s).

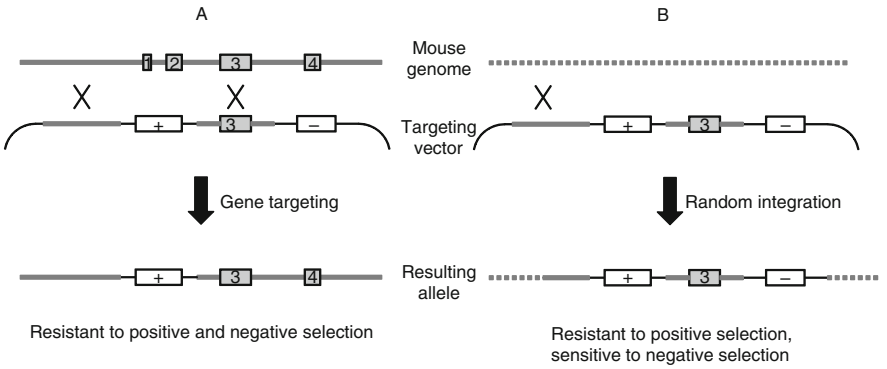

Fig. 2 Illustration of positive-negative selection for gene targeting. *Filled box with number* inside represents an exon of a target gene. *Box with "+" or "–"* inside represents a positive or a negative selection cassette. Both selection cassettes contain a promoter, an antibiotic-resistance gene, and a polyadenylation signal. Thick line represents mouse target genomic DNA; dashed line represents mouse non-homologous genomic DNA, and thin line represents non-mouse DNA. "X" represents an integration site. (**a**) A targeted integration event removes the negative selection marker. (**b**) A random integration event results in inclusion of the negative selection marker

In addition to the selection scheme, screening techniques required to identify the recombined clones by polymerase chain reaction or Southern blotting should also be considered in the design of a targeting construct and tested prior to the embarkment of a targeting project. Most of all, the principal consideration to design a targeting vector is the strategy of gene targeting and the type of mutation to be generated, which will be discussed in detail below.

Manipulation of Embryonic Stem Cells

An embryonic stem cell is an unusual type of cell that has virtually unlimited powers of differentiation. Embryonic stem cells are primarily isolated from the inner cell mass of a mammalian blastocyst [23, 48], which is an early stage of embryonic development comparable to the blastula stage. Murine pluripotent embryonic stem cells have been derived from primordial germ cells [50], epiblasts [11], preblastocyst embryos [72], and blastomeres [16].

Pluripotency of embryonic stem cells can be maintained by culturing them in vitro under conditions where the cells grow and proliferate. The embryonic stem cells are then transfected with a constructed targeting vector, routinely using electroporation. In eletroporation, cells are mixed with DNA in cuvettes containing electrodes that deliver a brief electric pulse. Application of the current causes the plasma membrane to become transiently permeable to DNA molecules, some of which find their way into the nucleus. By mechanisms that are poorly understood but are similar to what occurs during meiosis and mitosis when homologous chromosomes align along the metaphase plane, the engineered targeting construct finds the target gene and recombination takes place within the homologous sequences. The recombination may take place anywhere within the flanking DNA sequences, and the exact location is determined by the cells and not the investigators. Through this procedure, embryonic stem cells that are heterozygous for the target gene are produced (Figs. 1 and 2).

The transfected embryonic stem cells are cultured and grow in the presence of antibiotics for colony selection. In cases when both *neo* and *TK* are used in the targeting vector, neomycin and ganciclovir (or 5-iodo-2′-fluoro-2′-deoxy-1-β-D-arabino-furonosyluracil; FIAU) are added in the culture medium for positive and negative

selection, respectively. Cells without the targeting construct incorporation will often die, because they contain no neomycin resistance gene, as well as cells with the targeting construct inserted randomly in the genome, because they contain an intact thymidine kinase gene. The grown colonies of embryonic stem cells are isolated, screened, and analyzed by polymerase chain reaction and/or Southern blotting to detect the desired homologous recombination in the specific target locus. The average frequency to identify a positive clone is about one in 100–200 colonies, although less than 1/500th is not unusual.

Generation of Gene-Targeted Mice

A number of individual embryonic stem cells from the identified positive clone are taken up into a fine glass micropipette and injected into the blastocele of a recipient early mouse embryo. The recipient embryo is then implanted into the oviduct of a female pseudopregnant mouse that has been hormonally prepared to carry the embryo to term. As the embryo develops in its surrogate mother, the injected embryonic stem cells join and collaborate with the host embryo's own inner cell mass and contribute to formation of embryonic tissues, including the germ cells of the gonads, in favorable cases. Most often, embryonic stem cells are utilized selectively from a strain with a coat color different from the strain that donates the recipient blastocysts. A highly chimeric mouse can be identified by looking at the color of its fur (e.g., mostly brown and only a few black spots). The greater the level of chimerism, the greater the chance that the embryonic stem cell has contributed to the germ cells during embryonic development. The highly chimeric mice are then mated to a member of an inbred strain to produce the heterozygous offspring, which contain one normal and one mutant copy of the target gene in all of their cells. When the heterozygotes, confirmed by germline transmission by Southern blotting or polymerase chain reaction, are in turn bred to one another, theoretically one-fourth of their progeny will be homozygous for the altered gene (Fig. 1). These are the gene-targeted mice.

Gene Targeting and Transgenesis

Compared with the development of gene targeting in the late 1980s, the transgenic technology appeared in the early 1980s, with the first transgenic mouse reported in 1980 [29]. The transgene constructs are microinjected into the pronucleus of the fertilized eggs isolated from the ampulla of the oviduct. The injected eggs are then implanted into the oviduct of a pseudopregnant female. The linearized transgene constructs can randomly integrate into the mouse genome as a single copy or multiple copies (up to 200 in tandem head-to-tail array) by the mechanisms that are not well understood. Transgenic founders are later identified by polymerase chain reaction or Southern blotting, usually around 15–20% among born pups. Although most transgenic founders have the transgene integrated at a single and yet different locus, 10–15% of the founders can have the transgene integrated at 2–3 different loci. Thus, transgene expression is highly variable from one founder to another, due to the copy number of the transgene and the influences of DNA sequences flanking the integration site(s). In contrast to gene-targeted mice, transgenic mice can be generated in a shorter period with relatively lower cost and effort.

The simplest transgenic construct consists of an enhancer/promoter, a transgene of interest, and a polyadenylation signal. The promoter determines when and where the transgene is expressed, either ubiquitously or in a tissue/cell-specific fashion, being constitutive or time-dependent, or even being drug-inducible. The transgene of interest in the transgenic construct is often derived from a cDNA sequence. However, to enhance transgene expression, a

heterologous intron containing a splice donor and an acceptor can be inserted at the 5′ or 3′ end of the transgene to increase mRNA stability and to improve the optimal chromosomal domain [56, 68]. The transgenic construct also contains a pre-engineered heterologous polyadenylation signal such as the rabbit β globin poly(A) to serve as part of the machinery for transcription termination and polyadenylation. In addition to these basic elements, several featured elements could be added into the transgenic vector to facilitate specific transgene expression. The internal ribosomal entry site, an element that allows for translation initiation in the middle of an mRNA sequence, can be introduced to express two transgenes at the same time with only one construct. The chicken 5′ β-globin insulator (cHS4) flanking the transgenic construct can effectively block the tissue-specific position effects and profoundly increase transgene expression in all tissues [61]. A transcriptional stop element can be used as an insulator for conditional transgenesis [43].

The generation of transgenic and gene-targeted mouse models facilitates the in vivo study of mammalian gene function. Combining the transgenic and gene targeting technologies provides investigators with more strategies and the freedom to design an optimal model to study the function of a gene in a specific tissue/cell during development or in postnatal life. As we will mention below, the various transgenic mice of recombinases are crucial for the realization of a variety of conditional gene targeting.

Strategies of Gene Targeting

Gene targeting is a complex technology with many factors and strategies involved. In the following subsections, we introduce some of the strategies for knockout, knockin, and conditional gene targeting. For more extensive coverage and fuller details of gene targeting, we suggest that readers refer to two textbooks about gene targeting [40, 76].

Knockout

The most commonly used application of gene targeting is to inactivate an endogenous gene by replacing it or disrupting it (by insertion) with an artificial piece of DNA, usually the positive selection marker. Homologous recombination allows investigators to remove completely one or more exons from a gene, which results in the production of a mutated or truncated protein or, more often, no protein at all. The phenotypes of knockout mice in appearance, behavior, and other observable physical and biochemical characteristics may thus provide valuable clues about what the target gene normally does, which helps to understand better how a similar gene can cause or contribute to disease in humans.

However, the phenotypes of knockout mice can be very complex because all tissues of the mouse are affected, though it is not uncommon for a knockout mouse to display embryonic lethality (developmentally essential) or to show no phenotype at all (nonessential). In some cases, it is possible that the absence of the gene product is compensated for by the product of another member of a gene family or an entirely different gene. Compensation by one gene for another can then be verified by producing mice that lack both of the genes in question (i.e., a double-knockout).

Knockin

The knockin strategy can be used to generate a site-directed transgene model with an insertion vector or a subtle site-directed mutation model with a replacement vector.

For transgene knockin, the insert is flanked by DNA from a selected non-critical locus, and homologous recombination allows the transgene to be targeted to that specific, non-critical integration site. In this way, the transgene does not incorporate itself into multiple locations, and the genetic environment surrounding the expression cassette is completely controlled. Compared

with the traditional transgenic mouse model, this site-specific knockin is present as a single copy and results in a more consistent level of expression from generation to generation. Because the knockin transgene is not likely interfering with other critical loci in the genome, it will be more certain to elucidate that any resulting phenotype is due to the exogenous expression of the gene. Several loci such as ROSA26 [66], hypoxanthine guanine phosphoribosyl transferase 1 locus [74], and procollagen type I α1 locus [4] have been favored for transgene knockin. Although the generation of knockin mouse does avoid many problems of a traditional transgenic mouse, this procedure requires significantly more time and effort.

For subtle mutation knockin, homologous recombination allows a fragment of DNA to be replaced by the DNA fragment that has been altered in vitro by site-directed mutagenesis without alteration of the rest of the genome. In this way, a single amino acid in an active site of a protein or a single nucleotide in a transcription promoter region of a gene can be changed purposely. As such, the method is quite useful to investigate the variations identified in forward genetic studies that confer susceptibility to human disorders. To get rid of the concomitant presence of an intragenic positive selection marker, the promoter of which often deregulates the targeted gene or the neighboring genes and generates a hypermorph, techniques such as "double-replacement" [67, 81], "hit-and-run" [35], and using the Cre-*loxP* recombinase system (see below) have been developed.

Conditional Gene Targeting

Many genes that participate in interesting genetic pathways are essential for mouse development, viability, or fertility. Therefore, a traditional knockout of the gene (ablation of the gene function) may never lead to the establishment of a knockout mouse strain for analysis. The development of the site-specific Cre-*loxP* and Flp-*FRT* recombination technology allows investigators to modify conditionally the gene of interest in only a subset of tissue/cells or at only a particular time, circumventing lethality (Fig. 3; or refer to an in-depth review [10]). The Cre-*loxP* recombination system is identified from the bacteriophage P1, whereas the Flp-*FRT* system is from *Saccharomyces cerevisiae*. Both *loxP* (*l*ocus *o*f *x*-over in *P*1) and *FRT* (*F*lipase *R*ecognition *T*arget) sites are small, 34-base-pair DNA fragments (8-base-pair asymmetric spacer plus two 13-base-pair inverted repeats) specifically recognized by their particular recombinases, 38 kD Cre (Circularization recombinase) and 48 kD Flp (Flipase), respectively. The pair of elements, recombinase and its specific site, work together to provide versatile tools for in vivo genetic engineering of associated DNA—deletion, insertion, inversion, or translocation. In Fig. 3, we demonstrate a couple of examples using the site-specific recombination systems for conditional gene modification.

Because gene targeting can be modulated both spatially and temporally by controlling the recombinase expression, the function of a given gene can thus be studied in the desired cell types and/or at a specific time point if an inducible promoter is applied for the recombinase expression. This refined genetic dissection with conditional gene modification allows investigators to define gene function in development, physiology, or behavior.

Knockouts in Addiction Studies

Since the development of gene targeting technology, hundreds of mice carrying various null alleles have been generated by disrupting the endogenous genes. A comprehensive and public resource for all publicly available knockout mice is available at the Web site of the KnockOut Mouse Project, a trans-National Institutes of Health initiative (http://www.komp.org or http://www.knockoutmouse.org). Valuable information has been obtained by the analysis of animals carrying these mutations.

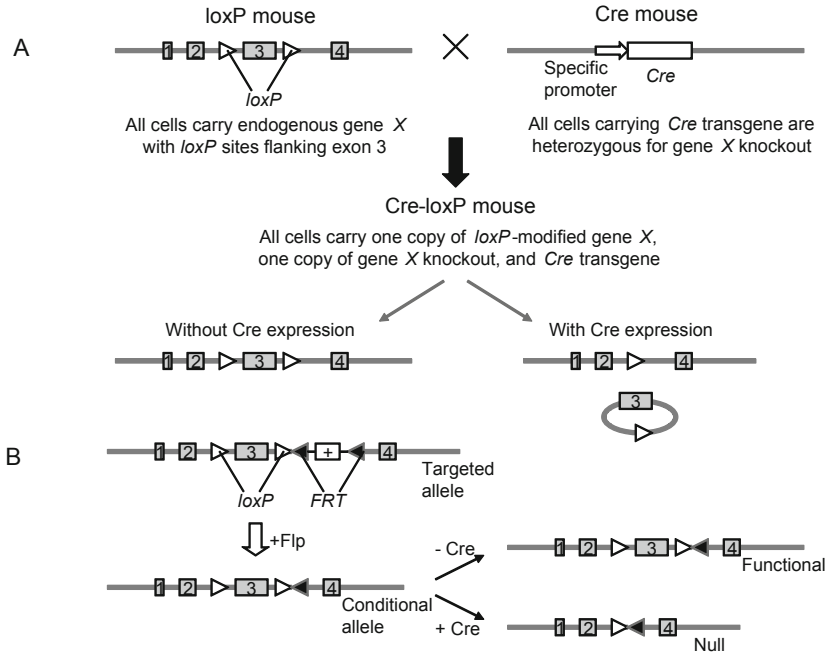

Fig. 3 Conditional gene targeting using the site-specific recombination system. (**a**) Cre-*loxP* recombinase-mediated gene disruption. Two *loxP* sites are inserted on each side of an essential exon (3) of the gene (i.e., *X*) by homologous combination, which does not disrupt gene function. Expression of transgene *Cre* is driven by a tissue/cell-specific promoter designed for temporal and spatial control. The expression of recombinase Cre in the Cre-loxP mouse, produced from the mating of a loxP mouse and a Cre mouse, will result in a deletion of the *loxP*-flanked (floxed) exon 3 with the precise excision at the *loxP* sites. (**b**) Application of both Cre-*loxP* and Flp-*FRT* recombination systems. The positive selection cassette (box with "+" inside) is flanked with two *FRT* sites (flrted) and can be removed by the expression of Flp recombinase, whereas the floxed exon 3 can be conditionally knocked out by the expression of Cre recombinase

Knockout Genes and Addictive Traits

Until now, more than 100 mouse gene knockouts and transgenics have been tested in the alteration of addiction-related behaviors [28]. Most of them have known functions and are suspected to influence addictive traits directly or indirectly. These genes include: (1) receptors and their subunits for neurotransmitters such as acetylcholine, dopamine, inhibitory γ-aminobutyric acid, excitatory glutamate, and serotonin; (2) neuropeptides and their receptors such as neuropeptide Y, substance P, neurokinins, and corticotropin-releasing factor; (3) receptors for other substances such as endocannabinoids and opioid peptides; (4) neurotrophins and their receptors such as brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4, and Trk receptors; (5) monoamine transporters such as the dopamine transporter, serotonin transporter, norepinephrine transporter, and vesicle monoamine transporter 2; (6) metabolic enzymes for neurotransmitters such as dopamine β-hydroxylase, tyrosine hydroxylase, monoamine oxidase, and catechol-*O*-methyltransferase; (7) metabolic enzymes for drugs of abuse (e.g., alcohol) such as alcohol dehydrogenase and aldehyde dehydrogenase; (8) gene products involved in signaling pathways relevant to addiction such as G-proteins coupled to metabotropic receptors, protein kinase A, protein kinase C, dopamine- and cyclic AMP-regulated phosphoprotein, and cyclin-dependent kinase 5, and (9) transcription factors such as ΔfosB and cyclic AMP-response element binding protein. For the most part,

these genes have been revealed to contribute to the development of addiction to various drugs of abuse [19, 54], indicating their significant roles in the responses to drugs of abuse and the vulnerability for addiction. Recently, knockouts of circadian rhythm genes such as *Period 1*, *Period 2*, and *Clock* have also been shown to be involved in the development of addiction [52], reflecting the diversity of pathways leading to addiction and the complexity of addictive traits.

The knockout mice with ablation of a particular gene product are subjected to a variety of behavioral tests to assess their responses to drugs of abuse. The phenotypic traits most often used in mice to model human addictive behaviors include sensitivity and tolerance to addictive drugs, withdrawal syndrome, locomotor activity, locomotor sensitization, conditioned place preference and/or aversion, voluntary drinking (for alcohol addiction study), self-administration, and conditioned reinforcement paradigms. For details about addiction behavioral tests in rodent models, please refer to the other chapters in this textbook.

Double-Knockout

Almost all drugs of abuse induce increased levels of neurotransmitter dopamine in the mesolimbic circuitry, which has been postulated to be an integral mediator of a reward response causing certain aspects of addiction. The signaling effects of neurotransmitter dopamine are mediated by dopamine receptors in neurons. However, the released dopamine in the synaptic cleft is removed by the dopamine transporter and deposited back into surrounding neurons, thereby terminating the signal of the neurotransmitter. As one of the plasma membrane monoamine transporters, the dopamine transporter is recognized as an important integral protein in the mesolimbic dopaminergic system to facilitate regulation of the dopamine signal.

Cocaine blocks the dopamine transporter by binding directly to the transporter and reducing the rate of transport, thus increasing extracellular dopamine levels. In homozygous dopamine transporter knockout mice ($Dat^{-/-}$), dopamine persists at least 100 times longer in the extracellular cleft [27], demonstrating the critical role of the dopamine transporter in regulating dopamine neurotransmission. However, the mice lacking the dopamine transporter surprisingly express intact cocaine reward in conditioned place preference [65] and self-administration paradigms [62], although the cocaine-induced locomotor hyperactivity is absent [27]. The results indicate that the reinforcing effects of cocaine are beyond the dopamine transporter, although not beyond dopamine, challenging the theory of the dopamine transporter as the major target for cocaine's reinforcement effects. Due to the constitutive elimination of the dopamine transporter, it was suggested that developmental compensatory mechanisms might occur. Other monoamine transporters such as the serotonin transporter and the norepinephrine transporter are most likely to take over the charge, mediating the reinforcing effects of cocaine beyond the dopamine transporter. Subsequent evidence revealed that in the absence of the dopamine transporter, there is greater participation of the serotonin transporter and norepinephrine transporter in cocaine reward. Both serotonin transporter and norepinephrine transporter blockers (fluoxetine and nisoxetine) produced significant conditioned place preference in $Dat^{-/-}$ mice but not in wild-type mice [34]. In contrast to $Dat^{-/-}$ mice, homozygous serotonin transporter knockout mice ($Sert^{-/-}$) have enhanced cocaine reward as assessed in the conditioned place preference paradigm [65]. Similarly, the mice lacking the norepinephrine transporter ($Net^{-/-}$) are hyper-responsive to locomotor stimulation induced by cocaine [82].

To investigate the developmental compensation between monoamine transporters, double-knockout mice have been generated. Whereas the dopamine transporter and serotonin transporter combined double-knockout mice ($Dat^{-/-}$/$Sert^{-/-}$) strikingly eliminate cocaine reward [64], the norepinephrine transporter and serotonin transporter combined

double-knockout mice ($Net^{-/-}/Sert^{-/-}$) display greater increased cocaine reward [34]. These studies bring together evidence that cocaine acts through diverse and not exclusive mechanisms. To explain dynamically cocaine's rewarding and reinforcing effects, several genes in monoaminergic systems, particularly in dopaminergic and serotonergic systems, would need to be investigated.

Knockins in Addiction Studies

Whereas knockout generally disrupts endogenous genes by insertion or replacement, knockin can subtly modify endogenous genes by replacement. As genes that confer susceptibility to human addiction disorders are identified in forward genetics, introducing corresponding mutations into the mouse genome and generating a knockin model will be possible and useful for studying the pathophysiology and treatment of addictive behaviors. We provide below two examples of the application of knockin gene-targeting technology in addiction genetic studies, both of which applied the Cre-*loxP* recombinase system to remove the selection marker (*neo*) for subtle point mutation.

Knockin Mouse Model of Brain-Derived Neurotrophic Factor (BDNF) Met Allele

As the most abundant neurotrophic factor in the brain, brain-derived neurotrophic factor plays established roles in neuronal survival, differentiation, and synaptic plasticity. BDNF exerts its influence in the brain through two receptors: high-affinity TrkB receptor (a tyrosine kinase receptor) and low-affinity p75 receptor. Since BDNF gives trophic support and contributes to the survival and differentiation of midbrain dopamine neurons, the center of the reward system that is activated by most drugs of abuse, BDNF is suggested to be one of the pivotal players in drug addiction. In animal studies, cocaine self-administration and subsequent withdrawal from the drug result in profound long-lasting increases in BDNF within the mesolimbic dopamine system [32]. Infusion of BDNF into the mesolimbic dopamine system dramatically enhances the rewarding effects of cocaine as measured by the conditioned place preference paradigm [37] and self-administration trait [30]. In contrast, injection of antibody against BDNF decreases potently the animal's motivation to work for cocaine [30]. Although homozygous Bdnf knockout mice ($Bdnf^{-/-}$) display profound neuronal loss and often die prior to their third postnatal week, heterozygous knockout mice ($Bdnf^{+/-}$) are viable and display roughly half of the wild-type Bdnf levels [18]. As assessed in the conditioned place preference paradigm and locomotor activity, $Bdnf^{+/-}$ mice are less responsive to cocaine's rewarding and locomotor activating effects [33, 37].

Forward genetic studies have also revealed modest associations of BDNF with substance abuse, including smoking and nicotine dependence [8, 44], methamphetamine and heroin [15, 38], alcohol [51, 75], and others [46, 83]. Specifically, a functional SNP G196A (dbSNP ID rs6265), producing valine (Val)-to-methionine (Met) substitution at codon 66 (Val66Met) of the BDNF prodomain region, has received extensive attention through linkage and association approaches in several psychiatric disorders and measures of cognitive function, in addition to addictive behaviors. A recent meta-analysis restricted to individual case-control studies demonstrated that the Val/Met and Met/Met genotypes of the Val66Met variant in BDNF confer a 21% protective effect in substance-related disorders and increase the risk for eating disorders up to 33%, whereas the homozygous carrier Met/Met has a 19% increased risk of schizophrenia with respect to the heterozygous state [31]. In in vitro neuronal culture studies, the Val66Met polymorphism does not affect mature BDNF function, but it has been shown to alter the intracellular tracking and packaging of the BDNF

precursor (pro-BDNF) and, thus, to affect regulated secretion of the mature protein [14, 22].

Polymorphism Val66Met is found only in humans and is common in human populations with an allele frequency of approximately 18% in Caucasians and approximately 41% in Asians. To address fundamental questions about in vivo consequences of this SNP in humans, Chen et al. generated a $Bdnf_{Met}$ knockin mouse model that reproduces the phenotypic hallmarks in humans with the variant Met allele [13]. Because the transcription of the knocked-in $Bdnf_{Met}$ allele is regulated by endogenous Bdnf promoters, the expression levels of Bdnf in heterozygote $Bdnf^{+/Met}$ and homozygote $Bdnf^{Met/Met}$ mice are similar to those of wild-type controls. Although no difference is observed in constitutive secretion of either $Bdnf^{+/Met}$ or $Bdnf^{Met/Met}$, a significant decrease of regulated secretion in hippocampal-cortical neurons is shown from both $Bdnf^{+/Met}$ and $Bdnf^{Met/Met}$. This decrease of Bdnf-regulated secretion in $Bdnf_{Met}$ knockin mice is somehow comparable to the roughly 50% expression loss of $Bdnf_{Met}$ in heterozygous knockout $Bdnf^{+/-}$ mice, resulting in a significant reduction of hippocampal volume, a significant decrease in dendritic complexity in dentate gyrus neurons, significantly less context-dependent memory, and increased body weight, intermale aggressiveness, and anxiety-related behaviors, as compared with wild-type mice. The results are consistent with human studies reporting that humans heterozygous for the Met allele have smaller hippocampal volume [12, 57, 70], and help to foster the argument of whether the Met allele has significant genetic association with an increased anxiety trait [13, 39, 69].

The majority of BDNF is released from the regulated secretory pathway in neurons [47]. Impaired regulated secretion from $Bdnf^{Met/Met}$ neurons represents a significant decrease in available BDNF, comparable to that in $Bdnf^{+/-}$ neurons. Accumulating evidence on BDNF function suggests that the Val66Met polymorphism may be a critical modifying genetic factor in the expression of a number of normal and abnormal brain conditions. Thus, $Bdnf_{Met}$ knockin mice represent a unique model that links directly the variant of BDNF to a defined set of in vivo consequences. Although the addictive behaviors of $Bdnf_{Met}$ knockin mice remain to be investigated, results from human genetic studies and Bdnf knockout mice suggest that $Bdnf_{Met}$ knockin mice may serve as a valuable model for us to gain a better understanding of the neurobiology of BDNF contributing to addictive behaviors and to identify novel pharmacologic approaches to treating addictive disorders.

Knockin Mouse Model of Nicotinic Acetylcholine Receptor (nAChR) α4 Subunit

The neuronal nAChRs are a family of pentameric ligand-gated ion channels widely expressed in the central and peripheral nervous systems. They are activated by the endogenous neurotransmitter acetylcholine, as well as by nicotine, the primary addictive component of tobacco smoke. Activation of nAChRs can potentiate neurotransmitter release (when expressed at presynaptic terminals) and neuronal excitability (when expressed at postsynaptic terminals) throughout the brain. As a result, nAChRs contribute to a wide range of brain activities that include cognitive functions and neuronal development and degeneration. Nicotine dependence is initiated through the activation of nAChRs. Chronic nicotine exposure produces the long-lasting physiological and behavioral changes associated with addiction, including nAChR up-regulation, gene expression alteration, and long-term potentiation and depression induction at glutamatergic synapses.

Of the heteromeric and homomeric nAChR subtypes formed by 12 nAChR subunits (α2–α10 and β2–β4) identified so far, the highest-affinity and most abundant nicotine binding in the brain is the subtype of nAChR containing α4 and β2 subunits (denoted α4β2*). Compared with wild-type mice, α4 and β2 knockout mice do not

respond with increased release of the pleasure-causing brain chemical dopamine [49, 60], a reaction thought to be a key factor in the development of nicotine addiction, although α4 knockout mice express a higher basal level of striatal dopamine. In addition, β2 knockout mice self-administer cocaine but fail to maintain self-administration when the cocaine is switched to nicotine [60], whereas α4 knockout mice exhibit a prolonged motor activity response to cocaine [49]. Results from both α4 and β2 knockout mouse models suggest that α4β2* nAChRs are necessary for proper regulation of dopamine release and the maintenance of self-administration and reinforcement. In contrast, human genetic analyses in genes *CHRNA4* and *CHRNB2*, encoding α4 and β2 subunits, respectively, detected a significant association of *CHRNA4* [25, 45], but not *CHRNB2* [24, 45, 63], with nicotine dependence in various populations.

The necessity of the α4 subunit in the development of nicotine addiction has been indicated in genetic studies of humans and animal models. To address the question of whether the nAChR with the hypersensitive α4 subunit is sufficient to initiate the addictive behaviors, Lester and colleagues produced α4 knockin mice by point mutations [42, 71]. The substitution of leucine (Leu) with serine (Leu9'Ser) or alanine (Leu9'Ala) within the putative pore-forming M2 domain of the α4 subunit renders the α4* nAChR hypersensitive to nicotine and acetylcholine. However, knockin of Leu9'Ser results in a severe phenotype: perinatal death of animals that carry either a single copy of the dominant *neo*-deleted allele (heterozygote of subtle knockin) or two copies of the *neo*-intact mutant allele (homozygote of knockin containing the *neo* selection marker). The viable *neo*-intact heterozygous α4 knockin mice exhibit increased anxiety, impaired motor learning, excessive ambulation that is eliminated by very low levels of nicotine, and a reduction of dopaminergic function upon aging [42]. In contrast, both homozygous and heterozygous Leu9'Ala animals are viable and fertile in subsequent knockin mice generation. Intriguingly, the genetically modified Leu9'Ala mice are exceptionally sensitive to the effects of nicotine and show dependence-related behaviors, including reward, tolerance, and sensitization, in addition to functional nAChR up-regulation when exposed to nicotine doses that are far too small to cause similar effects in unmodified mice [71]. The results suggest that activation of the α4* nAChR is likely sufficient for nicotine addiction, and the work represents a significant step forward in understanding how nicotine hijacks the brain's normal signaling process. Because of the dramatically increased sensitivity in Leu9'Ala knockin mice, one can selectively and potently activate the α4* nAChR by applying low doses of agonists that do not activate other nAChR subtypes. In view of this, the Leu9'Ala knockin mice represent an excellent model for studies on molecular, behavioral, and pharmacological aspects of nicotine addiction.

Conditional Gene Modification in Addiction Studies

The brain is a complex nervous system with many individual molecules fulfilling distinct functions within neurons and neural circuits, depending on their sites and time of expression. Molecular mechanisms of specific brain disorders such as addiction may be restricted to subsets of neurons at specific time points during development and maturity. Therefore, the complete elimination of a specific gene expression throughout the nervous system with conventional knockout may prove ineffective toward understanding fine molecular processes in higher brain functions. As such, conditional gene targeting, which is able to control gene knockout both spatially and temporally and to circumvent the potential for lethality and developmental perturbations, has become a powerful approach for the refined investigation.

Cre Mice and Conditional Knockout in Addictive Behavior Studies

Many conditional gene targetings have been conducted in the nervous system [26]. Of them, the Cre-*loxP* recombination system is the most popular one applied to control the inactivation of genes of interest. Since Cre expression is crucial for the success of conditional gene modification, a variety of Cre mouse lines expressing Cre recombinase under various promoters have been developed [26] and are expanding rapidly. These promoters driving Cre expression are responsible for the temporal and regional control of the conditional genetic recombination. A definitive Cre mouse database can be found in the Nagy Laboratory's Web site (http://www.mshri.on.ca/nagy/Cre-pub.html).

So far, only a few conditional knockouts have been done to address molecular mechanisms of addictive behaviors. Using the CamKII-Cre transgenic line in which Cre expression is driven by the calcium/calmodulin-dependent protein kinase II promoter, the conditional knockout of the adenosine A_{2A} receptor (*Adora2a*) impaired behavioral sensitization and augmented locomotor responses to repeated amphetamine administration [3]; the conditional knockout of Bdnf attenuated opiate withdrawal reactions [2], whereas the conditional knockout of calcineurin (*Ppp3ca*) maintained the locomotor stimulatory effects of amphetamine [53]. Using the Nestin-Cre transgenic line in which Cre expression is driven by the nestin promoter, the selective inactivation of the transcription factor cyclic AMP-response element binding protein reduced the behavioral expression of morphine abstinence but had no modification of motivational responses to morphine and cocaine [80]; the selective inactivation of the glucocorticoid receptor (*Nr3c1*) flattened the dose-response function for cocaine self-administration and suppressed behavioral sensitization [20], whereas the selective inactivation of neurotrophin-3 decreased somatic symptoms and aversion of opiate withdrawal [1]. In addition, more conditional ablation data have been accumulated in exploring the molecular basis of synaptic plasticity underlying learning and memory processes, locomotion activity, and emotional responses [26], all of which may contribute significantly to our understanding of the complex biological mechanisms underlying drug addiction.

Conditional Knockout of Cyclin-Dependent Kinase 5 (Cdk5)

Cyclin-dependent kinase 5 is a serine/threonine protein kinase that has been implicated as an important player in the cellular and physiological responses to drugs of abuse [5]. It regulates numerous aspects of neuronal function, including cyclic AMP and Ca^{2+} signaling transduction cascades, presynaptic machinery, and synaptic plasticity. In the mesolimbic circuitry involved in reward-motivated behavior, Cdk5 controls dopamine neurotransmission through the regulation of the protein phosphatase-1 inhibitor, dopamine- and cyclic AMP-regulated phosphoprotein, and presynaptic components of dopamine synthesis and release.

Constitutive Cdk5 knockout mice are perinatal lethal and have congenital abnormalities, which hamper the study of Cdk5 function in behavioral paradigms. To generate a Cdk5 conditional knockout mouse model, exons encoding vital Cdk5 catalytic-domain components were flanked with *loxP* elements. When homozygous floxed Cdk5 mice were crossed with a CamKII-Cre transgenic line, the mice losing Cdk5 in the adult forebrain increased the psychomotor-activating effects of cocaine and enhanced the incentive motivation for food. These behavioral changes were accompanied by increased excitability of medium spiny neurons in the nucleus accumbens. When homozygous floxed Cdk5 mice were injected locally in the nucleus accumbens region with the recombinant adeno-associated viruses expressing Cre recombinase, the virus-mediated gene transfer caused region-restricted loss of Cdk5. This regional targeted

knockout of Cdk5 facilitated cocaine-induced locomotor sensitization and conditioned place preference for cocaine [6]. In addition, homozygous floxed Cdk5 mice were crossed with animals bearing an inducible Cre-ERt recombinase transgene under the control of the prion protein promoter. The Cre-ERt is a chimeric protein with Cre recombinase fused to the mutated ligand-binding domain of the estrogen receptor, the activity of which is dependent on the presence of an anti-estrogen, tamoxifen or hydroxytamoxifen [24]. Conditional Cdk5 knockout was then achieved by administration of hydroxytamoxifen, which induces Cre-ERt recombinase activity. It was revealed that conditional knockout of Cdk5 in the adult mouse brain improved performance in spatial learning tasks and enhanced hippocampal long-term potentiation and *N*-methyl-*D*-aspartate receptor-mediated excitatory postsynaptic currents [36]. This example with homozygous floxed Cdk5 mice demonstrated multiple strategies for cell-, region-, and time-specific conditional knockout. The findings from these intelligently designed conditional knockout experiments disclosed significant roles of Cdk5 in the behavioral effects of cocaine, motivation for reinforcement, and learning, memory, and plasticity, which definitely advanced our understanding of the molecular mechanisms underlying addictive disorders and substance abuse.

Summary and Perspective

With the development of the gene targeting approach, genetically engineered mouse models have become increasingly useful for assessing individual genes and genetic polymorphisms contributing to specific behaviors in mice. The technology has provided a very useful alternative to the pharmacological approach to dissecting complex biological mechanisms, and has shown great promise in animal behavioral research. However, attention must be paid to interpreting the behavioral phenotypes relevant to addiction. First, addictive behaviors are complex, may compete with each other, and do not occur in isolation. Thus, it is important to place the focus of analysis on the behaviors themselves rather than allowing a single behavior to represent the complexity of addiction liability. Second, addiction is a complex trait that is not mediated solely by a single gene. Thus, it is important to recognize that the observed behaviors are from the collective effects of multiple genes' interaction in addition to the focused single gene. Third, gene-targeted mice are usually generated on a mixed genetic background. The phenotypic consequences of targeted mutations may be influenced by modifying genes that differ among various inbred strains. In some cases, phenotypic abnormalities have been lost when mutants are bred to a new genetic background [17, 58]. Thus, it is important to use restricted controls with the same genetic background as the experiment group. Also, it is useful to examine the persistence of mutant phenotypes in the context of several genetic backgrounds. Fourth, in constitutive gene targeting, the potential for developmental perturbations is an additional concern. It is somehow difficult to determine whether a mutant phenotype reflects a normal adult role for the gene of interest or an indirect effect of the mutation attributable to perturbed development. Such an effect may lead to over- or under-estimation of the functional significance of the target gene in adult animals.

Translating complex traits into their constituent genetic influences is not an easy task. However, as forward genetic analysis data are accumulating from humans and animals, more and more genes and genetic polymorphisms will be identified with certainty as being associated with various addictive behaviors. Nonetheless, proof of their function will require examination in laboratory animal models. The application of genetic-engineered mouse models not only provides insights into the functional significance of particular genes in neural processes relevant to addictive behaviors, but resembles features of human disorders and provides platforms for the trials of therapeutic prevention and treatment. Fortunately, the pace of development of the relevant technologies in both

forward and reverse genetic studies is accelerating. Genome-wide association studies with millions of SNPs are becoming widespread in addiction genetic research. Combinatorial application of transgenic, gene-targeting, knockdown, and virus-mediated gene transfer technologies with intelligent designs is facilitating the uncovering of neural mechanisms through which mutations alter neural systems to impact addiction behaviors. Such integrated multidisciplinary translational research brings us increasing hope that our converging knowledge of the molecular mechanism underlying addictive behaviors could lead to better therapeutic prevention and treatment of addiction disorders in humans. Of note, although multiple genes are involved in complex disease traits, it may not be necessary to identify all the influential genes to devise novel strategies for prevention and treatment.

Acknowledgments The preparation of this book chapter was supported in part by National Institutes of Health grants DA-12844 and DA-13783 to Ming D. Li.

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Vulnerability to Substance Abuse

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Contents

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Family, Adoption, Twin, and Molecular Genetic Data Each Support Substantial Polygenic Heritability for Addictions

Current models for the genetic architecture for substance dependence in the population are

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_10,

based on information from family, adoption and twin studies that each support substantial heritability for addictions. Twin data, in which concordance in genetically identical monozygotic and genetically half-identical dizygotic twins are compared, also document that most of this heritable influence is not substance-specific. Further, linkage-based (and genome-wide association) studies fail to provide evidence for genes of major effect (e.g., for any single gene whose variants produce substantial differences in addiction vulnerability) for substance dependence.

Support for the idea that vulnerability to addictions is a complex trait with strong genetic influences largely shared by abusers of different legal and illegal addictive substances [60, 128, 131, 138] comes from classical genetic studies. Family studies document that first-degree relatives (e.g., siblings) of addicts display greater risk for developing substance dependence than more distant relatives [89, 138]. Adoption studies find greater similarities between levels of substance abuse between adoptees and their biological relatives than between adoptees and (genetically unrelated) members of their adoptive families [138]. Twin studies consistently show differences in concordance between genetically identical and vs. genetically half identical fraternal twins. These twin datasets provide major support for our understanding of the heritability of vulnerability to addictions [1, 45, 48, 60, 63, 64, 130, 148]. Based on these data, it has been proposed that about 50% of the total addiction vulnerability is heritable.

Twin data also allow us to separate the environmental influences that are shared by sibs from those that are not. Consistent data indicate that the environmental influences on addiction vulnerability that are not shared among members of twin pairs are much larger than those that are shared by members of twin pairs. Thus, e2 > c2 in nearly every such study. Most environmental influences on human addiction vulnerability are thus likely to come from outside of the immediate family environment.

Twin Data Document that Most of this Heritable Influence Is Not Substance-Specific But Provides "Higher Order" Pharmacogenomics

We can also evaluate the extent to which the genetic influences on addiction vulnerability are specific to one substance. Data from studies of identical vs. fraternal twin pairs assesses the degree to which one twin's dependence on a substance enhances the chances of his/her co-twin becoming dependent on a substance of a different class. Results of these analyses document that many of the genetic influences on addiction vulnerability are common to dependence on multiple different substances, although others appear to be substance-specific [1, 63, 131]. These features suggest that many of the genetic influences on vulnerability to addiction are more likely to be related to underlying brain mechanisms that are common to addictions, and that fewer may be specific to the primary pharmacological properties of specific drugs, such as aspects of absorption, distribution, metabolism or excretion.

Elsewhere [135] we have suggested levels of analysis for pharmacogenomics and pharmacogenetics: (1) "primary" pharmacogenomics that describes the genetics of individual differences in the adsorption, distribution, metabolism and/or excretion of a drug; (2) "secondary" pharmacogenomics that describes individual differences in drug targets, such as the G-protein coupled receptors, transporters, and ligand-gated ion channels that are the primary targets of opiates, psychostimulants, and barbiturates, respectively, and (3) "higher order" pharmacogenomics that provide individual differences in post-receptor drug responses. Such post-receptor drug responses are more likely to be common to actions of abused substances that come from several different chemical classes and act at distinct primary receptor or transporter sites in the brain. Based on the twin data that are currently available, we thus postulate that much of the human genetics of addition vulnerability represents "higher order" pharmacogenomics.

Failure to Document Evidence for Substance Dependence Genes of Major Effect in Most Populations

There are few careful studies of the ways in which most human addiction vulnerabilities move through families (e.g., segregation analyses). No such study indicates a "major" gene effect on addiction vulnerability in most current populations. There is an exception: the "flushing syndrome" variants at the aldehyde dehydrogenase and alcohol dehydrogenase loci in Asian individuals do provide genes of major effect in this population. Individuals with these gene variants are at lower risk of becoming dependent on alcohol than individuals with other genotypes [22] in Chinese [23, 126], Korean [117], Japanese [50, 51, 52, 86, 92, 125] and other populations [83, 112]. Homozygous aldehyde dehydrogenase ALDH2*2 individuals are strongly protected from alcohol dependence [50, 51]. This locus thus provides a good example of "primary" pharmacogenomics, though in a restricted population.

Quantity-frequency data for smoking also provide evidence for a replicable "secondary" pharmacogenomic effect of moderate magnitude. Markers in the chromosome 15 gene cluster that encodes the α3, α5 and β4 nicotinic acetylcholine receptors display different allelic frequencies in heavy vs. light smokers in each of several studies [10, 11, 109]. This chromosome 15 locus is likely to provide a good example of "secondary" pharmacogenomics, since it has not been associated as reproducibly with dependence on other substances.

Linkage-based analyses for addiction vulnerabilities would be expected to reproducibly identify many of the genes whose variants exerted major influences on human addiction vulnerability. However, existing linkage data for human dependence on alcohol, nicotine and a number of other substances fails to provide any highly reproducible results that would support any major gene locus ([24, 41, 47, 53, 71, 76, 81, 99, 110, 135, 152] and references therein). These results appear to point to a negative conclusion: that no locus individually contributes a large fraction of the vulnerability to dependence on any addictive substance in most individuals. There are caveats. Many of these data come from subjects with largely European ethnic/racial backgrounds [9, 12, 28–31, 34, 40, 47, 97, 100, 101, 106, 108, 113, 150, 152]. Rare variants might well contribute disproportionate amounts to the vulnerability of individuals within a relatively few pedigrees. Nevertheless, as with many complex human disorders in which initial hopes for a easier (e.g., oligogenic, caused by variants in only a few genes) underlying genetic architecture supported use of linkage approaches, the linkage peaks that are identified in each individual study may be more likely to arise on other bases when the underlying architecture is, in fact, polygenic [46].

Current Models for the Genetic Architecture of Human Dependence

Our current understanding of the genetic architecture of vulnerability to dependence on legal and illegal addictive substances in the population is thus that each is influenced roughly 50% by polygenic genetic influences, that is by variants in individual genes that each contribute modest amounts to this overall genetic vulnerability. These models for genetic architecture indicate that many of these genetic vulnerabilities increase risk for addcition to several pharmacologic classes of abused substances, but that some of these genetic influences are specific to drugs of one class [135].

Analyses of twin data for vulnerability to develop dependence on a substance fit with large additive genetic components (a^2), large components for nonshared environmental influences (e^2) and small components for c^2 terms that represents familial or other environmental influences that are shared between members of the twin pair [1, 45, 48, 60, 63, 64, 130, 148]. What about the possibility that there could be large interactions between these genetic and environmental terms (G × E interactions)? Such large

interactions might even reduce the validity of additive models for genetic and environmental contributions to addiction vulnerabilities.

G × E correlations of three types have been described [98, 111]. In one terminology, "passive" G × E correlation occurs when parents transmit both genetic and environmental influences on a trait [84, 103]. "Active" G × E correlation occurs where subjects of a certain genotype actively select environments that are correlated with that genotype. "Reactive" G × E correlation occurs when an individual's genotype provides different reactions to stimuli that come from the environment. Small values for c^2 influences of common environments shared by members of sib pairs appear to provide evidence against "passive" G × E correlations. "Active" and "reactive" G × E correlations remain possible. One influential train of thought [35, 103] suggests that G × E correlations are best regarded as parts of the genetic variance because "... the non-random aspects of the environment are ... consequence(s) of the genotype(es)...".

Large interactions between genetic and environmental components would be likely to lead to differences in estimates of heritability from samples obtained in different environments and to differences in molecular genetic findings in individuals from different environments. As we have noted, data from studies of twins who were sampled from a number of different environments is nevertheless similar. Such convergence supports relatively modest G × E interactions between genetic and environmental influences on addiction vulnerability, at most. Modest G × E influences are also consistent with genome-wide association molecular genetic results that identify substantial overlaps between molecular genetics of vulnerability to dependence on illegal substances in samples from substantially different environments, such as the United States and Asia (see below).

Gene—gene interactions (G × G) of some magnitude appear likely, a priori, to make at least some contributions to addiction vulnerability. However, if there were large amounts of epistasis, G × G interactions in which specific alleles at one gene locus are required for expression of the effects of allelic variants at a second gene locus, segregation analysis data might provide uneven patterns of familiality. With large amounts of epistasis, second-degree relatives (e.g., cousins) of addicts would be much less likely to display specific combinations of G × G alleles than first-degree relatives (e.g., siblings). Substance dependence rates would thus drop more precipitously between first- and second-degree relatives of addicts than they would if most risk alleles exerted largely independent effects on addiction vulnerability.

There in only a modest amount of family data that allows us to compare concordance in first- vs. second-degree relatives. However, the existing evidence does not support less concordance in second-degree relatives than we would anticipate based on the observed concordance in first-degree relatives and the assumption that most risk alleles produce largely independent effects ([15] and T. Thorgeirsson et al. (2008), "personal communication").

The Genetic Architecture for Substance Dependence in Individuals

What about the genetic architecture for substance dependence in individuals? Both "between-locus" heterogeneity and "within-locus" heterogeneity are likely. Polygenic models for addiction vulnerability imply that each dependent individual might even display a nearly distinct set of risk-elevating or risk-reducing allelic variants. As an illustrative example, we might postulate that (a) an individual must display at least 75 risk alleles to significantly elevate his likelihood of acquiring a substance dependence disorder and (b) there are 300 genes that contain common allelic variants that can augment addiction risk. Under such circumstances, it is easy to see that the exact genetic recipe for addiction vulnerability found in one addicted individual might be replicated in only a relatively few other addicted individuals.

Such an underlying genetic architecture would be consistent with the failure of linkage-based methods to provide reproducible results in addictions, since linkage relies on identifying consistent patterns in the ways that specific DNA markers and phenotypes move through many families that display high densities of the disorder.

As noted above, the best documented genetic heterogeneity for addictions comes from the chromosome 4 major gene effects found in poorly alcohol-metabolizing ("flushing") Asian individuals [50, 51, 52, 83]. The best documented substance-specific influence comes from the chromosome 15 nicotinic acetylcholinergic receptor gene cluster. There are likely to be other examples of between-locus genetic heterogeneity and of genes whose variants exert substance-specific effects on use and/or dependence that have yet to be elucidated.

We also postulate that within-locus heterogeneity is likely, though not yet clearly documented in addiction, to our knowledge. Many common Mendelian disorders and rarer Mendelian phenocopies of common disorders display substantial heterogeneity within their pathogenic loci [32, 121]. Evidence for within-locus heterogeneity in complex disorders is just beginning to be accrued; such evidence now includes data from neurexin gene family variants in autism [2, 3, 4, 122].

"Epigenetics" and Individual Differences in Vulnerability to Addiction and Related Phenotypes

"Epigenetics" is now used with both classical and a more recent definitions. Classical defintions of "epigenetic" emphasize influences of variations that are not encoded in primary DNA sequence but nevertheless inherited "... a change in the state of expression of a gene that does not involve a mutation, but that is nevertheless inherited in the absence of the signal (or event) that initiated the change" [105]. More recent definitions of "epigenetic" emphasize gene regulatory mechanisms that do not alter primary DNA sequence while paying less attention to documenting heritability [105].

In the context of this chapter, heritable epigenetic influences are most relevant. One example of a classical, heritable epigenetic influence is imprinting. Imprinting conveys information from parent to child through mechanisms that include DNA methylation or histone acetylation. These mechanisms retain the primary DNA sequence but can dramatically alter function of specific genes. DNA methylation at CpG sequences in the promoter regions of genes can profoundly alter gene transcription. Since methylation during the course of maternal oocyte (or paternal sperm) development is key to this process, familial patterns of gender-specific transmission can provide evidence for this subset of heritable epigenetic influence.

The modest quality of current family datasets for addiction renders them a relatively weak basis for any strong inferences concerning parent-of-origin effects. Nevertheless, there is no segregation data of which we are aware that supports strong parent-of-origin effects on substance dependence. Thus, while there are obvious and large roles for nonheritable "epigenetic" influences in the biology of addiction, there is no current compelling evidence that there are any strong effects of overall heritable "epigenetic" influences, as classically defined. We nevertheless need to be alert for such influences as we unravel effects of variants in specific genes.

The Nature (and Likely Evolutionary Sources) of the Allelic Variants Likely to Contribute to Individual Differences in Vulnerability to Addiction and Related Phenotypes

A number of the assumptions about genetic architecture and analytic strategies for identification of the individual allelic variants that predispose to addiction vulnerability are based

on the idea that common disease/common allele models hold for many of the variants that alter vulnerabilities to addiction and related phenotypes [72]. Rare variants may also explain significant fractions of the genetic risk for addiction and other common diseases. However, increasing evidence supports roles in addiction vulnerability for allelic variants that are currently common and are thus likely to be "old" in an evolutionary sense. Data indicating that such variants can be identified in diseased individuals from European, African, and Asian genetic backgrounds also point, in general, to variants of substantial age.

Our current understanding of human history increasingly points to long periods when most humans lived in Africa in relatively small groups that remained in relative genetic isolation from each other for many millenia [7]. Such small groups can be viewed as "competing" with each other to provide the ancestry of most modern humans within and outside Africa.

In thinking about how genetic selection might act on common functional allelic variants, it is thus important to consider how selective processes might act in early African environments of small groups of humans. No study of these early environments finds any strong evidence for the presence of any potent addictive substance, to our knowledge. We thus need to consider the ways in which selective proceses might have operated in the absence of both addictive substances and in the absence of selective evolutionary pressures that can be attributed to use of addictive substances.

As one starting point, it is conceivable that some currently common allelic variants could exert polygenic influences on addiction vulnerability without exerting any significant positive or negative selective effects during lengthy evolutionary histories. However, most such neutral variants would be expected to display evidence for genetic drift and related stochastic mechanisms that would provide fixation for their alleles long before current human populations were born (e.g., one allele would disappear on stochastic grounds).

It thus also seems likely that many allelic variants that influence addiction vulnerability must have provided balancing selection. Balancing selection provides one of the few theoretical means for maintaining common allelic variants over extended periods of time. "In the era of molecular population genetics, … balancing selection (refers to) loci (that display) levels of nucleotide polymorphism that exceed neutral expectation" [91]. We think of balancing selection as providing influences that are favorable in some individuals or organs or circumstances and unfavorable in other individuals or organs or circumstances.

Thinking about such balancing selection could have several consequences:

(1) First, the biology of some genes might allow for common, functional allelic variants that could escape selective pressures or exert balancing selection over many generations. By contrast, other genes might not be able to harbor such allelic variations without engendering selective pressures that would reduce the frequency of all but one of the allelic variants in the population over time.

    Common allelic variants that are able to influence addiction vulnerability are thus likely to be restricted to a subset of the genes whose products are involved in addictive processes. An important consequence of this logic follows: if a gene fails to display variants that influence vulnerability to addiction, the gene's products are not at all excluded from involvement in addiction.

(2) Secondly, the nature of balancing selection suggests strongly that addiction vulnerability alleles that display great evolutionary ages were likely to experience both positive and negative selection pressures that "balanced" based on their effects on other pheotypes, not addiction. Below, we summarize some of the current evidence that many addiction-vulnerability allelic variants might provide "pleiotropic" influences on a variety of related, heritable phenotypes.

In the context of this evolutionary discussion, balancing selection thus requires that an allelic variant influence a phenotype that can be subjected to balancing selection pressures in the absence of addictive substances. Put in another way, convincing data that implicates a gene's common variants in addiction should prompt us to consider mechanisms whereby such variants might provide balancing (e.g., both positive and negative) selective influences in the differing environments through which the ancestors of current human populations have passed.

It is important to note that this logic is different from the logic of many other brain disorders that: (1) are also influenced by complex genetic determinants, but (2) which lead to reduced fertility in current populations and are thus likely to have provided substantial negative selection pressures in older environments [54]. Such logic would lead to the conclusion that more "newer" allelic variants would be identified for these disorders.

How does this discussion of common disease/common allele hypotheses relate to the postulates of genetic heterogeneity noted above? None of the above discussion about common alleles and common variants precludes (or even reduces the likelihood of) contributions of rarer (or even "private") allelic variants, including those that have arisen more recently in evolutionary time. Recently arising variations would be much more likely to persist for a number of generations even in the face of even moderately negative influences on survival or fertility. Indeed, based on experience with other genetic disorders, it may be worthwhile to actively search for effects of rarer "phenocopy" variants in genes that are initially identified based on common (and evolutionarily older) allelic variants [124]. A rarer copy number variant might contribute to addiction vulnerability by altering levels of expression of a gene that also contains more common allelic variants that alter expression via SNPs in other gene elements, for example [2–4, 122]. Such considerations support searches within identified loci for molecular genetic heterogeneity relevant to addiction.

Genome-Wide Association Results for Addiction

Genome-Wide Association

Genome-wide association is now increasingly the method of choice for identifying allelic variants that contribute to complex genetic disorders, especially those with polygenic genetic bases (e.g., derived from effects at many gene loci, each with modest effects, as well as from environmental determinants) [6, 11, 25, 33, 37, 42, 75, 114, 144]. Substance dependence was one of the first complex phenotypes for which replicated association-based genome scanning data was reported [11, 56, 78, 79, 127, 141]. There is now a torrent of information from genome-wide association studies of both substance dependence and other heritable brain-based phenotypes that co-occur with addictions more than expected by chance and are thus good candidates to display genetic overlaps with addiction (reviewed in [136]). Genome-wide association (also termed "whole genome association" or "association genome scanning") [11, 58, 78, 79, 109, 137, 139, 140, 141, 144] asks how addiction phenotypes and genetic markers (genotyped approximately every 1/500,000th to every 1/1,000,000th of the genome in current datasets) are found together in nominally unrelated individuals (although we are all distantly related to each other, of course). We and others have developed these methods, relying on the increasing densities of single nucleotide polymorphism markers that can be assessed using "single nucleotide polymorphism chip" microarrays of increasing sophistication [58, 78, 79, 137, 139, 140, 141]. Genome-wide association gains power as densities of genomic markers increase. Association identifies much smaller chromosomal regions than linkage-based approaches. Association thus allows us to identify variants in specific genes rather than in large chromosomal regions. Genome-wide association fosters pooling strategies that preserve confidentiality and reduce costs, as we discuss below [16, 17, 18, 58,

78, 79, 87, 88, 95, 115, 141]. Genome-wide association provides ample genomic controls. Proper genomic controls can minimize the chances that disease vs. control differences are confounded by occult stratification, such as the stratification that might arise from unintended occult ethnic mismatches between disease and control samples.

It is important to note that there is no single approach to designing genome-wide association studies or to analyzing genome-wide association data is now universally accepted. There is now no universal standard for considering genome-wide association results "significant" in ways that allow us to identify polygenic allelic variants in reasonably sized single experiments.

In analyzing data from addiction vulnerability samples, we focus here and in a recent review [136] on clusters of genomic markers whose allele frequencies distinguish control individuals from those with substance dependence or addiction-related phenotypes. We identify chromosomal regions that contain clusters of such nominally positive results in replicate samples for addiction vulnerability. We then describe evidence for generalization that arises from identification of overlapping chromosomal locations of clustered positive results for different phenotypes. These data thus support pleiotropic influences (e.g., contributions of the same allelic variants to multiple phenotypes) of common allelic variants on several of the brain-based phenotypes. The data thus document overlapping heritable influences on several interesting brain phenotypes.

In the analyses presented in this chapter, we focus on addiction-associated allelic variants that lie in genes. Evolutionarily old common haplotypes (e.g., groups of nearby variants that travel together through generations) that lie within genes are among the most likely to be tagged by single nucleotide polymorphism markers that are represented on current microarrays. Haplotypes that involve genes are thus among the most likely variants to exist in currently reported datasets. It seems reasonable to postulate that many of these allelic variants that lie within genes provide regulatory variants that alter expression or regulation. Other variants are likely to alter mRNA halflives or mRNA splicing. Variants that alter mRNA splicing could occur at the locus of the affected gene (*cis*) or at genes at different loci that alter generic mRNA splicing processes (*trans*). Reproducible association of A2BP1 gene variants with addiction vulnerability, for example [78], provide a good candidate for *trans* effects on mRNA splicing, since this gene's product regulates splicing and thus are likely to modify the functions of a number of other genes expressed in brain. It seems likely that only a minority of the addiction-associated variants will involve missense effects on expressed proteins.

It also seems likely that many addiction-associated variants will lie outside of genes, at least as we currently understand them. Loci reproducibly associated with diabetes/body mass, for example, lack conventional hallmarks of "genes", such as expressed sequences [37]. While the analyses in this chapter focus on the identification of variants within genes, we should also remain alert for roles for "intergenic" variations in chromosomal regions that lie between currently understood genes.

Samples for Genome Studies of Human Addiction Vulnerabilities and Related Phenotypes

As we have recently reviewed [136], genome-wide association data for addiction vulnerability samples from European, African and Asian genetic heritages is now available. As of this writing, these data come from European-American research volunteers, African-American research volunteers, Asian individuals who largely presented to emergency facilities with methamphetamine psychosis and matched controls, dependent and non smokers, largely of European ancestries and individuals sampled as parts of epidemiological studies.

These data can be compared to data from four studies of individuals of European ancestries

with bipolar disorder compared matched controls, individuals of European ancestry who were assessed for ratios between frontal and intracranial brain volumes based on magnetic resonance imaging scans, smokers of European ancestry who participated in clinical trials for smoking cessation, African-American individuals who participated in tests of cognitive ability, individuals of European ancestry with Alzheimer's disease and individual of European ancestry studied for personality triats.

Substance Dependence vs. Controls

Substance dependent individuals, when compared to control individuals, reproducibly display association signals of modest sizes that identify genes. Monte Carlo simulations provide a basis for assessing how often there reproducible association signals might be found by chance. In comparison of the data from a number of samples, these simulations identify convergent data that is virtually never found by chance (reviewed in [136]).

These analyses provide some of the strongest molecular genetic support for the classical genetic studies of addiction vulnerability. They also provide substantial support for the idea that many of the allelic variants that predispose to addiction vulnerability are evolutionarily "old", since strongly convergent findings are found in comparing substance dependent to control individuals of European-, African- and Asian genetic backgrounds. These analyses also provide support for the idea that dependence on substances of different classes is influenced by substantially overlapping genetic influences. We have identified overlaps that are much greater than chance for dependence on a number of illegal substances (including methamphetamine), alcohol and nicotine (reviewed in [136]). None of the results that compare substance dependent vs. control individuals identifies any gene's allelic variants that appear to provide large effects. These observations are consistent with the failure of linkage-based studies for substance dependence to identify any highly reproducible loci, even though similar *Diagnostic and Statistical Manual of Mental Disorders* and Fagerstrom diagnoses were used for linkage.

We list some of the genes that are identified by these reproducible findings in Table 1. While the nature of these genes is likely to be complex for many readers of this chapter, it is worth noting that many of these genes' products are expressed in the brain and that many are likely to be involved with the ways in which the brain forms and adapts during adulthood. These genes thus fit with the memory-like components that are clinically observed as major parts of addiction, as we have reviewed elsewhere [135].

Genome-Wide Association Results for Other Heritable Phenotypes that Co-Occur with Addiction and Display Overlapping Molecular Genetic Findings

Phenotypes that Might have Contributed to Balancing Selection of Addiction-Related Alleles

It is interesting to speculate about the phenotypes that may have provided the basis for balancing or other selective processes for the common allelic variants that are observed in several current populations and influence vulnerability to substance dependence in current environments. Heritable, interrelated influences on cognitive abilities and brain volumes, especially of the frontal lobe, provide interesting examples of such phenotypes. Both of these phenotypes are substantially heritable in data from twin studies. The heritability of both of these phenotypes is substantially correlated in twin study data. Samples of substance dependent individuals, though of modest size, reproducibly display smaller frontal lobes and poorer performance on tests of cognitive function. It is easy to see how cognitive function might have provided a selective

Table 1 "Cell adhesion" and "drug target" genes identified in multiple genome-wide association studies of addiction and related disorders

Chr	Base pair	Gene symbol	Description	Samples with clustered positive SNPs (from [136])	Monte Carlo convergence p value
6	69,404,158	BAI3	Brain-specific angiogenesis inhibitor 3	1,2,3,7,9,10,17	< 0.00001
16	81,218,079	CDH13	Cadherin 13	1,2,3,4,5,6,7,8,9,11,12,13,14,15,16,17	< 0.00001
3	141,136,897	CLSTN2	Calsyntenin 2	3,4,5,7,8,10,12,13,14,15,16,17	< 0.00001
7	145,444,386	CNTNAP2	Contactin associated protein-like 2	3,4,5,6,7,8,9,11,14,15,16,17	< 0.00001
8	2,782,789	CSMD1	CUB and Sushi multiple domains 1	1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17	< 0.00001
2	79,593,634	CTNNA2	Catenin α 2	3,4,5,6,7,8,9,13,14,15,16,17	< 0.00001
1	57,236,167	DAB1	Disabled homolog 1	3,4,5,6,7,8,9,12,14,15,16,17	< 0.00001
21	40,306,213	DSCAM	Down syndrome cell adhesion molecule	1,2,3,4,5,7,8,12,13,15,16,17	< 0.00001
2	50,000,992	NRXN1	Neurexin 1	3,4,5,6,9,11,14,15,16,17	< 0.00001
9	8,307,268	PTPRD	Receptor protein tyrosine phosphatase D	1,2,3,4,5,6,8,11,13,14,15,16	< 0.00001
8	13,991,744	SGCZ	Sarcoglycan zeta	1,2,3,4,5,8,9,10,11,13,14,15,16,17	< 0.00001
9	118,227,328	ASTN2	Astrotactin 2	1,2,4,5,6,8,9,13,15,16,17	0.000070
3	2,117,247	CNTN4	Contactin 4	1,2,3,6,8,9,11,15,16	0.000110
3	1,109,629	CNTN6	Contactin 6	1,2,3,4,6,8,9,10,15	0.000120
2	140,705,466	LRP1B	Low-density lipoprotein-related protein 1B	1,2,3,5,6,8,9,10,11,13,15,16,17	0.000150
8	32,525,295	NRG1	Neuregulin 1	3,4,5,6,7,11,15,16	0.000240
7	20,337,250	ITGB8	Integrin β 8	1,2,8,9,15,16	0.000260
18	7,557,817	PTPRM	Receptor protein tyrosine phosphatase M	1,2,3,4,5,7,11,13,15,16,17	0.000290
1	64,012,302	ROR1	Receptor tyrosine kinase-like orphan rec 1	4,5,7,8,9,13,15,16	0.000290
5	14,196,829	TRIO	Triple functional domain/PTPRF interact	1,2,9,11,13,14,15	0.000690
1	33,752,196	CSMD2	CUB and Sushi multiple domains 2	1,2,3,4,7,8,11,14,17,18,17	0.000830
11	98,397,081	CNTN5	Contactin 5	1,2,3,5,6,7,8,9,11,14,15,17	0.000980
10	67,349,937	CTNNA3	Catenin α 3	1,2,3,5,6,7,8,13,15,16,17	0.001090
9	27,938,528	LRRN6C	Leucine rich repeat neuronal 6C	1,2,3,4,5,6,7,8,9,11,15,16,17	0.001340
5	11,024,952	CTNND2	Catenin δ 2	1,2,3,5,6,9,15,16	0.003270
12	97,653,202	ANKS1B	Ankyrin repeat sterile α domain 1B	1,2,5,6,9,15,16,17	0.003410
7	80,209,790	SEMA3C	Semaphorin 3C	1,2,9,16	0.006310

Table 1 (continued)

Chr	Base pair	Gene symbol	Description	Samples with clustered positive SNPs (from [136])	Monte Carlo convergence p value
15	31,390,469	RYR3	Ryanodine receptor 3	1,2,3,4,5,6,7,8,9,13,15,16,17	< 0.00001
10	12,431,589	CAMK1D	Calcium/calmodulin-dependent protein kinase ID	1,2,7,8,9,13,15,16,17	< 0.00001
7	29,200,646	CHN2	Chimerin 2	1,2,3,7,8,10,13,14,15,16	< 0.00001
3	59,710,076	FHIT	Fragile histidine triad gene	1,2,3,4,5,6,7,8,9,10,13,15,16,17	< 0.00001
10	52,504,299	PRKG1	cGMP-dependent protein kinase I	1,2,3,4,5,6,7,8,9,11,12,13,14,15,16,17	< 0.00001
14	93,914,451	SERPINA1	Serpin peptidase inhibitor A 1	1,2,5,13,14	< 0.00001
22	31,999,063	LARGE	Like-glycosyltransferase	3,4,5,7,9,13,14,15,16	0.00002
6	149,110,157	UST	Uronyl-2-sulfotransferase	1,2,6,15,16,17,18	0.00017
9	89,302,576	DAPK1	Death-associated protein kinase 1	1,2,3,5,13,14,15,16	0.00024
11	11,248,999	GALNTL4	UDPNAc-α-D-galactosamine:polypeptide NAcgalactosaminyltransferase-like 4	1,2,3,4,5,,9,15,16,17	0.00040
2	30,799,141	CAPN13	Calpain 13	1,2,3,5,6,8,15	0.00042
5	58,302,468	PDE4D	cAMD-specific phosphodiesterase 4D	1,2,4,5,6,8,9,15,16,17	0.00055
15	83,724,875	AKAP13	Protein kinase A anchor protein 13	1,2,4,6,8,13,14,15,16	0.00062
1	76,312,992	ST6GALNAC3	αNAcneuraminyl-2,3-β-galactosyl-1, 3-NAcgalactosaminide α2,6-sialyltransferase 3	4,5,6,9,11,13,14,15,16,17	0.00063
14	93,900,404	SERPINA2	Serpin peptidase inhibitor A 2	1,2,13,14	0.00080
7	14,153,770	DGKB	Diacylglycerol kinase β	1,2,3,8,9,13,15,16,17	0.00138
13	101,173,036	FGF14	Fibroblast growth factor 14	1,2,3,6,7,12,15,16	0.00001
3	6,877,927	GRM7	Metabotropic glutamate receptor 7	1,2,3,5,6,7,8,11,14,15	< 0.00001
2	132,891,086	GPR39	G protein-coupled receptor 39	1,2,8,14,15	0.00033
13	94,470,090	ABCC4	ATP-binding cassette C 4	1,2,5,10,15,16	< 0.00001
20	19,141,290	SLC24A3	Solute carrier family 24 member 3	3,4,5,7,8,11,14,15,16	0.00033
8	56,177,571	XKR4	XK family member 4	1,2,3,4,5,11,15,16,19	0.00091
3	144,466,754	SLC9A9	Solute carrier family 9 member 9	1,2,3,4,6,8,9,13,15	0.00134

Columns list gene symbol, gene description, chromosome, basepair of gene start, samples in which clustered nominally positive single nucleotide polymorphisms (SNPs) are found and overall p value for this gene in this entire dataset, based on 100,000 Monte Carlo simulation trials. Note that genes that are identified strongly in a single sample will not be included on this list. Sample numbers are: 1–6 substance dependence, 7–9 bipolar disorder, 10–11 brain volume, 12–14 success at quiting smoking, 15–16 cognitive abilities, 17 neuroticism

Adapted from Uhl et al. [136]

pressure. When we consider the substantial mortality that cephalopelvic disproportion is likely to have caused in the environments in which our distant ancestors lived, it is easy to develop a plausible "balancing selection" hypothesis.

We have identified substantial, reproducible data for both of these phenotypes from genome-wide association datasets, and identified large overlaps between the genes identified on the basis of cognitive abilities vs. the genes identified on the basis of frontal lobe brain volumes, as expected (reviewed in [136]).

Interestingly, there is also significant overlap, more than expected by chance, between these sets of genes and those identified in comparing addicted vs. control samples (reviewed in [136]).

Personality traits that display substantial evidence for heritability are also found in substance dependent individuals at rates different from those in the general population [26]. A genome-wide association dataset for the most addiction associated personality feature, neuroticism, displays highly significant overlap with data for substance dependence as well.

Psychiatric and Neurologic Comorbidity

Data for the highly heritable psychiatric diagnosis, bipolar disorder, is now available from four largely independent samples from European ancestries. Our clustering analyses for these datasets provide ample evidence of overlap between the results for bipolar disorder (59). Interesting, these data also overlap with the molecular genetic results for substance dependence to extents greater than chance.

Success in Smoking Cessation

Twin studies support the idea that at ability to successfully quit at least one of the major addictive substances, tobacco smoking, is substantially heritable (reviewed in [136, 140]). Much of this heritability apparently is not the same as the heritability for vulnerability to substance dependence, although some does overlap. We have recently reported genome-wide association analyses of three datasets of smokers who were successful vs. unsuccessful in quitting smoking in the context of a clinical trial. These results display gratifying convergence with each other and more modest, but still significant, overlap with results from vulnerability to become substance dependent, as would have been predicted by the results of classical genetic studies.

Failure of Control Experiments to Support Alternative Hypotheses for the Observed Genome-Wide Association Results

There is also no evidence that many of the clustered, reproducibly positive single nucleotide polymorphisms identified in these data cited above and a number of control comparisons, including controls for occult racial/ethnic differences and assay noise within each comparison group.

Ethical Issues in High-Density Genotyping of Individuals Who are Selected Due to Self-Reported Illegal Behaviors

Individuals who are individually genotyped in relationship to addiction and related phenotypes are subject to a number of potential risks. Some of these risks are shared with individuals who are subjected to high-density genotyping in relationship to other disorders and phenotypes. Other risks are more likely to come to the fore in studies of illegal behaviors.

Concerns relating to insurability, employability, paternity determination and providing (or not providing) genotyped individuals with

access to their genotypes and/or genetic counseling are shared by individuals with other complex disorders [70, 82, 147]. Recent passage of genetic nondiscrimination legislation in the United States mitigates several of these concerns.

However, as we review elsewhere [136], high-density, individual genotyping of DNA from individuals who are addicted to illegal substances raises additional issues. Many of these individuals are likely to have experienced involvement in criminal activities that goes beyond use of illegal substances. Since the risks of high-density individual genotyping in this population have not been as generally discussed elsewhere, we provide several lines of information that may inform thinking about these special ethical issues.

Increasingly ubiquitous DNA testing related to criminal activities lies at the heart of these concerns. In the United States, each state has a DNA database that collects information from crime scenes and from offenders convicted of particular offenses. A combined DNA index system (CODIS) operates local, State, and national DNA profile databases from convicted offenders, unsolved crime scenes and missing persons. Numerous suspects have been identified through matches between DNA profiles from crime scenes and profiles from convicted offenders. A relevant website reports that the "success of CODIS is demonstrated by the thousands of matches that have linked serial cases to each other and cases that have been solved by matching crime scene evidence to known convicted offenders". The European Union is just one of the other international entities with a similar system (http://www.interpol.com/Public/Forensic/dna/dnafaq.asp).

"Core" CODIS data comes from genotypes at 13 simple sequence length polymorphic loci. These loci lie near single nucleotide polymorphism markers that provide information about virtually all of these loci, providing a ready means of translating between single nucleotide polymorphism and simple sequence length polymorphic genotypes. Other mitochondrial, sex chromosome and autosomal markers are also genotyped on substantial numbers of these DNA samples.

A recent, October 2007 analyses of the CODIS-linked DNA index system revealed individually identifying genotype profiles for more than 5 million convicted offenders, as well as almost 200,000 DNA profiles from crime scenes (www.fbi.gov/hq/lab/codis/).

Classes of Genes that are Identified in Multiple Genome-Wide Association Samples for Multiple Phenotypes: Focus on Cell Adhesion-Related Genes

One approach to describing the convergence between the datasets, presented above, relies on the overall convergence between the results obtained in each study. A different approach focuses on convergence of data concerning specific genes and classes of genes, especially when most are expressed in the brain. Many of the genes that we identify in this analysis of convergent genome-wide association findings are involved in "cell adhesion" processes whereby neurons recognize and respond to features of their environments that are important for establishing and maintaining proper connections (Table 1). Others are involved in enzymatic activities, protein translation, trafficking and degradation; transcriptional regulation, receptor, ion channel and transport processes, disease processes and cell structures.

Cell Adhesion-Related Genes

The genes whose products are involved in cell adhesion processes provide a number of especially interesting results (Table 1). Cell adhesion mechanisms are central for properly establishing and regulating neuronal connections during development. Cell adhesion mechanisms can play major roles in mnemonic and other

neuroadaptive processes in adults [8, 145]. It is interesting to note that most of the cell adhesion related genes that we identify in these genome-wide association studies are expressed in developing and adult brains. Altered expression of several of these genes can alter neurite extension [21, 38, 62], activate signaling pathways [27, 55, 57, 66, 96, 149] and alter mnemonic processes [62]. Almost all of these cell adhesion-related genes are expressed in memory-associated brain regions that include hippocampus and cerebral cortex (http://brainmap.org) [65, 69, 74, 123]. By contrast, substantial expression in mesolimbic/mesocortical dopamine "reward system" neurons is not documented for many of them.

"Cell adhesion" related genes identified by these genome-wide association studies encode members of several structural cell adhesion molecule subfamilies. Those that are anchored to cell membranes by glycophosphoinositol anchors, those that display apparent single-transmembrane topologies, those that display apparent seven transmembrane topologies and those that produce soluble products are each represented.

Cell Adhesion Molecules with the Strongest Levels of Cumulative Support

One of the cell adhesion molecules that achieves the most striking nominal p values in these analyses is an "atypical" member of the cadherin gene family, CDH13. Cadherin 13 is a glycophosphoinositol-anchored cell adhesion molecule. CDH13 is expressed in neurons in brain regions that are likely to play roles in addiction, including hippocampus, frontal cortex, and ventral midbrain [123]. CDH13 can inhibit neurite extension from select neuron populations [38, 123] and activate a number of signaling pathways [55, 57, 66, 96]. It is thus a strong candidate for roles in brain mechanisms important for both developing and quitting addictions.

Other cell adhesion related genes that manifest intermediate p values in these analyses include BAI3, CLSTN2, CNTNAP2, CSMD1, CTNNA2, DAB1, DSCAM, NRXN1, PTPRD and SGCZ. Data from NRXN1 associations in smoking have been recently reviewed [93]. We discuss several of the other genes here.

DSCAM

DSCAM is a single-transmembrane domain cell adhesion molecule with immunoglobulin and fibronectin domains that is expressed strongly in brain [5, 149] and in hippocampus in ways that are required for appropriate neuronal connections to form in memory-associated circuits in model organisms [21, 62]. Different dendritic processes of the same neuron do not often cross each other; this self-avoidance mechanism depends on expression of a large array of tightly regulated DSCAM isoforms [39, 146]. Simplifying this repertoire substantially disrupts appropriate formation of neuronal networks *in vivo* [49]. Indeed, flies with altered DSCAM expression display altered memories for both rewarded and punished behaviors [62].

CLSTN2

CLSTN2 contains allelic variants that are identified in genome-wide association studies of individual differences in memory and executive function as well as the cognitive ability/Alzheimer's disease vulnerability and frontal brain volume phenotypes reviewed here [67, 77]. CLSTN2 is expressed in frontal cortex and hippocampus [74]. CLSTN2 is well-positioned to provide calcium-dependent cell adhesion functions in the brain regions that include hippocampus and in the postsynaptic densities where it is highly expressed. The structure and expression of CLSTN2 make it a good candidate to function as a single transmembrane domain

cell adhesion molecule in which variants could alter the ways in which neuronal and synaptic connections develop, the ways in which they are maintained and reorganized in adult brains or both.

DAB1

DAB1 interacts with and participates in signaling from several cell adhesion molecules. DAB1 has long been identified with signaling through the cell adhesion molecule reelin in ways that alter formation and maintenance of neuronal processes [85]. More recent evidence also supports roles for DAB1 in signaling through other cell adhesion/cell regulatory mechanisms, including those that utilize the amyloid precursor protein cell adhesion molecule [151]. DAB1 expression in many brain neurons includes those in hippocampus and mid to deep cerebral cortical layers [74] (http://brain-map.org). Mice with DAB1 disruption display substantial alterations in cerebral cortical development accompanied by gross motor and other behavioral phenotypes [116].

BAI3

BAI3, a seven transmembrane domain cell adhesion molecule, as well as PTPRM, a single transmembrane receptor tyrosine kinase that mediates homophilic cell recognition and is supported at a more modest level of statistical confidence, are both expressed in vasculature [61, 68]. Identifying these genes fits with the idea that control and regulation of angiogenesis and vascular functions plays important roles in determining the richness of cerebral cortex and other areas of adult brains [61] in ways that have consequences for a variety of interesting brain-based phenotypes. In addition, there is substantial neuronal expression of PTPRM in cortical and cerebellar cortical neurons [68, 74].

PTPRD

PTPRD is expressed in brain, and displays prominent hippocampal expression. Its extracellular ligands have not been elucidated, though it can bind to liprin [94]. PTPRD knockout mice display altered hippocampal long-term potentiation and spatial learning [133], which fit well with the human phenotypes related to cognitive function. Mice with deletions of both PTPRD and a related PRP sigma (but not with either knockout alone) die at birth due to failure to innervate appropriately [132]. SCGZ participates in protein complexes with cell adhesion-like [19]. High levels of SGCZ expression in the brain are confirmed by Allen brain atlas images [74]. Biochemical studies identify expression in Schwann cells of peripheral nerves [19]. SCGZ can be found in complexes with αδ or with εβδ sarcoglycans, demonstrating specificity of the context of its function in brain [118].

CSMD1

CSMD1 is substantially expressed in adult brain regions that include hippocampus [69]. High levels of CSMD1 expression in growth cones of neurons cultured from developing brain support substantial roles in development as well [69]. Less striking levels of evidence implicate variants in CSMD family members CSMD2 and CSMD3 in several of these brain related phenotypes [73].

Potential Roles for Cell Adhesion-Related Genes

The cell adhesion genes identified here provide an attractive way to bridge the gap between (1) the remarkable observed overlap between the molecular genetics of the clinical and cognitive phenotypes reviewed here and (2) the brain differences, especially those that might manifest in

the quantity and/or quality of neuronal connections, that might underlie these shared heritable influences.

Summary and Conclusions

It is an exciting time to be able to summarize and review the rapidly emerging data on the complex genetics of human addiction vulnerability and of related phenotypes. Genome-wide association results for dependence on several different classes of addictive substances converge with each other in striking fashion that is highly unlikely to be due to chance. Studies of dependence phenotypes in samples of individuals from several different racial and ethnic backgrounds support the idea that many of the allelic variants that predispose to these common disorders are so evolutionarily old that they are present in members of each major current human population. These data, combined with the varying results from linkage-based studies, fit a genetic architecture for addiction that is based on polygenic contributions from common allelic variants. Such a genetic architecture is quite consistent with data from family, adoption and twin classical genetic studies.

The identification of genes with markers whose allelic frequencies distinguish addicts of several different ethnicities from matched controls supports "common disease/common allele" genetic architecture [90] for at least much of addiction vulnerability. The convergent data derived from studies of individuals with addictions to substances in several different pharmacological classes supports the idea that "higher order pharmacogenomic/pharmacogenetic" variations enhance vulnerability to many addictions. These results do not exclude additional contributions to addiction vulnerability from genomic variants that influence vulnerability to specific substances or variants that are found only in specific populations. Nevertheless, the findings presented here provide promise for enhancing understanding of features that are common to human addictions in ways that could facilitate efforts to personalize prevention and treatment strategies for debilitating addictive disorders.

Identification of addiction-associated variants in genes that are likely to alter the quality of brain connections provides a first step toward defining a new neurobiology for the underpinnings of specific diseases and phenotypes. For many of these diseases and phenotypes, only little current research focuses on direct study of brain connections. The "connectivity constellation" concepts that we introduce here support studies that develop and use current and novel means for assessing the qualities and quantities of brain connections, especially in contexts in which they assess their functional properties. We have identified contributions of connectivity constellation genes to volumes of the same brain regions in which many of these genes are expressed. This convergence may provide new insights into data that documents individual differences in frontal lobe volume and/or in function, detected by volumetric, deoxyglucose positron emission tomography and/or functional magnetic resonance imaging, for virtually all of the "connectivity constellation" phenotypes or disorders noted here [20, 114].

The addiction vulnerability genes identified in this work contribute to the growing body of data that implicates cell adhesion and related memory-like and other cognitive processes in addiction. Studies that alter reconsolidation and other memory-related processes using knockout mice, protein synthesis inhibitors and/or pharmacologic treatments demonstrate powerful influences on addictions [142, 143]. This empirical evidence enriches theoretical work that increasingly recognizes memory-like features for addiction [134] and work that implicates memory-associated brain regions in relapse to addiction . Such work also complements clinical observations which document that addicts' enhanced vulnerabilities to substance abuse relapse can persist for decades after their last prior use of addictive substances.

There is also substantial evidence for generalization of these results from addiction. This evidence comes from the significant overlaps

between the molecular genetics of addiction and the molecular genetics of a number of related phenotypes and disorders. Overlap with bipolar disorder provides one of several likely psychiatric diagnoses for which shared genetic influences are likely a priori, based on the substantial heritabilities of both addiction and the high frequency of addiction/bipolar disorder comorbidity [119, 120]. This same logic suggests that abundant shared genetics may well also underpin the frequent comorbidities between addictions and antisocial personality/conduct disorders [107]. Less compelling evidence points to overlaps with other depressive, anxiety and schizophrenic disorders as well [107].

We have sought evidence for genetic influences that are shared between addiction and (1) frontal lobe brain volumes and (2) cognitive function. Hypotheses about such shared genetic influences are based, in part, on initial observations that so many of the genes that we and others have identified in addiction genome-wide association relate to cell connections. These molecularly based hypotheses were reinforced by the evidence for substantial, complex genetic components to each of these phenotypes. These hypotheses were strengthened by evidence, though often from small samples, that appears to document (1) small frontal lobe volumes in samples of addicts [36, 80], (2) lower performance levels on tests of cognitive and executive function in samples of addicts [13, 14, 44], and (3) large roles of heritability vs. little role for the drug exposure itself in determining the cognitive abilities of twin pair members who are discordant for cannabis use [129]. These hypotheses are further reinforced by twin data that document strong shared genetic influences on frontal brain volumes and cognitive function measures [102, 104].

Disease-associated markers both within and between genes can all begin to allow us to assess individual differences in vulnerability to addiction based on profiles of genotypes. In settings in which prevention of addiction is sought, addiction vulnerability genomic profiles could help to target more (or different) prevention resources to individuals at the most (or at different) genetic risk. When a therapeutic opiate is being considered for chronic, non-cancer pain, for example, the costs of engendering substance dependence are likely to be sufficient to justify genotyping even if the results provide only partial information about risk assessment and minimization for prescribing physicians. When treatment for an established dependence on nicotine, opiates or alcohol is being contemplated, a number of different therapeutic options with different pharmacological mechanisms of action are now available [43]. Subsets of the single nucleotide polymorphisms that we have associated with success in quitting smoking appear to provide selective influence success in responding to bupropion, while others appear to provide selective influences on success in response to nicotine replacement. Replication and extension of these observations to treatments for alcohol, opiates and other addictive substances will make it more and more likely that single nucleotide polymorphism markers will increasingly aid "personalization" of antiaddiction therapies within the near future, in ways that are now impacting the design of clinical trials in this area.

This work, taken together, supports the idea that the heritable brain bases for individual differences in addiction vulnerability lie squarely in the midst of the repertoire of common complex determinants of individual differences that are manifested in many heritable complex brain disorders and phenotypes. Such conclusions place the biology of addictions squarely in the midst of important biologies of a number of brain phenotypes and disorders, hopefully in ways that will benefit them all.

Glossary

A priori: Existing in the mind prior to and independent of experiments.

Balancing selection: A natural process that results in the survival and reproductive success of individuals or groups best adjusted to

their environment and that leads to the perpetuation of genetic qualities best suited to that particular environment.

Between-locus heterogeneity: A single disorder, trait, or pattern of traits caused by mutations in genes at different chromosomal loci.

Common disease and common allele model: The illness results from the cumulative impact of multiple common small-effect, genetic variants, interacting with environmental exposures to exceed a biological threshold.

Complex genetic phenotype (polygenic and multifactorial traits)*:* Any *phenotype* that results from the effect of multiple *genes* at two or more loci, with possible environmental influences too.

Epigenetic: Changes in the regulation of the expression of gene activity without alteration of DNA sequence.

Epistasis: A mutation in one gene masks the expression of a different gene.

Genetic heterogeneity: A single disorder, trait, or pattern of traits caused by genetic factors in some cases and non-genetic factors in others.

Genetic selection: Differential and non-random reproduction of different genotypes, operating to alter the gene frequencies within a population.

Genome-wide association study: Any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition.

Linkage: The tendency for genes or segments of DNA closely positioned along a chromosome to segregate together at meiosis and therefore be inherited together.

Linkage analysis: Testing DNA sequence polymorphisms that are near or within a gene of interest to track within a family the inheritance of a disease-causing in a given gene.

Linkage disequilibrium: In a population, co-occurrence of a specific DNA marker and a disease at a higher frequency than would be predicted by random chance.

Pharmacogenetics: The study focused on specific genes, such as drug-metabolizing enzymes.

Pharmacogenomics: The study of how an individual's genomic system affects the body′s response to drugs.

Pleiotropy: Multiple, often seemingly unrelated, physical effects caused by a single altered gene or pair of altered genes.

Segregation analysis: The determination of the number of progeny that have inherited distinct and mutually exclusive phenotypes.

Susceptibility gene: A gene mutation that increases the likelihood that an individual will develop a certain disease or disorder. When such a mutation is inherited, development of symptoms is more likely but not certain.

Transitive: Passing over to or affecting something else.

Within-locus heterogeneity: A single disorder, trait, or pattern of traits influenced by several different variants at a single chromosomal locus

Acknowledgments We thank the subjects for each of these samples. We also thank our collaborators, including H Ujike and the JGIDA methamphetamine investigators, SK Li and the Taiwan methamphetamine investigators, Jed Rose, Caryn Lerman, Ray Niaura, Sean David, Gary Swan, Christina Lessov-Schlaggar. We are grateful to Framingham study investigators, the NicSNP group and the Wellcome Trust Case-Control Consortium for access to genotype data analyzed here. S Seshadri and J Pollock were of especial help with obtaining access to the Framingham and NicSNP datasets cited here. We are grateful for dedicated help with clinical characterization of NIDA subjects from Dan Lipstein, Fely Carillo, Carlo Contoreggi, Fred Snyder and other Johns Hopkins-Bayview support staff. We benefited from passionate discussions of statistical issues with Dr Daniel Naiman and from the Baltimore Epidemiology Catechment Area follow up study that was generously provided by Dr J Anthony. We thank NHLBI staff and the twin study technicians and investigators, PA Wolf, BL Miller, T Reed, L Epstein, L Hawk, P Shields, F Patterson, A Pinto, M Rukstalis, W Berrettini, R Brown, E Richardson, FM Behm, P Kukovich, EC Westman and G Samsa for their rigor in overseeing data collection at their research sites. We acknowledge financial support from NIH-IRP (NIDA), DHHS and are also grateful for support for some of the studies discussed in detail here from the Taiwan and Japanese Ministries for Science and Technology, NIH grants

P50CA/DA84718, RO1CA 63562, HL32318, DA08511, P50CA84719, 1K08 DA14276-05, HL51429, support from the Welcome Trust (076113), the Pennsylvania Department of Health (which specifically disclaims responsibility for any analyses, interpretations, or conclusions), GlaxoSmith Kline, Inc and unrestricted support for studies of adult smoking cessation from Phillip Morris USA.

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The Pharmacogenomics of Addiction

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Contents

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Introduction

The Genetics of Vulnerability and the Pharmacogenetics of Addictions

Addictions are multi-step pathologies featuring persistent, compulsive, and uncontrolled use of an agent or activity. Repetitive use induces neuroadaptive changes that establish tolerance, craving, withdrawal, and affective disturbance. These problems persist after consumption of the addictive agent ceases and serve as a basis for cue- and stress-induced relapse and rapid reinstatement of use. Genetic variations that play roles in the addictions act at various levels, including: (1) inborn emotionality, behavioral control, and cognition, (2) the initial and adaptive responses to addictive drugs, and (3) differential responses to medications used to treat addictions to drugs and other agents. The heritability of addictions and progress in mapping genes predisposing to vulnerability are discussed elsewhere in this volume and have been reviewed elsewhere [25, 40]. In this chapter, we tell the story of the role of pharmacogenetic variation determining differences in response to addictive drugs and differences in responses to medications used to treat addictions. The pharmacogenetics of

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_11,

addictions overlaps with the genetics of vulnerability, but it will be seen that it is primarily a story of the action of specific functional alleles involved in drug metabolism and response. It is not the purpose of this chapter to review comprehensively the linkage studies of addictions, but it is notable that several of the genes that have emerged from linkage studies of addictions fall in the category of pharmacogenetic factors. An alcoholism-linked region of chromosome 4q contains the alcohol dehydrogenase gene cluster [45], and a chromosome 4p region contains a gamma-aminobutyric acid receptor-A gene cluster [1, 18, 20, 41]. In the Collaborative Study on the Genetics of Alcoholism sample, there is evidence for linkage of alcoholism to chromosome 2 at the location of an opioid receptor gene [54] and for linkage of cannabis dependence to a cannabinoid receptor [2]. Nicotinic acetylcholine receptors are important gatekeepers for nicotine's action, and a nicotinic acetylcholine receptor gene (CHRNA5) has emerged as an important candidate from genome-wide association studies of nicotine dependence [4–7, 49].

Pharmacokinetic and Pharmacodynamic Variation

Pharmacogenetic variation can be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic variation encompasses ingestion, absorption, distribution, metabolism, and excretion. Drugs of abuse are ingested by different routes, leading to the potential for pharmacogenetic variation at that level. The effects of pharmacokinetic variation can be powerful and unexpected. For example, in mice, a major genetic influence on preference for morphine in a liquid diet is the quinine taste locus although a second major opioid preference quantitative trait locus contains the mu-opioid receptor [3]. Reduced sensitivity to bitter taste may contribute to the risk of smoking [21] and alcohol dependence [30]. Once ingested, many drugs are metabolized to active metabolites that are long-lived in the body and that can cause different secondary effects, as has been observed with several antipsychotic medications. The result is differing profiles of treatment response, side effects, and addictive potential. Methylphenidate, as compared with amphetamine, is useful more directly as an agonist therapy for attention-deficit hyperactivity disorder because of its slower absorption and distribution. Methadone, as compared with heroin, is useful more directly as an agonist therapy of opioid addiction as compared with heroin and other opioids because of its long half-life. Also, the addictive liability of several drugs, including nicotine, opioids, amphetamine, and cocaine, is related directly to the ability to administer them in ways that people find acceptable and such that there is a very rapid upslope in concentration of the drug, thereby overwhelming rapid tolerance. As will be discussed, ethanol's active metabolite, acetaldehyde, exerts a variety of effects: it can discourage drinking via the flushing reaction; it is a carcinogen responsible at least in part for the carcinogenicity of alcohol, and—in the brain—it also may be rewarding. From these few initial observations, it is apparent that any pharmacogenetic variation that disturbs the delicate balance of absorption, distribution, metabolism, and excretion is likely to alter a drug's addictive profile and the treatment profile of medications used to treat addiction.

Other Concepts: Gatekeeper Genes, Allostatic Shifts, and Teratogenicity

Pharmacodynamic genetic variation in the reaction of cells and tissue to particular drugs influences both the initial and chronic responses to drugs. It includes variation in the ability to smell or taste the drug, thus altering palatability and appeal. Pharmacodynamic variation includes differences in receptors, which are gatekeepers for the actions of specific drugs. It includes variation in modulatory pathways.

Long-lasting neuroadaptive changes lead to allostatic shifts in the function of the brain stress system and the function of the hypothalamic-pituitary-adrenal axis [37], and certain genetic polymorphisms influencing stress response have already been shown to play important roles in addictions, in this context. These long-lasting effects are due in part to changes in brain structure as well as cellular changes. At the cellular level, long-lasting epigenetic changes lead to altered gene expression accompanying and enabling changes in neuronal function.

The developing brain is more sensitive to drug exposures. A pharmacodynamic consequence is drug-induced teratogenic disorders, including fetal alcohol syndrome and fetal alcohol spectrum disorders, which affect 1 out of 100 live births at an annual cost of >$20,000 each, cigarette-induced low birth weight, and drug × gene interactions during development that potentially enhance liability to addictions but also other disorders, including schizophrenia. As will be discussed, the pharmacogenetics of these drug-induced teratogenic and developmental disorders is poorly developed yet critically important.

Pharmacogenetic Effects Independent of Addiction Diagnosis

Clinically Under-Recognized Differences in Level and Pattern of Use

A deficiency of the *Diagnostic and Statistical Manual of Mental Disorders*' proposed treatment of addictions is that it does not capture quantitative and qualitative aspects of drug use that affect pharmacokinetics. Mode of administration and level and pattern of use are substantially irrelevant to the *Diagnostic and Statistical Manual of Mental Disorders* diagnoses even though these are profoundly important for outcome. For example, binge drinking—a pattern of alcohol use characterized by episodic bouts of intense drinking—is common and, while generally seen in the context of alcohol dependence, is a strong independent predictor of problems in all four *Diagnostic and Statistical Manual of Mental Disorders* addiction major symptom areas: social, work, physical, and violence/lawlessness [45]. Level and pattern of alcohol consumption and associated factors including diet correlate with risk of developing organ damage such as liver cirrhosis at both the individual and population levels [24]. Genetic variation interacts with alcohol exposure to determine vulnerability to cirrhosis. The distinction between intravenous and oral consumption of drugs is important from a clinical perspective. Intravenous drug users are at dramatically higher risk for HIV infection, infection, and pulmonary disease. They also may have a different profile of vulnerability factors and require different counseling approaches. Susceptibility to infections associated with intravenous drug use is itself modified by a host of genetic factors, such as the chemokine (C–C motif) receptor 5, which moderates risk of progression to AIDS following infection with HIV. However, a starting point for assessment of vulnerability to these negative outcomes is the understanding that the individual is an intravenous drug user, even if intravenous use is only occasional.

Genetic Modifiers of Drug Consequences Independent of Addiction Diagnosis

Drug use that does not meet *Diagnostic and Statistical Manual of Mental Disorders* criteria for abuse or dependence constitutes a critical problem, leading, to violence and dyscontrolled behavior, motor and cognitive impairments critical in the causation of accidents, problems with the law, and loss of livelihood. In this regard, the circumstances, pattern, and quantity of use are frequently critical to whether the use of the drug, which might never be repeated more than once, has a devastating impact on the person's life.

The alcohol-naïve young woman who becomes intoxicated, drives, and dies in a motor vehicle accident is equally as dead as the alcohol-dependent individual who has suffered the same sad fate. These negative outcomes also can be influenced by pharmacogenetics. With reference to this example, and as will be discussed, some individuals are more sensitive to alcohol than others, such that a first exposure would more likely lead to an automobile accident. Finally, the general population is at high risk for suicide, with a lifetime risk of about 1%; however, the risk in various populations of addicted individuals is several-fold higher, varying with the addictive agent.

Gene/Stress Prediction of Suicide Risk

As shown in Fig. 1, in populations of addicted individuals, genotype can interact powerfully with environment to alter the risk of suicide.

Teratogenicity and Developmental Effects

In the United States, approximately 30% of women consume alcohol during pregnancy. Alcohol crosses the placental barrier, thereby entering the fetal circulation, and can impair fetal brain development even if exposure occurs in the third trimester. As a result, fetal alcohol syndrome occurs in 0.2–2.0 out of 1,000 live births. Fetal alcohol syndrome—induced cognitive disabilities include deficits in memory, attention, behavioral inhibition, and reasoning. Fetal alcohol syndrome children are more vulnerable to psychiatric disorders and addictions, perpetuating a cycle of risk. Furthermore, a broader spectrum of fetal alcohol spectrum disorders has been recognized, and fetal alcohol spectrum disorders occur in approximately 1 out of 100 live births. These numbers provide an intriguing indication that there is a strong pharmacogenetics of fetal alcohol syndrome; if 30% of pregnant women drink, why should the incidence of fetal alcohol syndrome be <1%? Studies performed in rodent animal models of fetal alcohol syndrome indicate that there is wide variation of fetal response to the same drug exposure because fetuses that share the same womb have different outcomes—one animal being affected and the other not. Also, some strains of mice are more likely to produce fetal alcohol syndrome offspring than are others. Finally, and most interestingly, there is wide variation in outcome even with inbred mouse fetuses in the same womb and sharing the same genotype. This suggests that small animal-to-animal differences, including differences in early epigenetic and cellular developmental states, influence outcome in profound ways.

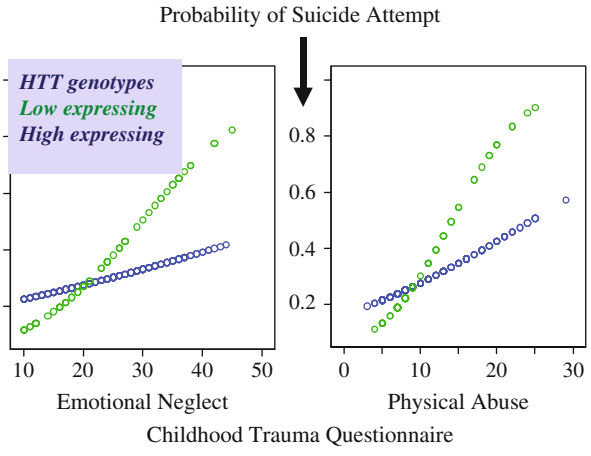

Fig. 1 Suicide risk in 306 African-American participants with addiction to cocaine, heroin, or alcohol was strongly modified by the effect of childhood neglect and trauma combined with a functional serotonin transporter (HTT) promoter polymorphism. Adapted from Roy et al. [46]

Longitudinal studies reveal that genes influence the risk of addictions both during development and across the lifespan. Certain addiction-related behaviors such as alcohol consumption are not heritable early in life, when the child is unable to independently choose, but become highly heritable later. This probably holds true for the consumption of other drugs as well as alcohol. In a study of the developmental expression of inherited vulnerability to addictions conducted in the Virginia Twin sample, Kendler and colleagues [36] found that gene effects that are undetectable in early adolescence gradually grow in importance and reach their peak in young adulthood, whereas the effect of common environment shared by siblings decreases. These data raise the issue of gene × environment correlation. To what extent does genotype shape drug exposure, rather than the response to drugs? Although adolescent alcohol and drug use is associated with adverse outcomes [26], age of first exposures—for example, the age at first drink—is itself genetically influenced [43], raising the question of whether early drug users already are different.

Pharmacogenetics of Intermediate Phenotypes

Addiction-Associated Intermediate Phenotypes and Endophenotypes

One way to better disentangle predisposition from exposure is to use predictive intermediate phenotypes that are heritable and stable and pre-exist exposure. Intermediate phenotypes that access mediating mechanisms in addictions have been a powerful tool for detecting the effects of genes. Endophenotypes are intermediate phenotypes that are disease associated and heritable [25]. Addiction-associated intermediate phenotypes include heritable variations of the resting encephalogram and evoked responses. Such phenotypes have frequently yielded promising genetic association findings [14, 33], although the basis of none of these is really understood.

Alcohol-Induced Flushing: Alcohol Dehydrogenase, Aldehyde Dehydrogenase, Alcoholism, and Cancer

Alcohol-induced flushing is a heritable phenotype that is protective against alcoholism but is a risk factor in the development of oropharyngeal cancer and perhaps also breast cancer [10, 11]. Acetaldehyde derived from the metabolism of ethanol is under ordinary conditions rapidly converted to acetate, and levels of acetaldehyde remain very low—i.e., in the nanomolar range. Acetaldehyde is a potent releaser of histamine, thereby triggering the aversive flushing reaction. Symptoms include headache, nausea, palpitations, and flushing of the skin, as shown in Fig. 2.

If aldehyde dehydrogenase is blocked by disulfiram (which is used to help alcoholics maintain abstinence) or certain medications used to treat protozoal infections (e.g., metronidazole), then the flushing reaction is observed after the ingestion of only small quantities of alcohol.

The genetic origin of alcohol-induced flushing is variation in alcohol metabolic genes.

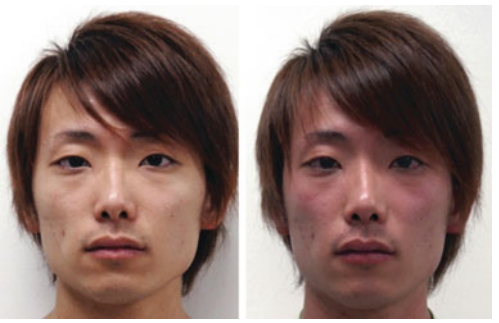

Fig. 2 The alcohol flushing response. Facial flushing in a 22-year-old aldehyde dehydrogenase 2 heterozygote before (*left*) and after (*right*) drinking alcohol. The individual pictured in this figure has given written consent for publication of his picture using the PLoS consent form. Reprinted from Brooks et al. [11]

Alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 are enzymes that catalyze consecutive steps in alcohol metabolism. In adults, these enzymes play an important role although there are also several other enzymes that can carry out both of these metabolic steps, including catalase, cytochrome P450, and additional enzymes in the alcohol dehydrogenase and aldehyde dehydrogenase gene families. In the liver, three alcohol dehydrogenase genes are expressed at high levels and to some extent at different times of development, and these three enzymes are primarily expressed in hepatocytes. However, despite this complexity of enzyme action in alcohol metabolism, individual functional alleles that alter the function of only one enzyme are sufficient to exert a major biochemical effect and an effect on risk. This probably is because of the relatively greater importance of alcohol dehydrogenase 1B in the adult liver and its lower K_m and higher capacity for metabolism as compared with some of the other enzymes.

The aldehyde dehydrogenase 2 enzyme is an aldehyde dehydrogenase that is encoded in the nuclear genome but translocated to the mitochondrion, where it plays a critical role in the ability of hepatocytes and other cells throughout the body to metabolize acetaldehyde. The main roles of the enzymes that have maintained these genes through at least 80 million years of mammalian evolution are in fact somewhat obscure. Mice and rats, in their natural environment, are not heavy consumers of alcoholic beverages! Yet our distant mammalian cousins possess a full complement of these enzymes. Perhaps the reason for this is that although the liver metabolizes ethanol ingested in beverages, it also has to utilize alcohols that are the product of bacterial fermentation in the gut.

As mentioned, acetaldehyde is a toxic intermediate that may react with a variety of biomolecules. Indeed, acetaldehyde adducts with DNA, and both it and alcohol are formally recognized as mutagens by the International Agency on Risks of Carcinogens. If acetaldehyde accumulates, the individual is at substantially increased risk of upper gastrointestinal cancer, and this can occur due to either pharmacologic blockade of aldehyde dehydrogenase or natural genetic variation. Both the alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 polymorphisms, described below, have been associated with enhanced risk of cancers of the oropharynx and esophagus [10, 55]. These are factors that physicians may wish to consider in counseling individuals who drink despite carrying the common genetic variations that lead to elevated acetaldehyde levels [10, 11].

Nature has provided natural examples of genetic predisposition to alcohol-induced flushing, and it is not surprising that the enzyme variants that lead to flushing are protective against alcoholism. The most important functional loci at alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 are the alcohol dehydrogenase 1B His47Arg missense polymorphism, in which Arg47 is a hyperactive allele acting in codominant fashion, and aldehyde dehydrogenase 2 Glu487Lys, in which the Lys487 allele inactivates aldehyde dehydrogenase 2 dominantly (a manifestation of the tetrameric structure of the enzyme). Higher activity of alcohol dehydrogenase 1B, conferred by Arg47, or lower activity of aldehyde dehydrogenase 2, conferred by Lys487, leads to accumulation of acetaldehyde following alcohol consumption and the flushing reaction. In East Asian populations (e.g., China and Japan), where both His47 and Lys487 are highly abundant, and Jewish populations, where His47 is abundant, many individuals carry genotypes that are protective against the development of alcoholism. The protective effect seems to vary across environments [51] and shows genotype–genotype additivity [48]. Both of these functional polymorphisms appear to be ancient in human populations, occurring on characteristic and highly diverged haplotypes. On that basis, it is unlikely that the Arg47 and Lys487 alleles were selected to high frequencies in East Asian populations as protective alleles against alcoholism. One possibility, which is still speculative, is that the polymorphism alters susceptibility to protozoal infections of the gut, including amoebiasis, because an action of metronidazole

(an antiprotozoal medication of unknown mechanism) is to inhibit aldehyde dehydrogenase [23]. However, regardless of the forces responsible for their high frequencies, the pervasive environmental exposure to alcohol that occurs in modern societies has added other dimensions to their effects.

As mentioned, the genetics of alcohol dehydrogenase is complex—there are seven genes in the alcohol dehydrogenase gene cluster on chromosome 4, and there are others with linkage disequilibrium (non-independence in populations) occurring for many of the variant loci. For example, alcohol dehydrogenase 1C has a pair of linked amino acid substitutions. Furthermore, within humans, the aldehyde dehydrogenase 1 gene also has common inherited functional variation. It is highly likely that these and other functional variations also will play a role in vulnerability to alcoholism.

Alcohol Response and the Gamma-Aminobutyric Acid-A Receptor

Low response to the effects of alcohol is a heritable intermediate phenotype (again, an endophenotype) [29] predictive of risk of alcohol use disorders [47], and it also predicts higher alcohol consumption in strains of rodents. In the prospective longitudinal study by Schuckit at the University of California, San Diego, alcohol response in young, relatively alcohol-naïve college males was the strongest predictor of future alcoholism [47]. In both humans and mice, the level of response to alcohol mainly reflects pharmacodynamic variation in response rather than metabolism.

An important target for the action of alcohol is activation of gamma-aminobutyric acid receptors, which are ligand-gated chloride channels that dampen neuroexcitability when activated. Gamma-aminobutyric acid is the primary inhibitory neurotransmitter in the brain, and its activations of chloride currents through the gamma-aminobutyric acid receptor-A receptor channels are facilitated by various drugs including ethanol, benzodiazepines, and barbiturates. Strong pharmacobehavioral evidence suggests that gamma-aminobutyric acid is involved in cross-tolerance among alcohol, benzodiazepines, and barbiturates. In the mouse, a series of ethanol-related behaviors, including preference, withdrawal, and sedation, map to regions where gamma-aminobutyric acid receptor-A receptor-gene clusters are located [24].

The human gene encoding the subunit alpha 6 of the gamma-aminobutyric acid receptor A has an amino acid substitution (Pro385Ser) that may alter level of response to both alcohol and benzodiazepines [32]. In the rat, an Arg100Gln missense variant located in the gamma-aminobutyric acid receptor-A alpha-6 subunit gene (GABRA6) was associated with variation in ethanol and benzodiazepine sensitivity [38]. GABRA2, which was originally implicated positionally in family linkage analysis, appears to alter vulnerability to alcoholism and is associated with alcoholism-related electroencephalographic variation—the same alleles and haplotypes having been replicated across studies [1]. GABRA2 also has been implicated in nicotine addiction and polysubstance use, but those findings are not well replicated [40].

Nicotinic Acetylcholine Receptors: Gatekeepers for Nicotine and Other Drugs?

Nicotinic acetylcholine receptor genes have been associated with nicotine dependence and lung cancer, seemingly as an example of the gatekeeper role of these receptors for nicotine's action. However, most of the 12 known nicotinic acetylcholine receptor genes are not required for nicotine's reinforcing actions, and several of these receptors also have been associated with vulnerability to alcoholism and cocaine addiction, pointing to the possibility of their wider involvement in the neuropharmacology of addiction. For nicotine response, a critical receptor

is the one formed by the alpha-4 and beta-2 subunits because mice lacking that combination do not self-administer nicotine or release striatal dopamine in response to nicotine [42]. These mice also show abnormalities in cocaine responses. As reviewed [40], there have been several positive association studies of CHRNA4 to nicotine dependence, but the evidence for CHRNB2 is less clear. Certain genes carry common functional variation, and others do not. Rarer CHRNB2 variants could be critical to the vulnerability of particular individuals.

The CHRNA5-A3-B4 cluster has been implicated in genome-wide association studies of nicotine dependence and lung cancer [4–7, 49]. For example, in one study, the phenotype for the nicotine addiction was number of cigarettes per day regularly smoked in two European populations totaling 7,500 persons. Although no genetic marker reached genome-wide significance, a trend toward association was found for a common haplotype in the CHRNA3–CHRNA5 nicotinic receptor gene cluster on chromosome 15, and this result was replicated in 7,500 additional Europeans [7]. Among the implicated variants is a missense allele in CHRNA5, which appears to play a role in nicotine dependence [6] as well as lung cancer, but may be protective in cocaine dependence [27]. This Asp398Asn substitution is common and non-conservative and may affect function via altered trafficking of the receptor.

Neuroimaging, a New Frontier in Pharmacogenetics

For pharmacogenetic studies of addiction, neuroimaging provides access to the neuronal mechanisms underlying emotion, reward, and craving and, therefore, represents an extraordinary tool to link genes to the neuronal pathways that produce behaviors. For example, amygdala activation after exposure to stressful stimuli predicts anxiety and captures inter-individual differences in emotional response and stress resiliency [28]. Amygdala activations and other brain responses are modulated by common functional genetic variants at genes such as the serotonin transporter promoter polymorphism [28] and the catechol-*O*-methyltransferase missense variant Val158Met [57]. Similarly, neuropeptide Y, an anxiolytic neuropeptide that shows moderate associations with alcoholism and anxiety, strongly predicts brain imaging responses to emotion and pain [56]. On the other hand, the activation of the prefrontal cortex during working memory performance is used to evaluate prefrontal cognitive function that is impaired in several psychiatric diseases including addictions, and these activations are modified by the same catechol-*O*-methyltransferase polymorphism [17]. The association of catechol-*O*-methyltransferase with addictions [19, 50, 52] is, therefore, likely to be complex and potentially mediated either by an effect on cognition and behavioral control or via effects on emotion and resilience. The combination of genetic analysis with brain imaging illustrates the power of cross-disciplinary science and its complexity (or, to put it another way, its limitations).

The Mystery of Comorbidity: Agent-Specific and Non-Specific Factors

Comorbidity among the addictions and between addictions and other psychiatric diseases occurs in excess of what would be expected based on the frequencies of these diseases [26] and by multiplying the probabilities of the events as if they were independent. Twin studies have shown that one origin of comorbidity is the existence of genetic factors shared between addictive agents, and these studies also showed that there are large substance-specific genetic factors [22, 34, 35].

The agent-non-specific genes include ones that affect neurobiological networks involved in responses and adaptations to many different types of addictive agents, as well as the vulnerability to other psychiatric diseases. Categories

of mechanisms that may underlie shared vulnerability include reward, stress resiliency, behavioral control, and personality. These can be viewed as pharmacodynamic effects. For example, dopamine activations are fundamental for the reward and reward-anticipation effects of addictive agents. The dopamine receptor DRD2 gene has been linked to different types of addictions [53], albeit with some inconsistencies. Similarly, opioid neurotransmitters play an important role in reinforcement, and a functional polymorphism of the mu-opioid receptor (OPRM1) has been associated with addictions, but again with some inconsistencies [39, 44].

Gene × Environment in Genes Affecting Pharmacodynamics

Addictions are similar to other complex diseases, including cancer, diabetes, cardiovascular diseases, infectious diseases, and hematologic diseases, where the effects of genetic variation have come to be understood first by their ability to moderate resiliency or vulnerability to environmental exposures (e.g., pathogens, carcinogens). The gene effects are much greater in the context of the measured exposures. Childhood stress and neglect increase vulnerability to multiple psychiatric diseases including addictions [16, 46]. However, there is wide inter-individual variation in stress resiliency. Functional loci that influence inter-individual variation in stress resiliency include monoamine oxidase A [12, 15], the serotonin transporter gene (SLC6A4) [13], catechol-O-methyltransferase [20], the corticotrophin-releasing hormone receptor 1 gene [9], neuropeptide Y [56], and FKBP5 [8]. Monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine, are modulators of emotionality, cognition, reward, and behavioral response to stimuli. Therefore, it is unsurprising that genes encoding the enzymes and transporters that regulate synaptic levels of these neurotransmitters would be important in the addictions. These are, of course, not addiction specific and have been implicated in vulnerability to other psychiatric diseases and response to drugs that alter monoamine levels, and, for example, response to serotonin-specific reuptake inhibitors has been linked to SLC6A4 [31].

Pharmacogenetics in the Treatment of Addictions

The maintenance of abstinence for multi-year periods, reductions in drug use, and delay in the return to heavy drug use have enormous benefits. The multidimensional nature of addictions paradoxically increases the range of opportunities for interventions. The identification of genes altering liability and recovery could provide new

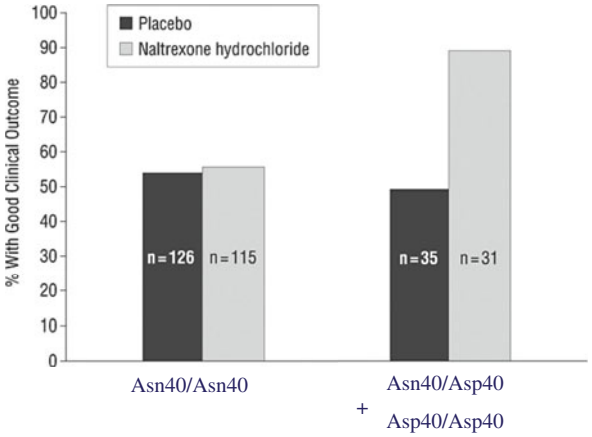

Fig. 3 A functional OPRM1 polymorphism (Asn40Asp) predicted good clinical outcome in alcoholics treated with naltrexone, but not placebo, in the multicenter COMBINE study. Adapted from Anton et al. [3]

therapeutic targets and an ability to individualize treatment. The common functional missense variant of the mu-opioid receptor (OPRM1 Asn40Asp) appears to predict good clinical outcome in alcohol-dependent individuals treated with naltrexone (Fig. 3) [3, 41] and may alter nicotine-mediated reinforcement [44] and therapeutic response in smokers treated with nicotine replacement [39].

Conclusion

Addictions are common, complex disorders in which genetic variation alters pharmacokinetic and pharmacodynamic responses, leading to differential vulnerability and differences in the liability to other negative outcomes consequent to drug exposure. Both the teratogenicity and carcinogenicity of alcohol are influenced by genetic factors. Addictions are consequent to a gene × environment interaction. Furthermore, several of the genes that alter addiction vulnerability work through the stress axis, providing a specific role for gene × stress interactions. In terms of the variance in liability explained, the pharmacogenetics of addiction is still a relatively young field, but the genes discovered so far act in a variety of ways including altered drug metabolism, drug receptor function, and general mechanisms of addiction.

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Metabolomics in Drug Response and Addiction

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What Is Metabolomics?

Metabolomics is the newest addition to the "omics" science. An "omics" has been defined as a neologism referring to a holistic view on biologic macromolecules, such as in genomics or proteomics [9]. Genomics aims to understand the structure and function of the genome by studying all nucleotide sequences, including the structural genes, regulatory sequences, and noncoding DNA sequences in the chromosomes of any organism. It also examines the molecular mechanisms that maintain genomic integrity, allow its transmission and the expression including any interplay of genetic and environmental factors in disease. Proteomics involves the identification and study of complete set of proteins in a species and the determination of their role in physiologic and pathophysiologic functions [2, 57]. Together with these and other "omics" technologies, metabolomics contribute to the detailed understanding of the in vivo function of gene products, biochemical analysis and regulatory networks. The metabolomics represents the collection of all low molecular weight molecules found in a given cell and can provide a "snapshot" of the physiology of a cell at a given time during development and differentiation including responses to food, drugs, and other challenges [19].

Biochemist view metabolomics as metabolites profiling or the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_12,

or genetic modification [36]. Biologist, particularly geneticist on the other hand view it as the science of highly complex and organized biochemical network in which small molecules, such as metabolic substrates and products, lipids, small peptides, vitamins, amino acids, signaling molecules and other protein cofactors, are interacting between them and with other biological macromolecules in the metabolome [9]. These small molecules are acting usually at very low concentrations in tissue signaling functions [17]. Along with the understanding of the in vivo interaction of gene products, metabolomics also contributes a great deal in the mathematical description and simulation of the whole cell in the systems biology approach. Systems biology tries to integrate genomic, proteomic, transcriptomic and metabolomic information to give a more complete picture of living organisms (Fig. 1). Here, the biological events in organisms are systematically interpreted through the combination of complex measurements from various methods resulting in high-throughput data. In this chapter, we will discuss addiction as a problem of systems biology with emphasis on metabolomics.

Substance Abuse and Its Effect on Health and Economy

Substance use, abuse, and addiction that include but are not limited to alcohol [41, 62], nicotine [16], opioids [49], cocaine [35], cannabinoids [1], methamphetamine, and amphetamine [33] continue to be a significant public health concern and pose tremendous cost to our society. In the United States alone, in 1998 the economic cost associated with illicit drug use was estimated to be US$280 billion, for nicotine US$158 billion [7], and for alcohol abuse US$185 billion with an average annual increase of 3.8% per year [21]. This brings the combined total estimated economic impact of substance abuse in the United States to over half a trillion dollars [62]. Recent data indicate that approximately 1.6 million people in the United States abuse or are dependent on prescription opioids [49]. In the United Kingdom, the cost associated with alcohol abuse is approximately $39 billion each year [41]. Drug and alcohol abuse is a major cause of morbidity and mortality both in the United States and worldwide. Alcohol use disorders including

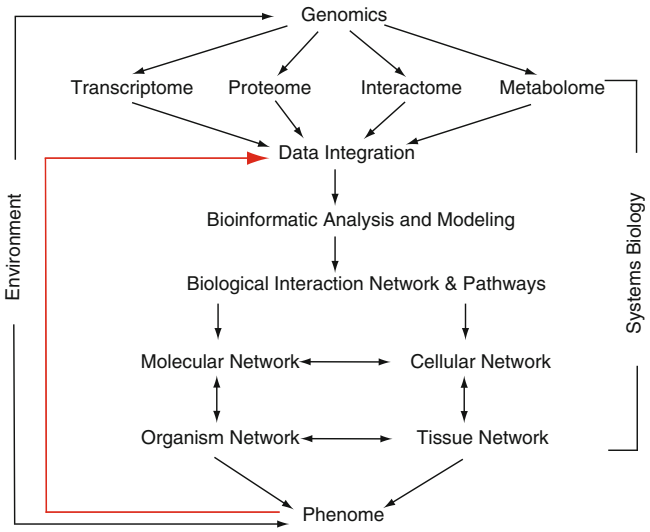

Fig. 1 Connection between "omics" sciences and systems biology. Functional genomics and other technologies are used to map the transcriptome (complete set of transcripts), proteome (complete set of proteins), interactome (complete set of interactions), metabolome (complete set of metabolites) and other "omics" knowledge bases. Bioinformatics analysis is done to model and infer network pathways from integrated data. Experimentally valid biological network of cells, tissues and organs from particular organism are integrated with phenome (complete set of phenotypes) to obtain the complete picture about specific mechanism and disease

liver and heart diseases account for 4% of the global burden of disease and cause 1.8 million deaths [41]. The excessive burden of drug abuse to our health and economy makes it necessary for us to better understand how these drugs affect metabolomics of our cellular systems, mechanism of action in different parts of the body and factors that determine the variability of addictive responses. A better insight into these mechanisms will offer a better understanding of the problem as well as identify effective treatment and preventative approaches for addiction that remains insidious in most societies.

Substance Abuse Leads to Addiction

At the center of the problem of substance abuse is addiction to these substances. It has been long hypothesized that the combination of genetic and environmental factors following drug use and abuse alter cellular physiology. This alteration is expected to be cell and organ specific. In due course, it may follow physiological adaptation leading to an urge for the drug response and the development of addiction [27, 37, 62]. Evidence for the involvement of genes in the process of drug addiction comes from classical epidemiological and genetic studies. Data from both animal and humans support the importance of genetic influences in substance abuse and dependence [4, 24, 34, 56]. Twin studies, for example, have shown robust genetic components for alcohol, opiate, cocaine, and tobacco addictions [28, 44, 55].

The major target of virtually all drugs in the human or animal body, either directly or indirectly, is the nervous system specifically one or more pathways deep within the brain [25, 26, 29, 39]. Drug-related, especially alcohol-related, brain damage and associated neurophychological changes have been well documented (see review [38, 39]). There is increasing evidence that long-lasting changes in the brain result from the progression of casual user to addict [37]. Acute drug intoxication is accompanied by highly localized and dynamic patterns of brain activation and deactivation [5, 48], as well as complex cascades of transcriptional reprogramming [63, 64].

All compounds with abuse potential have the ability to disrupt the processing of information in the brain by subverting or affecting the expression of gene(s) involved in one or more of the common neurotransmitter systems (i.e., gamma-aminobutyric acid, glutamate, acetylcholine, dopamine, serotonin, and opioid peptides). However, an early increase in dopamine signaling has been one of the most consistent observations across studies of the reinforcing effects of drugs of abuse [12, 40, 62]. Though studies with various knockout mice have emphasized the role of specific gene products working in the brain (see review [34]) such as Homer 2 [50], opioid receptors [8], and alpha 4 nicotinic receptors [51] in conferring either protection from or increased risks of addiction. It is also apparent that the contribution of any single gene in the development of addition for any drug is only a small part of the picture. Like most familial behavioral phenotypes, drug and alcohol use disorders result from the complex interaction of multiple genes [47]. This complexity may account for ongoing challenges associated with the development of addiction and solutions to deal with them. Needless to say that multiple genes exert their effects in the context of genetic networks, which are typically under the influence of environmental factors. These early effects initiated by the gene product induced by drugs or alcohol most likely cascades through the signaling pathways and generates a domino effect [60]. In order to understand the complete molecular or gene expression changes that may occur in the brain due to drug and alcohol effect, it is important to capture those changes as a whole and perform a systematic analysis. One very novel and effective approach that has been used in recent years to decipher and unravel this complex mystery is metabolomics.

Metabolomics: The Beginning

The completion of the human genome project has made it possible to investigate the whole genome using high-throughput technologies and analyze data via "systems approach" (Fig. 1). Derivation of molecular-based strategies, development of new computer application and technologies and the application of bioinformatics are accelerating the elucidation of molecular underpinnings of human diseases as well as to more effectively prevent, diagnose, and treat these diseases. These strategies can also be successfully applied in addiction related disorders.

Since the beginning of molecular biology, biological questions have been successfully approached mainly by studying individual gene function(s) and gene products, one or few at a time. Despite understanding the cause of many biological problems, however, many fundamental biological questions remain to be answered. This is mainly because the majority of gene products function together interacting with other gene product influencing multiple pathways. Therefore, biological processes should be considered as complex networks of interconnected components. In addition to studying the components individually, it is important to study the combined nature of these gene products in the metabolomic networks and pathways.

Metabolomics in Addiction Research: Current Approach

Selection of Technology to Capture Metabolomic Changes

Recent advances in latest technologies allow the profiling of all metabolic components in a biological system at any given time, investigating dynamic changes in components quantity or quality in a system under external stimuli or perturbation and finally analyzing the changes of one component in relation to another. The goal here would be to generate protein–protein, protein-DNA or other component-component mapping of the networking pathways involved. Gene expression microarray is one such high throughput technology that allows detection of cellular changes at the transcript level and has been used extensively in research on alcohol and other drugs of abuse [14, 15, 54]. Gene expression profiling using microarray chips has been proved to be the most successful genome-wide technology to capture the temporal-spatial expression pattern of a cell. Since the expression microarrays are RNA-based method, they are highly effective in the simultaneous identification and measurement of virtually all transcript that are differentially expressed between any two samples representing treatment (e.g., ethanol) and control. Transcript profiling using microarrays is the most widespread functional genomics technique because of their relative technical simplicity, low cost and short turnover time. In recent years the development of high-density microarray chips has allowed us to present the entire transcriptome of more complex organisms such as human and mouse on a single chip. The availability of improved algorithms and easy to use software has made it possible to interpret and analyze the microarray data without much computer knowledge. Of all the addictions, such studies have been extensively used in alcoholism.

During the last 5 years, studies on humans and animal models using microarray have contributed to our knowledge of the molecular effects of alcohol and identified a number of potential candidate genes of interest in the context of alcohol response alone. In addition, microarray experiments generate a large number of ethanol-responsive genes some of which are repeatedly identified as such in multiple reports regardless of experimental paradigm. However, it would be extremely difficult and time consuming to investigate this large number of genes using single or candidate gene approach. Since these genes belong to multiple biochemical pathways including stress response, gene regulation, apoptosis, cell growth and cell signaling [54, 58],

we need to analyze them altogether in the context of cell and tissue system.

Tissue and Organ of Interest

In order to investigate the effect on gene expression following drug or alcohol exposure, cells or tissues from participants and their matched controls are needed. In most cases brain and brain regions are viewed as most appropriate. However, matched samples of brains are not available for such studies. The next best option is to make use of brain bank samples. This too is not always practical. More importantly, matching participant and control brains is not an easy task as they differ in a large number of parameters that may affect gene expression. We will not discuss this issue any further except to state that in the lack of human brain matched samples, and due to the problem of manipulative experiments on humans most studies have relied on a number of animal models. Of course this approach has its own drawbacks. With this realization, we will focus this discussion on one of the favored animal model (e.g., mouse). It has a number of advantages. Established genetic strains of mice are available and widely used which differ in responses to various drugs including preference to voluntary alcohol consumption. For example, strain C57BL/6 J consistently demonstrate high ethanol preference which is about 60% in comparison to strains A/J (26%), BALB/CJ (30.4%) and DBA/2 J (11.8%) given the free choice of water and 10% ethanol over a 14 day period [31]. Once a suitable genetic animal model is selected and their drug preference phenotype is reconfirmed with in-house study, they can be used in necessary experimental treatment with the drug under study following suitable methods. It allows collection of desired organ following appropriate treatment along with strain/genotype, age and sex matched controls. The drug treatment may involve various modes and durations as appropriate. It is also possible to include various environmental manipulations including stresses before or after the exposure to the addictive drug being investigated. The tissue of interest (e.g., brain) is collected at appropriate time and processed for studies on DNA, RNA, and protein including structural and developmental alterations that may be affected in any drug response including addiction. Although such studies in the past have concentrated on the RNA and protein including cellular changes, it is important to point out that futuristic studies may include DNA and protein changes reflecting epigenetic modifications. In fact it is likely that the addiction for a drug which is acquired following repeated exposures may involve epigenetic changes (DNA methylation, histone modification including chromatin alterations), that has remained on the side line of such a research. We will not go in any detail except to point out that such changes will explain a variety of RNA and protein changes that have been reported in response to drugs and drug addictions. For the main stream research in the new genome era, the tissues of interest are harvested from an experimental animal model and used for RNA isolation. The purified RNA is hybridized to a suitable expression array, which allows identification of genes that are affected as a result of drug exposures.

Generating Gene List

Microarray is hybridized, scanned and analyzed following manufacturer's recommended method and software. Microarray experiments generate a large number of genes which are analyzed further using bioinformatics tools and software. It is beneficial to develop a list of genes that show significant difference in expression between treatment, gender and age or any other selected parameters. This list can be further refined by primarily excluding genes for which no information is available in the public databases such as NCBI (http://www.ncbi.nlm.nih.gov/), Ensembl (http://www.ensembl.org/index.html), GO (http://www.geneontology.org/), UCSC (http://genome.ucsc.edu/), etc. (see [60] for

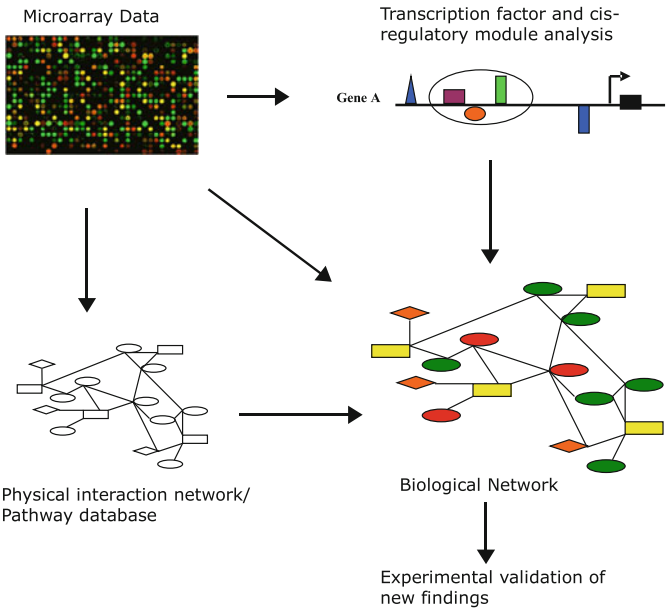

Fig. 2 Overall view of an integrated approach to constructing pathway or regulatory interaction network. Data generated from microarray experiment can be used to perform transcription regulatory network and/or biological interaction network

an example). These genes are used in the subsequent analysis as explained in Fig. 2.

Bioinformatics Tools and Analysis

It is apparent that in most cases a single gene may carry out several functions in the cell by interacting with other genes in the network. In this way, the action of one gene product dynamically affects the action of others in a cascading fashion in the cellular pathways, generating a complex global network [22]. In order to identify how a particular gene interacts in a subsystem, how all the subsystems co-ordinate into a particular pathway, and how the collective actions of multiple implicated pathways emerge into a global network in the metabolome causing multi-faceted alcohol or drug effect, the genes are analyzed using specialized software to predict biological association network. Currently there are many biological pathway analysis and visualization software available today. Some of the commercial and free software is listed in Table 1.

Genes from the list above are used as input in pathway analysis software to study the neuro-metabolomics and to predict biological association (Fig. 3). These programs are generally connected with underlying database(s) and allow user to query the database(s) for genes of interest. These databases for human, mouse, rat, yeast or any other organisms are compiled by retrieving relevant published scientific information from public databases such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) using automated natural language processing or other data mining techniques. The retrieved information is then curated and stored in the database for example, in the form of cellular events such as regulation, interaction and modifications among proteins, cell processes and small cellular molecules. Upon query to the database, the software program will construct a biological interaction network and provide visualization in a graph format for further exploration, examination and prediction. Some of the program also has built-in Gene Ontology search while others have additional features such as integrated transcription factor and *cis*-regulatory sequence analysis option, e.g., Bibliosphere. Commercial pathway analysis software are generally easy to

Table 1 Useful bioinformatics software tools and databases for protein–protein interaction and transcription regulatory network pathway analysis

Type of resource	Web address (URL)
Pathway databases	
EcoCyc	http://ecocyc.org/
KEGG	http://www.genome.jp/kegg/
MIPS	http://mips.gsf.de/genre/proj/yeast/
PathGuide	http://www.pathguide.org/
REACTOME	http://www.reactome.org/
SigPath	http://www.sigpath.org/
Pathway analysis, visualization and prediction tools	
Bibliosphere (commercial)	http://www.genomatix.de/products/BiblioSphere/
BioLayout *Express*3D (free)	www.biolayout.org
Cytoscape (open source, free)	www.cytoscape.org
GENECENSUS	http://bioinfo.mbb.yale.edu/genome/
GenMAPP (free)	http://www.genmapp.org/introduction.html
GNA (Genetic Network Analyzer)	http://ralyx.inria.fr/2008/Raweb/ibis/uid16.html
Ingenuity Pathway Analysis (commercial)	http://www.ingenuity.com/products/pathways_analysis.html
Osprey (free)	http://biodata.mshri.on.ca/osprey/servlet/Index
Pathway Studio (commercial)	http://www.ariadnegenomics.com/products/pathway-studio/
VisANT	http://visant.bu.edu/
Transcription regulatory databases	
DBTSS	http://dbtss_old.hgc.jp/hg17/
EPD	http://www.epd.isb-sib.ch/
JASPER	http://jaspar.cgb.ki.se/cgi-bin/jaspar_db.pl
PReMOD	http://genomequebec.mcgill.ca/PReMod/
Rvista	http://genome.lbl.gov/vista/index.shtml
TRANSFAC	http://www.gene-regulation.com/pub/databases.html
TRED	http://rulai.cshl.edu/cgi-bin/TRED/tred.cgi?process=home
TRRD	http://wwwmgs.bionet.nsc.ru/mgs/gnw/trrd/
Regulatory network analysis tools	
GEMS Launcher (commercial)	www.genomatix.de
Gene Regulation Tools	http://zlab.bu.edu/zlab/gene.shtml
GeneExpress	http://wwwmgs.bionet.nsc.ru/mgs/systems/geneexpress/
RSAT	http://rsat.ulb.ac.be/rsat/
Toucan (open source, free)	http://homes.esat.kuleuven.be/~saerts/software/toucan.php
Protein interaction databases	
3DID	http://3did.irbbarcelona.org/
AfCS	http://www.signaling-gateway.org/
BIND	http://bond.unleashedinformatics.com/
DIMA	http://mips.gsf.de/genre/proj/dima2/
DIP	http://dip.doe-mbi.ucla.edu/
HPRD	http://www.hprd.org/
INTACT	http://www.ebi.ac.uk/intact/site/index.jsf
iPfam	http://ipfam.sanger.ac.uk/
MINT	http://mint.bio.uniroma2.it/mint/Welcome.do
PDZBase	http://icb.med.cornell.edu/services/pdz/start
PIBASE	http://modbase.compbio.ucsf.edu/pibase/queries.html
Prolinks	http://mysql5.mbi.ucla.edu/cgi-bin/functionator/pronav
SCOPPI	http://www.scoppi.org/

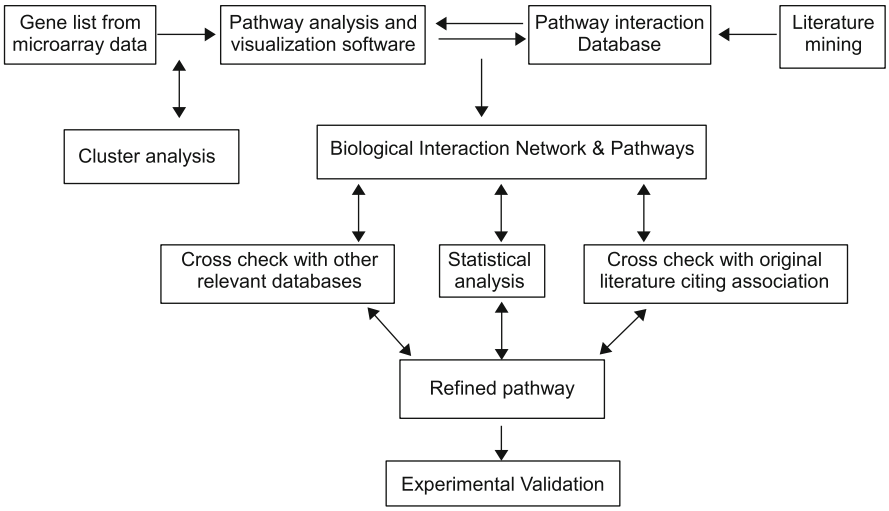

Fig. 3 Workflow of constructing meaningful biological interaction network and pathways from microarray data

use with available guides and tutorials where the open source or free software requires an extra learning curve and customization based on user's need.

An initial output from such analysis may generate a network graph that may seem highly complex due to the presence of all possible association among all matching gene products upon query to the database. Figure 4 is showing an example of a simplified view of one such initial output from PathwayStudio pathway analysis software. In this example, mouse affymetrix chips were used to assess the relative expression of genes in the brain in response to acute ethanol treatment on two genetic strains of mice (DBA/2 J or D2 and C57BL/6 J or B6) that are known to differ with respect to their responses to alcohol [54]. The expression array results showed that the genes fall into two main categories, which are strain-specific and strain-specific ethanol-responsive genes. Only ethanol-responsive gene data set containing about 60 genes was then used in cluster analysis to predict genes that tend to co-express in response to ethanol treatment. The results revealed that eight of the genes show down-regulation at the same level in both B6 and D2 mice in response to ethanol and nine demonstrate upregulation which is higher in D2 mice than in B6 mice, while 24 of the genes show up-regulation at the same magnitude in both B6 and D2 mice. This last cluster was further analyzed in the PathwayStudio software. The output was filtered to include only protein, cell complex, functional class, cell process and cell object. All irrelevant interactions and association were removed from the network and the result as shown in Fig. 4 represents the most relevant biological associations among 24 ethanol-responsive genes. A network graph like this one is generally composed of "nodes" and "lines". Nodes are shown by symbols of different shapes and sizes (e.g., circular, oval, triangle, rectangle etc. of different colors) which can represent any biomolecule such as protein, enzyme, cell complex, cell process, treatment, DNA, RNA, and metabolite. Nodes are connected by lines (straight or curved) representing physical interaction, association or relationship between nodes, e.g., protein–protein, protein-DNA, protein-cell process, etc. The lines can also be of different types to indicate the type of association such as binding, regulation and expression. A positive or negative sign can be associated with each type to represent the specific nature of the interaction. Color code can be used to include metabolomic category of the genes being studied. In a transcription regulatory network the nodes generally represent transcription factors, cofactors and DNA *cis*-regulatory elements. Lines in a regulatory

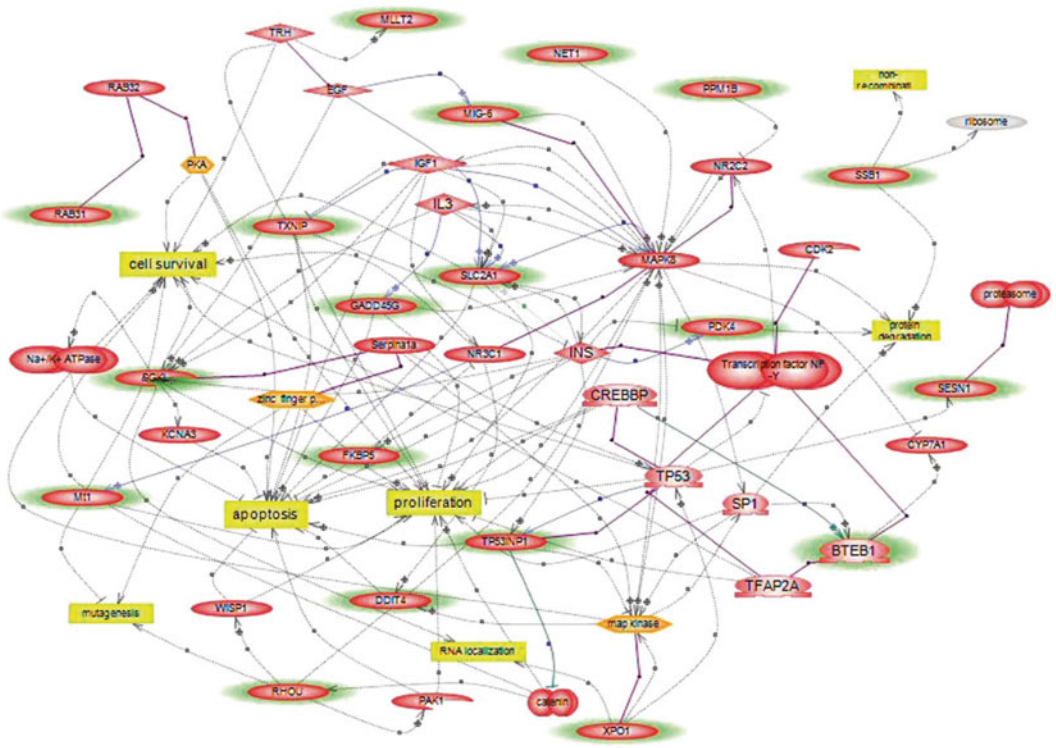

Fig. 4 Functional interactions of 24 ethanol-responsive gene products. Ethanol-responsive gene products (*orange ovals* shaded in *green*) are shown with other cellular objects such as protein (*orange ovals*), cell complex (e.g., transcription factor NFY, Na+/K+ ATPase), cell process (*yellow rectangles*), etc. These interactions could be of several different types: expression (e.g., *blue lines* connecting two cell objects), regulation (e.g., *grey lines*), binding (e.g., *purple lines*), etc. The interactions of these ethanol-responsive genes contribute directly or indirectly to a number of cell processes, specifically apoptosis, cell survival and proliferation. (Reprinted from Uddin and Singh [58] with permission from Elsevier.)

network would indicate physical interaction between transcription factors and *cis*-regulatory elements, i.e., protein-DNA interactions.

Once the initial network is developed, each interaction between two nodes (e.g., cell processes, proteins, enzymes, cell complex, treatment, etc.) should be individually verified by examining the cited curation and literature(s). Any irrelevant and indirect relationship should also be excluded from the network during final analysis. The result is also further cross-checked with other relevant database entry and can be statistically validated using appropriate algorithm. This kind of rigorous exercise helps reveal significant and fruitful information generally hidden in the network. For example, an analysis similar to the one described in Fig. 4 starting with all 60 ethanol-responsive genes was narrowed down to only 7 genes that showed direct connection to ethanol in closely interacting pathways in the brain (Fig. 5). The result shows that ethanol affects multiple cellular events that include synthesis and degradation, gene regulation, transcription, translation and expression, phosphorylation, molecular transport, biogenesis and various enzymatic activities. Through this and other subsequent downstream events, ethanol contributes both positively and negatively to a large number of biochemical pathways. Although drugs of abuse act on different receptor systems, they activate common downstream sequences of events, which underlie characteristic behavioral phenotypes such as compulsive drug-taking, craving, and relapse [42].

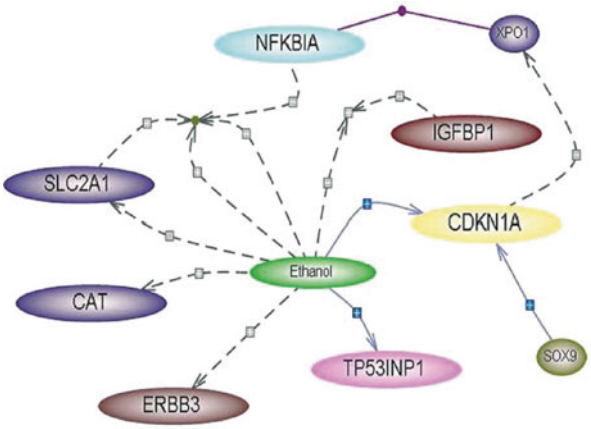

Fig. 5 An example of a final interaction network. A proposed pathway for ethanol's action on genes is shown where they directly interact with ethanol and other genes in the brain. This kind of small network showing most relevant association can be developed from an initial output of a pathway analysis software and can be used for further experimental validation. (Reprinted from Uddin et al. [60] with permission from Springer Science + Business Media.)

Transcription Regulatory Network in Drug Metabolomics

As we have learned above that ethanol and other drugs' action may be realized through the transcriptional control of gene expression, transcriptional regulators or factors and their combinatorial control on *cis*-regulatory elements play a critical role in the co-expression of these genes. This affects the interaction of genes in the metabolome and thus may affect signals that cascade through cellular pathways. There has been rapid progress in recent years in the development of a systems approach for identifying such transcriptional regulatory networks from high-throughput data generally generated from microarray experiments [3, 52, 59]. A summary of this powerful approach is outlined in Fig. 6.

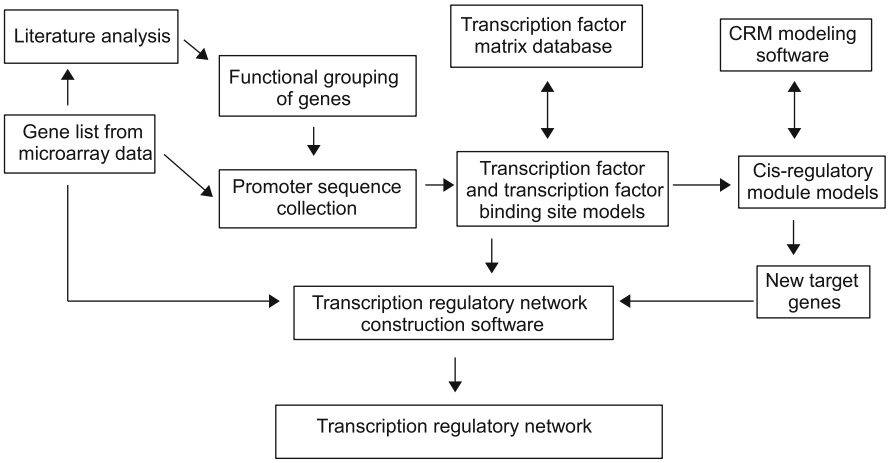

Fig. 6 Workflow of generating transcription regulatory network

Gene Selection and Literature Analysis

Since this approach can also use microarray technology, a list of genes showing significant difference between experimental and control cells or tissues can be developed using microarray experiments as described in the previous strategy or using similar comparable method. Now we need to investigate all possible physical interaction between transcription factors and between transcription factors and *cis*-regulatory elements, e.g., promoters, enhancers and other *cis*-acting regulatory elements on the promoter regions involving these genes. Various free and commercial software packages are available for this purpose (Table 1) that offer a number of modeling tools integrated with statistical algorithms and curated literature and transcription factor databases. The strategy outlined below can be performed using either free software tools such as the TOUCAN package or commercial software such as the GEMS Launcher package (Table 1).

Once the genes are selected they are used in literature analysis to identify possible transcription factors that interact with their promoter sequences either manually or by using commercially available software such as Bibliosphere (www.genomatix.de). This analysis is performed to subgroup initial gene set into overexpressed Gene Ontology groups based on the results from literature analysis. The stringency level can be set by the user, for example, for this analysis it can be set as that each transcription factor must be co-cited with at least two input genes, each transcription factor must be co-cited with one input genes at least two times and finally the co-citation should be at the sentence level in the abstract describing some function. Only subgroups that are statistically significant and bear meaningful association with the pathways potentially affected by the drug under study can be selected for further analysis.

Transcription Factor and Regulatory Elements Modeling

For modeling transcription factor and their possible binding sites it is necessary to obtain the promoter sequences of the genes. They can be retrieved from any public (e.g., NCBI and Ensembl) or commercial (e.g., Gene2Promoter www.genomatix.de) databases generally 500 bp–1 kb upstream and 100 bp–200 bp downstream of the transcription start site. The promoter sequences are then analyzed to construct common significantly conserved *cis*-regulatory modules generally consisting of two or more *cis*-regulatory elements where potential transcription factors or transcription regulator motifs bind on the promoter sequences of the input gene set [59] (Fig. 7).

Genes belonging to a Gene Ontology biological process group should be analyzed together as a subset. It is known that in eukaryotes, more than one transcription factor is required to regulate and initiate gene expression. Also, the co-regulation of mammalian genes usually depends on sets of transcription factors rather than individual factors alone, and *cis*-regulatory elements are often organized into defined modules of two or more transcription factor binding sites and clusters of such motifs [10, 13]. Therefore, the *cis*-regulatory modules identified in this way can be very useful in search for other potential new target genes that share the same framework of the known *cis*-regulatory modules. To identify possible *cis*-regulatory modules, first, the promoter sequences of the genes are scanned for matches to a transcription factor matrix library (e.g., MatInspector, www.genomatix.de or MotifScanner, http://homes.esat.kuleuven.be/~saerts/software/help/WebServices/motifscanner.htm). The transcription factor matches found are then used as basic motifs for the extraction of common *cis*-regulatory module models, for example, by FrameWorker (www.genomatix.de) or ModuleSearchers

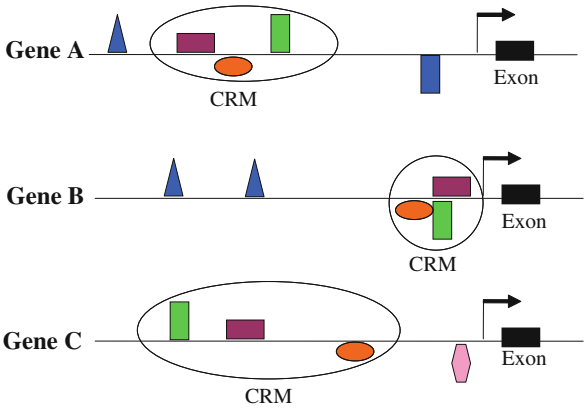

Fig. 7 Transcription factor and regulatory elements modeling. The figure shows a common *cis*-regulatory module (CRM) consisting of three common transcription factors (shown as *colored shapes*) shared by genes A, B and C

(http://homes.esat.kuleuven.be/~saerts/software/help/WebServices/modulesearcher.htm) program. The *cis*-regulatory module models with the best significant scores are selected to scan other DNA sequences (e.g., complete promoter database of organism or animal under study) for matches to these models. This would also verify the specificity of the models generated by the modeling software used. The bioinformatics tools that can be used for this search are, for example, ModelInspector (www.genomatix.de) or MotifSampler (http://homes.esat.kuleuven.be/~saerts/software/tutorial1/TOUCAN_Tutorial_MotifSampler.html). This approach also has the ability to identify other potential target genes of *cis*-regulatory module models predicted above.

The use of this strategy in research on drugs of abuse has shown promising results. For example, one research involving alcohol has shown that the alcohol-responsive metallothionein genes [31, 32], Mt1 and Mt2, are regulated by transcription factor cyclic AMP responsive element binding protein and metal-activated transcription factor 1 and primarily involved in zinc ion homeostasis [59]. Cyclic AMP responsive element binding is known to control gene expression for a variety of functions in the central nervous system and thought to be associated with both anxiety and alcohol preference. Haplodeficiency of the cyclic AMP responsive element binding gene and ethanol-induced decreases in cyclic AMP responsive element binding function have been shown to be associated with increased alcohol drinking in mice.

The search in the modeling databases for genes that share the same *cis*-regulatory module as cyclic AMP responsive element binding has revealed new target genes Synj1 (Synaptojanin 1) and Tph1 (tryptophan hydroxylase 1), potentially regulated by this module. Synj1 is known to be involved in the regulation of synaptic vesicle function and has been studied as a potential candidate gene for psychiatric disorders [43, 61]. Interestingly, the Tph1 gene product is known as a rate-limiting enzyme in the biosynthesis of serotonin and its activity is most abundant in the brain. Alteration in brain serotonin level has been implicated as an important contributing factor in many psychiatric disorders including alcoholism [20]. Altered arrangement of transcription factor binding sites in the module can direct the action of these and other target genes in intracellular signaling cascades, cell growth and/or maintenance. In addition to cyclic AMP responsive element binding, other key transcription factors identified are EVI1 (ecotropic viral integration site-1) and SP1. These modulate the contribution of the target ethanol-responsive genes in cell cycle regulation and apoptosis or programmed cell death. Multiple lines of evidence indicate that different groups of ethanol-responsive genes are involved in different biological processes and their co-regulation most likely results from different sets of regulatory modules.

Construction of Transcription Regulatory Network

The new target genes identified are added to the original list and the newly compiled list of genes is used to construct a regulatory network using the information available in the interaction databases. This way the microarray gene expression data profiles and transcription factor *cis*-regulatory module analysis data are integrated into protein–protein and protein-DNA interaction data available in the databases to obtain a broader systems view. Because gene expression and *cis*-regulatory module location data provide complementary information, integration of these data sources can emphasize the functional part of the network and thus make the inferred network more biologically relevant. There has been significant progress in the development of interaction databases (Table 1). These databases are constructed by storing curated published protein-DNA or protein–protein interaction obtained from extensive literature mining where in the literature protein-DNA interaction was validated using ChIP-chip analysis and protein–protein interaction was measured by two-hybrid system, Co-IP and mass spectrometry experiments. Results from other high-throughput technologies, such as genome-wide location analysis and cap analysis of gene expression, are also used that experimentally map many types of functional DNA elements on the genome. Though the use of different database in constructing the regulatory network may vary, however, the basic construction principle would be the same as constructing a pathway (Fig. 2).

A refined regulatory network constructed from an integrated approach can provide novel biological insight into cellular interactions in response to drugs and alcohol. This may predict new genes that are contributing in a particular pathway or indicate up or downstream effects of other pathways. Now would be time to experimentally validate these findings with rigorous testing. However, before jumping into experiment one must consider that the predicted networks are time, space and condition dependent, that is, different parts of the network will likely be active at different conditions. They have to be evaluated under specific condition of interest.

A network established this way is termed as a static network. This kind of network can be generated for a given dose of drug or alcohol for each cell, tissue or organ type for an animal system. A number of static networks can be connected and mapped together to generate a tissue- and drug-specific dynamic network (Fig. 1), which would provide significant knowledge toward our understanding of the metabolomics of drugs of abuse.

Application of Metabolomics in Solving Addiction Disorders

The strategies presented above has been successfully applied in studying tissue and disease specific regulatory networks for human diseases, including cancer [45, 53], cardiac hypoxia [11], innate immunity [18] and inflammation [6]. They were also used in the past to study the metabolomics of alcohol action [58–60]. Most recently [30], similar method was used to develop a common molecular network underlying addiction to different abusive substances. Using literature mining, a Knowledgebase of Addiction-Related Genes (KARG) was developed (http://karg.cbi.pku.edu.cn) that contains over two thousands items of evidence linking 1,500 human genes to addiction. Sequences of nearly 400 human addiction-related genes were analyzed using bioinformatics tools, e.g., KOBAS software [46] and mapped to statistically significant biologically meaningful experimentally validated pathways in the KEGG database [23]. Molecular pathways that were identified as significantly enriched for four drugs of abuse including cocaine, alcohol, opioids, and nicotine were selected as common pathways for drug addiction. This study found several pathways shared by all four addictive substances which are “long-term potentiation”, “MAPK signaling pathway”, “GnRH signaling pathway” and “Gap junction” and by connecting these

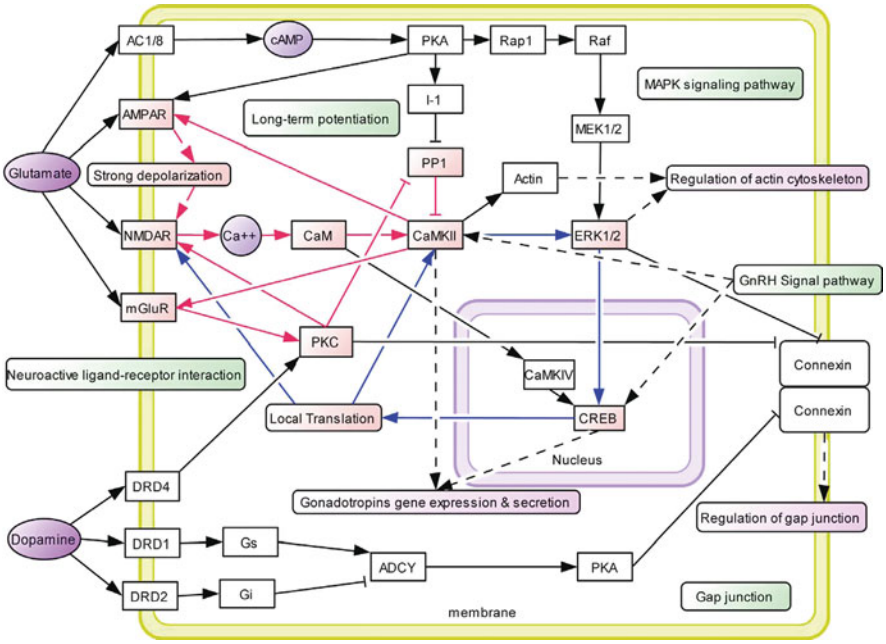

Fig. 8 Hypothetical common molecular network for drug addiction. The network was constructed manually based on the common pathways identified and protein interaction data. Addiction-related genes were represented as *white boxes* while neurotransmitters and secondary massagers were highlighted in *purple*. The common pathways are highlighted in *green boxes*. Related functional modules such as "regulation of cytoskeleton", "regulation of cell cycle", "regulation of gap junction", and "gene expression and secretion of gonadotropins" were highlighted in *carmine boxes*. Several positive feedback loops were identified in this network. Fast positive feedback loops were highlighted in *red lines* and slow ones were highlighted in *blue lines*. (Reprinted from Li et al. [30] with permission.)

pathways with additional protein–protein interaction data constructed a hypothetical common molecular network for drug addiction (Fig. 8). Interestingly, cyclic AMP responsive element binding, an important transcription factor implicated in alcohol research [59] has also been identified in this common pathway.

Integration of Systems Biology to Medication Discovery

Common human diseases are driven by complex networks of genes and a number of environmental factors. To understand this complexity in order to identify targets and develop medications against disease, a systematic approach is required to elucidate the genetic and environmental factors and interactions among and between these factors, and to establish how these factors induce changes in gene networks that in turn lead to disease.

The rapid progress in the development of large-scale high-throughput genetic screening technologies, availability of super computing power of modern specialized software and instant high-speed web access to numerous genetic data repository have enabled researchers to take a more systems biology approach to study complex traits like disease. Genotyping of hundreds of thousands of DNA markers, scanning through millions of single nucleotide polymorphisms, and profiling tens of thousands of molecular phenotypes simultaneously in thousands of individuals are now possible. This makes it possible to integrate data from all available sources and reconstruct complete genetic networks associated with disease. This can help

us identify common pathways in the intracellular signaling cascades shared by the causal factors driving disease, formulate clinical approach for prevention and develop effective treatments for a wide range of addictive disorders.

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Neurobiological Basis of Drug Reward and Reinforcement

David M. Lovinger

Contents

Introduction

Drug abuse and addiction to drugs involves a number of factors including genetic and environmentally influenced predispositions, the actions of the drugs themselves, the immediate environment, and the neurobiological mechanisms that promote and support drug actions and addiction. This chapter deals mostly with the latter aspect of drug use, abuse and addiction, as we will explore the ways in which the brain is built to adapt to environmental circumstances, and how these aspects of neural function can promote the continued use and abuse of certain drugs and ultimately promote behaviors we think of as addiction. We will then consider the mechanisms through which drugs of abuse interact with the brain systems that promote maladaptive drug use and addiction.

Addiction has been defined in several different ways, most of which stress the habitual or compulsive nature of addictive behavior, the physical, psychological and social damage produced by the behavior, and the trauma associated with cessation of the behavior. Compulsive drug use is certainly one type of addiction [21], but addictions are not limited to drugs of abuse, and can center on natural biological drives (e.g., sex, food consumption), physical activities (e.g., excessive exercise), relatively benign drugs (e.g., caffeine), as well as drugs of abuse (discussed in [86]). The latter substances will be the main focus of the present discussion. In addition, excessive use of drugs may lead to health and psychological problems even in the absence of an agreed-upon definition of addiction. Thus, it is important to understand the neural mechanisms that contribute to prolonged and maladaptive drug use.

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision [3] does not refer specifically to addiction, but instead covers what we generally think of as drug addiction under the heading of "Substance-Related Disorders". Within this classification, the manual defines substance dependence in the following way: "When an individual persists in use of alcohol or other drugs despite

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_13,

problems related to use of the substance, substance dependence may be diagnosed. Compulsive and repetitive use may result in tolerance to the effect of the drug and withdrawal symptoms when use is reduced or stopped." Common features of these descriptions are behavioral change that centers on the addictive substance or action (sometimes referred to as a "habit"), continued use despite negative consequences, and the possible negative consequences of cessation of the experience. All of these aspects of drug use disorders can be seen to relate to innate brain mechanisms underlying processes referred to as reinforcement and/or reward. In this context, it is important to discuss current ideas about the neural mechanisms of reinforcement and reward before discussing the impact of drugs of abuse on these processes.

Behaviorism and the Concepts of Reward and Reinforcement

An important aspect of the use, abuse, and addiction to a wide range of drugs is their reinforcing properties. A reinforcer is defined in experimental psychology as a substance or stimulus presented following a behavior that increases the incidence of the behavior above baseline levels. As Skinner [155] wrote, "The operation of reinforcement is defined as the presentation of a certain kind of stimulus in a temporal relation with either a stimulus or a response. A reinforcing stimulus is defined as such by its power to produce the resulting change [in the response]. There is no circularity about this; some stimuli are found to produce the change, others not, and they are classified as reinforcing and non-reinforcing accordingly." It is worth highlighting the dual use of the term stimulus by Skinner to refer to both the result of the action (the reinforcer), and a stimulus within the environment that can become associated with the response and the reinforcer. One definition of reinforcement, although not Skinner's position, is that it involves a strengthening of the ability of stimuli to elicit responses (the so-called stimulus-response model [70]), while a somewhat looser definition is a strengthening of the ability of the environment in general, including some neural activity within the animal itself and the animal's past history in that environmental context, to elicit the response [40].

The concept of reinforcement is best known from the work of Konorski and Skinner on what is now called operant or instrumental conditioning [82, 155]. However, the term reinforcement has also been used in the context of Pavlovian, or classical, conditioning. One use of this term is that presentation of an unconditioned stimulus subsequent to the conditioned stimulus "reinforces" the ability of the conditioned stimulus to elicit a conditioned response. This term has also been used to refer to the effects of stimuli that predict the value of a "rewarding" stimulus presented prior to presentation of food or another naturally desirable outcome [131, 149, 150]. For example, in the paradigm used by Schultz [149, 150], responding for food (licking) as well as neuronal activity related to stimulus presentation and responding can be measured. Dayan and Balleine provided a nice discussion of the distinctions between reinforcement in the context of Pavlovian and instrumental conditioning [35].

Two forms of reinforcement, termed positive and negative have also been postulated. Positive reinforcement refers to the process in which delivery of a desirable consequence increases the incidence of the behavior. This is quite easily understood in the context of the instrumental or operant conditioning paradigm in which delivery of palatable food will increase bar pressing by a rodent or key pecking by a pigeon [155]. Negative reinforcement occurs when the performance of an action results in omission of an undesirable stimulus (e.g., footshock), and the incidence of the behavior increases as a result of this learning process [157]. The initial phases of learning some skills, such as swimming, involve what might be termed negative reinforcement as the skill helps to reduce the undesirable effects of the environment. Many investigators do not subscribe to the idea that

positive and negative reinforcement are distinct processes, as both types of reinforcement basically refer to something that increases the incidence of a given behavior. However, negative reinforcement is a useful concept when measuring stimulus-behavior relationships, as it describes a condition in which increasing behavior leads to omission of a stimulus. Learning in everyday life will often involve both positive and negative reinforcement.

Two other terms that have come to be used in the context of instrumental learning and addiction are punishment and reward. Consideration of the conditions that promote cessation of behavior led to the definition of the undesirable outcome as punishment [7, 170], although the role of punishment has been hotly debated [156]. The term reward was not so readily accepted by early behaviorists, but has come into common use as a reference to the desirable outcome in an instrumental learning paradigm. The terms reward and positive reinforcement are often used interchangeably, but as we will discuss, these terms can be used to refer to different processes that control instrumental learning of actions, including drug self-administration.

Studies conducted over the last few decades have led to the refinement of the concepts of instrumental conditioning, reward and reinforcement based on the role of the outcome produced by a particular behavior in conditioning paradigms. Dickinson, Balleine, and others have shown that responses developed under certain types of conditioning schedules will rapidly diminish if the value of the outcome is decreased or if receipt of the outcome is no longer contingent on making the response [1, 10, 28]. This learning of "action-outcome" contingencies is best achieved with training schedules where the outcome is easily predictable and the probability of obtaining the outcome is enhanced with increased rates of responding (e.g., fixed or random ratio schedules). In this case, the outcome has been termed to have a "rewarding" action, based on its intrinsic value to the organism at the time of testing and association with the instrumental action itself.

In contrast, training with schedules where predictability is poorer and increasing rates do not increase probability of successful outcomes (e.g., random interval schedules) produces responding that is insensitive to outcome devaluation or non-contingent presentation of the outcome [10, 37, 67]. This "stimulus-response" type of conditioning can also occur with extensive training using schedules with higher predictability (discussed in [191]). In the case of stimulus-response learning, the association is made between antecedent environmental stimuli and the subsequent response, with the outcome serving as a reinforcer regardless of the immediate value of this outcome to the animal. As you can see, this is closer to the classical definitions of reinforcement favored by stimulus-response theorists, Donahoe, and perhaps Skinner [40, 155]. It should also be noted that White [183] drew a similar distinction between reward and reinforcement, albeit with a more traditional behaviorist emphasis on the definitions of these terms. Other investigators have defined reward in terms of positive reinforcement in combination with positive hedonic value [86], an idea that suggests more overlap between the two processes. While the separate definitions of reward and reinforcement in this context may be debated, there is strong evidence for the two instrumental conditioning processes themselves. Thus, the differentiation of the roles of stimuli/environment and outcome in the two different learning processes is important, and separate discussion of reward and reinforcement in these contexts is useful.

Before we consider how reward and reinforcement contribute to addiction it is worth discussing the adaptive purpose of these neural systems. Behaviors that lead to enhanced survival and/or reproduction are necessary for propagation of genes and species. Innate feeding, reproductive and harm-avoidance behaviors exist in all animals, but learning about features of the environment is necessary to obtain the opportunity to express these innate behaviors. Pavlovian conditioning is one such learning process whereby performance of something approximating an innate or reflexive behavior can come

to be elicited by stimuli that were originally neutral with respect to predicting a particular outcome (e.g., obtaining food or avoiding harm). Instrumental conditioning adds another layer of sophistication to this process. Animals with this capacity can learn to perform new actions and new sets of actions to obtain a positive consequence or avoid punishment. Both types of learning have obvious adaptive utility, as the animal can now integrate complex features of the world and new behavioral strategies into maintaining safety, as well as the quest for food and mating partners. The power of the neural mechanisms involved in reward and reinforcement likely derives from this relationship to survival and reproductive success.

However, there is the possibility that reward and reinforcement mechanisms will not always be used for adaptive purposes. One such example is the phenomenon of self starvation. Animals that are trained to perform an intracranial self-stimulation task, described later, will perform this task at the expense of sufficient eating if access to food is time-restricted [141]. Similar self-starvation is observed if animals are given the opportunity to run on a wheel when on a limited food access schedule [16, 142]. This particular form of self-starvation has been considered as a model of human anorexia nervosa [16], which itself is clearly an example of maladaptive behavior involving the brain systems we will consider. Stimuli that originally signal a positive outcome can change their predictive value (a certain location may contain food at one time and a predator at another). Furthermore, stimuli or substances that interact with the neural mechanisms involved in reinforcement may come to have reinforcing value even when they are not coupled to a favorable outcome, or even when they are associated with harmful results. Most drugs of abuse can act in this manner, and can lead to reinforcement of what we might call maladaptive behaviors. In the remainder of this chapter we will consider the brain circuitry and cellular and molecular mechanisms involved in reinforcement. Consideration of this topic will also entail some discussion of the experimental techniques used to uncover these mechanisms.

Neurotransmitters and Neural Circuitry: Involvement in Different Aspects of Reward, Reinforcement, and Addiction

While the concept of instrumental learning had begun to crystallize by the early 1930s mainly due to the work of Konorski and Skinner [82, 155, 193], little was known about the neural circuits involved in this behavior. Konorski and Divac both obtained evidence from studies involving lesions of the caudate nucleus implicating this part of the striatum in instrumental conditioning [39, 82]. The discovery by Olds and Milner [114] of intracranial self-stimulation provided an important clue as to the importance of at least one pathway within the basal ganglia. In the original intracranial self-stimulation paradigm, the animal was implanted with an electrode that could stimulate fibers in the medial forebrain bundle. Investigator-initiated stimulation at this site led the animal to repeat the behaviors that were ongoing at the time when the stimulus was delivered. Thus, activation of this neural pathway was in and of itself rewarding or reinforcing. It was later discovered that a key set of axons within the medial forebrain bundle supplied dopaminergic afferents to the forebrain regions known collectively as the striatum [31, 127, 186]. This finding stimulated work on the role of dopamine in brain mechanisms of reward and addiction that has continued to this day.

The dopaminergic pathways in the brain are now well known. The somata of the majority of neurons that use dopamine as a neurotransmitter are concentrated in contiguous ventral midbrain structures called the substantia nigra pars compacta (or A-9 nucleus) and the ventral tegmental area (or A-10 nucleus) [79]. The neurons in these two regions project to different striatal subregions and other forebrain targets. Neurons from the substantia nigra pars compacta primarily innervate the dorsal striatum (the caudate and putamen nuclei in primates). In contrast, dopaminergic neurons from the ventral tegmental area project strongly to the ventral portion of the striatum, particularly

a striatal subregion called the nucleus accumbens that sits in the ventromedial region of the striatum. Neurons within the ventral tegmental area also send dopaminergic afferents to the prefrontal, orbitofrontal (insular), and cingulate cortices, with more minor projections to other cortical regions such as the limbic cortical subregions [113].

The initial data suggesting that dopaminergic neuronal activity is crucial for intracranial self-stimulation was later supplemented by the finding that intracranial self-stimulation could be produced by stimulation within the ventral midbrain regions where the dopaminergic neurons reside. Intracranial self-stimulation is supported by stimulation in the ventral tegmental area, as well as at subregions of the substantia nigra pars compacta [31, 111, 132]. These studies did not rule out the possibility that stimulation of fibers that originated elsewhere and passed through the ventral midbrain contributed to intracranial self-stimulation. Nonetheless, the combination of these findings with those findings that dopaminergic manipulations alter intracranial self-stimulation strongly implicated dopamine coming from ventral midbrain neurons in the mechanisms that underlie reward and reinforcement during this process.

The focus on dopamine in the context of reward and reinforcement often overshadows the role of other neurotransmitters. Indeed, dopamine is a modulatory neurotransmitter that in and of itself is not capable of strong excitation or inhibition of neurons within this circuitry. Furthermore, there is evidence indicating that dopaminergic transmission is not required for certain aspects of behavior that are thought to involve reward or reinforcement. For example, gene-targeted mice that lack dopamine are still able to learn the location of food, but appear to require dopamine to express the learned behavior [135]. This finding and similar data from other studies seems to indicate that dopamine is necessary for the motivational aspects of reward seeking [11, 119] or "incentive salience" [15]. In addition, there is evidence that neurochemical lesions of the dopaminergic system do not eliminate self-administration of drugs of abuse such as heroin and ethanol [124, 130], suggesting that dopaminergic transmission may not be necessary for all of the rewarding or reinforcing effects of drugs of abuse. Thus, we need to consider the role of other neurotransmitters in reward, reinforcement and addiction. An exhaustive description of all the neurotransmitters involved in these processes is beyond the scope of the present paper. Instead, the role of particular neurotransmitters with intriguing roles in the brain reward/reinforcement circuitry will be discussed.

Within the central nervous system, the neurotransmitters glutamate and gamma-aminobutyric acid are responsible for the majority of fast synaptic transmission [79]. Glutamate directly excites neurons via the activation of ligand-gated cation channel-type receptors, while gamma-aminobutyric acid activates anion-preferring channels and generally has an inhibitory action. Both of these neurotransmitters have been implicated in brain mechanisms of reward, reinforcement, and drug actions [42, 52, 78].

One approach that has been used to examine the role of glutamate and gamma-aminobutyric acid in reward, reinforcement and addiction-related behaviors is blockade of receptors with specific antagonists, usually injected into a specific brain area [33, 34, 153, 160]. These approaches have proven to be effective in altering behavior, and have implicated certain subtypes of ionotropic glutamate receptors in reward and addiction-related behaviors. However, it is sometimes difficult to discern the specific behavioral role of glutamate and its receptors using antagonist blockade, as antagonists of ionotropic glutamate receptor will almost certainly decrease neuronal activity and disrupt circuit activity. Thus, the antagonist effect may not necessarily reflect a need for activation of the receptor so much as the necessity of activity of a particular set of neurons. The opposite case often obtains for gamma-aminobutyric acid (GABA)-ergic activity, as blockade of gamma-aminobutyric acid receptors, gamma-aminobutyric acid-A receptors in particular, tends to increase neuronal activity and may stimulate circuitry. For these reasons, much

recent research on gamma-aminobutyric acid and glutamate roles in reinforcement, reward and addiction has focused on the role of particular glutamate receptor and gamma-aminobutyric acid-A receptor subunit proteins.

The ligand-gated ion channels that mediate fast excitatory and inhibitory synaptic transmission are multimeric proteins that can be formed by numerous subunits and subunit combinations. Chronic exposure to addictive drugs alters the expression of particular ionotropic gamma-aminobutyric acid and glutamate receptor subunits [22, 75, 89]. Manipulating subunit expression can subtly alter receptor function without eliminating receptor activity. This has allowed investigators to explore the roles of these receptors in drug- and addiction-related behaviors without major disruption of the activity of neurons within the reward/reinforcement circuitry. This line of research has been boosted immensely by the development of techniques for transgenic receptor expression and gene-targeted receptor modification and disruption (i.e., so-called knockin and knockout techniques). It is now common for investigators to use transgenic and gene-targeting techniques to produce mice that express higher or lower amounts of a desired receptor subunit, while production of mice that express a slightly mutated version of a receptor has become more common. Viral-based gene overexpression, often involving microinjection of constructs into specific brain regions is now also being widely used to enhance protein function in neurons within reward/reinforcement circuitry. Altering expression of the GluR1 alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subunit in gene-targeted mice alters instrumental learning [74, 171], and reduces morphine dependence and sensitization [178]. Altered acute responses to drugs of abuse, as well as changes in ethanol tolerance and dependence have been observed in mice in which gamma-aminobutyric acid-A receptors have been altered by gene targeting of alpha2, alpha5 and delta subunits [94, 104, 174]. However, one caveat that must be added to this discussion is that neuronal activity has not been measured in vivo in the animals used in these studies, and thus, the extent to which subunit loss alters circuit activity has yet to be determined in any of the aforementioned experimental models.

The neuromodulatory transmitter serotonin (or 5-hydroxytryptamine) can influence the brain reward and reinforcement circuitry, in part through actions on dopaminergic neurons [52, 69]. Serotonin can also influence goal-directed and habitual behavior through its role in control of affect and in "impulsivity". The likelihood of choosing new actions without strong outcome control has been linked to disorders of brain serotonergic systems. Impulsivity is responsive to some treatments aimed at the serotonergic system [52, 121]. Because of the disregard for outcomes, impulsive responding may be a first step in the process leading to stimulus control of behavior and maladaptive habits. Measures of impulsivity in animal models have been suggested to predict a pattern of addiction-like drug taking in rodents [13]. Serotonin levels in several brain regions are elevated during administration of psychostimulant drugs such as amphetamine and cocaine, and there is evidence that excessive serotonergic transmission contributes to the addictive effects of these drugs, in addition to the well-characterized role of dopamine in these processes [51, 64, 69, 109, 162].

Opioid neuropeptides are widely distributed in the brain, including in the action/reinforcement/reward circuitry discussed at present [79]. These peptides, enkephalins and endorphins in particular, are perhaps best known for their roles in analgesia. However, it is now well established that opioid peptide production and release is increased in response to stressful stimuli and other environmental challenges [45, 126]. Brain opioid systems have also been implicated in mechanisms of reward, particularly in relation to food and drugs of abuse. Studies of food-related behaviors generally indicate that opioid peptides signal something about the hedonic value or desirability of the food, sometimes called "liking" [11, 14, 59]. Opiate drugs that act as agonists at mu and delta-type opiate receptors are self-administered in instrumental paradigms (reviewed in [56]),

and opiate agonists produce decreases in the threshold for intracranial self-stimulation [19, 181]. Opiate antagonists can also influence intracranial self-stimulation [182]. These findings indicate that activation of the brain opioid system has "rewarding" effects.

The brain endocannabinoid system has also begun to receive a great deal of attention as a mediator of instrumental learning and addiction. Endocannabinoids are lipid metabolites that act on the cannabinoid receptors, the receptors originally discovered as mediators of the psychoactive effects of drugs such as marijuana and hashish [112]. In the brain, endocannabinoid agonists act mainly through the cannabinoid-1 receptor to produce short- and long-lasting synaptic plasticity [93]. The role of the brain endocannabinoid systems in responses to a variety of drugs of abuse is a fascinating topic that has received a great deal of attention in recent years, and this subject will be discussed later in this chapter. Recent studies using instrumental conditioning techniques indicate that cannabinoid-1 receptors play a role in transition from action-outcome to stimulus-response (habit) learning [49, 62]. Thus, the endocannabinoid system may have an important role in reinforcement-based instrumental learning. It is not yet clear if alterations in dopaminergic transmission or effects on other neurotransmitter systems are involved in this habit-promoting effect of endocannabinoids. The cannabinoid-1 receptor is highly expressed throughout the brain circuitry thought to mediate instrumental conditioning [61, 66]. Within these circuits cannabinoid-1 receptors are expressed on axon terminals of glutamatergic and GABAergic neurons (reviewed in [93]), and may well regulate release of other neurotransmitters including catecholamines [166]. Thus, there are many possible sites where endocannabinoid-dependent synaptic plasticity may play a role in this type of learning and in addiction.

The foregoing discussion should make it clear that to better understand the neuronal mechanisms contributing to reward, reinforcement and addiction we need to understand more fully the brain circuits involved in the control of actions and the instrumental learning of actions and association of actions with stimuli. We must also gain a better understanding of the roles of particular neurotransmitters and receptors in different parts of these circuits. The forebrain, in conjunction with the ventral midbrain, can be conceptualized as a series of parallel cortex-basal ganglia-cortex circuits that can also be serially interconnected (see [191] for review). The ultimate function of these circuits is to modify cortical and brainstem output to control the selection, initiation and timing of actions to produce effective integrated behaviors. Neurons and synapses within these circuits can undergo plastic changes that are thought to contribute to learning of new actions and association of actions with conditioned stimuli.

In an admittedly simplistic scheme, this circuitry can be separated into at least 3 parallel circuits [191] (Fig. 1). (More recently, 4 such circuits have even been suggested [192], and undoubtedly further subdivisions will emerge.) Each of the circuits consists of a cortical component, a striatal component, downstream basal ganglia components, and a thalamic component. The "sensorimotor" circuit is comprised of the primary and secondary sensory and motor cortices and the substantia nigra pars compacta which project to the putamen (the dorsolateral striatum in rodents), which then projects to the motor regions of the globus pallidus, ultimately influencing the ventral thalamus and closing the loop back at the sensory and motor cortices (Fig. 1a). The "associative" circuitry involves similar connections between associative areas of the cortex (including the prefrontal and parietal regions), the substantia nigra pars compacta, the caudate nucleus (the dorsomedial striatum in rodents), associative regions of the pallidum, and the mediodorsal and ventral thalamus (Fig. 1b). The "limbic" circuitry involves the limbic cortices (including not only neocortical prefrontal and temporal areas, but also archicortical regions such as the hippocampus and basolateral amygdala), the ventral tegmental area, the ventral striatum/accumbens, the ventral pallidum, and the mediodorsal thalamus (Fig. 1c). One can even consider connections

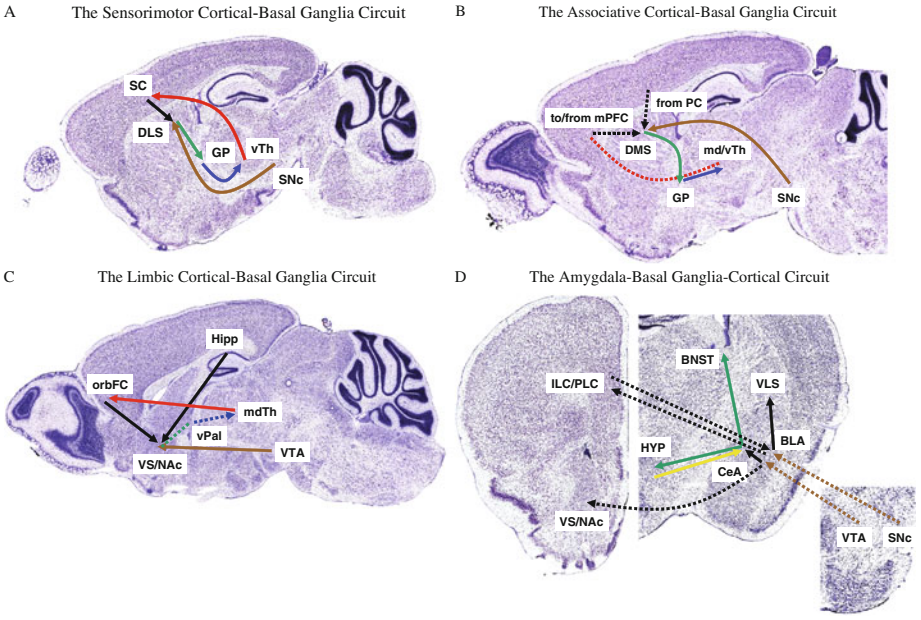

Fig. 1 Schbematic diagram of the reward/reinforcement circuits in the rodent brain. (**a**) The sensorimotor circuit (shown in a parasagittal orientation) contains glutamatergic connections from the somatosensory and motor cortices to the dorsolateral striatum (putamen equivalent in rodents), gamma-aminobutyric acid (GABA)-ergic connections from the dorsolateral striatum to the motor pallidum, GABAergic pallidal connections to the ventral thalamus, and glutamatergic thalamocortical projections back to the sensory and motor cortices. Dopaminergic inputs to the dorsolateral striatum come from the substantia nigra pars compacta. (**b**) The associative circuit contains glutamatergic connections from the medial prefrontal and parietal cortices to the dorsomedial striatum (caudate equivalent in rodents), GABAergic connections from the dorsomedial striatum to the pallidum, GABAergic pallidal connections to the mediodorsal and ventral thalamus, and glutamatergic thalamocortical projections back to the associative cortex. Dopaminergic inputs to the dorsomedial striatum come from the substantia nigra pars compacta. (**c**) The limbic circuit contains glutamatergic connections from the limbic cortical and limbic areas such as the orbitofrontal cortex, hippocampus, and basolateral amygdala to the ventral striatum/nucleus accumbens, GABAergic nucleus accumbens connections to the ventral pallidum, GABAergic pallidal connections to the mediodorsal thalamus, and glutamatergic thalamocortical connections back to the limbic cortex. Dopaminergic inputs to the nucleus accumbens come from the ventral tegmental area. (**d**) The basolateral and central amygdala connect to a variety of brain regions involved in motivation, reward, and reinforcement (shown here using separate brain sections). The basolateral amygdala receives dopaminergic input from the substantia nigra and ventral tegmental area, as well as glutamatergic input from the medial prefrontal cortex. Glutamatergic efferents from the basolateral amygdala innervate the medial prefrontal cortex, central amygdala, dorsal striatum, and nucleus accumbens. The central amygdala receives afferent input from the hypothalamus as well as glutamatergic input from the basolateral amygdala. GABAergic efferent output from the central amygdala innervates the hypothalamus and the bed nucleus of the stria terminalis. *Solid arrows* depict connections within the plain of the single brain section depicted, while *dashed lines* show connections that run out of the plain of the section. *Black arrows* = glutamatergic cortical afferents; *green arrows* = GABAergic striatal afferents; *blue arrows* = GABAergic pallidal afferents; *red arrows* = glutamatergic thalamic afferents; *brown arrows* = dopaminergic nigral and ventral tegmental afferents. Abbreviations: BLA = basolateral amygdala; BNST = bed nucleus of the stria terminalis; CeA = central amygdala; DLS = dorsolateral striatum; DMS = dorsomedial striatum; GP = globus pallidus; Hipp = hippocampus; HYP = hypothalamus; ILC = infralimbic cortex; mdTh = mediodorsal thalamus; md/vTh = mediodorsal and ventral thalamus; mPFC = medial prefrontal cortex; orbFC = orbitofrontal cortex; PC = parietal cortex; PLC = prelimbic cortex; SC = sensory cortex; SNc = substantia nigra pars compacta; VLS = ventrolateral striatum; VS/NAc = ventral striatum/nucleus accumbens; vPal = ventral pallidum; VTA = ventral tegmental area; vTh = ventral thalamus

within the amygdala to have a similar organization, with the cortical component being the basolateral amygdala, the ventral tegmental area projections providing the dopaminergic modulatory input, the striatal components being the central amygdala and bed nucleus of the stria terminals, and downstream targets leading ultimately to cortical outputs (Fig. 1d). Evidence for interconnections among the circuits at the level of striatonigralstriatal projections can help to coordinate the different systems [12, 68, 159, 191]. To fully understand reward and reinforcement-dependent learning and resultant behavioral output in the mammalian brain, it is necessary to consider all of the components in this circuitry.

Recent studies have begun to shed light on the role of these different forebrain circuits in instrumental and Pavlovian conditioning, and the ideas generated from these studies are now being applied to examination of drug actions [10, 41, 50, 191, 192]. Based on excitotoxic lesioning and local pharmacological manipulations, evidence has accumulated that the associative circuit involving the dorsomedial striatum and associated circuitry, including the basolateral amygdala [117, 118] has key roles in action-outcome learning. Afferent inputs from the prefrontal cortex to neurons in the dorsomedial striatum provide one source of input containing information relevant to action selection, and the cingulate cortex may provide input about discriminative stimuli [10]. The dopaminergic input from the substantia nigra may provide information about reward value. The contribution of action-outcome learning to drug taking is easy to conceptualize. Intrinsically rewarding effects of drugs likely control behavior even in recreational or social users seeking the euphoric effects of cocaine and amphetamine or the anxiety-reducing effects of alcohol. Indeed, studies in rat indicate that cocaine "seeking" behavior, measured as an instrumental response normally associated with drug availability is rapidly lost with devaluation under certain conditioning regimens [115]. It is not yet clear if action-outcome contingencies continue to drive drug seeking and self-administration after long-term drug use and in addicted individuals. It is tempting to speculate that addiction involves a shift in behavioral control from action-outcome/reward to stimulus-controlled/reinforcement mechanisms such as those described in the next few paragraphs. Interestingly, Pelloux et al. [122] have shown that rats given limited experience with cocaine seeking and taking will readily suppress seeking responses when intermittent punishment is given, while prolonged exposure to this paradigm reveals a subgroup of rats that will not show this punishment-suppression effect. Furthermore, rats allowed to orally self-administer cocaine continued to show instrumental responses associated with the drug even after cocaine devaluation [105]. Thus, evidence is developing that prolonged exposure to psychostimulants can lead to a shift from action-outcome to stimulus-driven behavior.

The sensorimotor circuit involving the dorsolateral striatum appears to have a prominent role in stimulus-response or habit learning. In this circuit the neocortical components and the dorsolateral striatum process information about the relationship between stimulus presentation and response performance, with the dopaminergic inputs from the substantia nigra (and the ventral tegmental area to some extent) providing a reinforcing signal to promote the stimulus-response association [10]. It has been suggested that the role of dopamine is required for the initial stages of this association, but that behaviors become engrained and resistant to dopaminergic manipulations once the stimulus-response association is formed and habitual behavior is in place [184]. Ultimately, output from the motor cortex is necessary for behavioral performance, and thus, this circuit can produce relatively straightforward throughput from sensory input to motor output. Habitual responding has been postulated to contribute to drug-taking behavior, such that when an individual is in the proper environment with the drug available, the actions involved in drug administration will be automatized and will often continue regardless of the specific outcome of drug usage. There is emerging evidence that this sort of responding may contribute to cocaine and alcohol-related behaviors in rodents

[38, 106, 122], but see also [146]. However, to date the role of stimulus-response associations in drug administration and relapse have not yet been thoroughly examined and fully dissociated from the stimulus-dependent forms of learning thought to be mediated by the limbic circuit (described below).

Among the roles of the limbic circuit is the integration of information for Pavlovian and instrumental conditioning in a type of learning called Pavlovian-instrumental transfer [32, 191, 192]. In this circuit, limbic neocortical areas such as the ventral prefrontal cortex provide information relevant to task outcomes to the nucleus accumbens. The basolateral amygdala provides input on reward and appetitive incentive value to the accumbens, where it is combined with the other cortical information. Dopaminergic inputs to the basolateral amygdala, limbic neocortex, and ventral tegmental area also provide information about reward value, while the orbitofrontal cortex may provide information important about the relationship of particular stimuli to task outcomes [116]. The role of the hippocampus and other limbic cortical regions that project to the nucleus accumbens is less clear. The net result is development of associations between environmental stimuli and task outcome (sometimes called stimulus-outcome learning), through which discrete stimuli gain control over particular instrumental responses. In this way the Pavlovian association of the stimulus transfers to the performance of the instrumental response. A role for this type of learning within the context of addiction is easy to postulate. It has long been thought that stimuli that are associated with, and predictive of, drug administration (e.g., needles, liquor bottles) can stimulate drug seeking and taking [50, 83, 139]. Indeed, there is experimental evidence that this sort of cue-induced relapse and drug craving can be induced in both humans and experimental animals [17, 25, 26, 83, 139].

The characterization of the limbic circuit as the mediator of reward and/or reinforcement is an idea that has captured the imagination of neurobiologists and addiction researchers [6, 53, 71, 80]. However, it is now becoming clear that the circuitry that includes the dorsal striatum has an equally important role in these processes (see [192] for review). In addition to the studies mentioned above that implicated the associative and sensorimotor circuits in action-outcome and stimulus-response learning, there is also evidence that dopaminergic innervation of the dorsal striatum plays important roles in instrumental learning. Stimulation of dopaminergic neurons in the substantia nigra pars compacta supports intracranial self-stimulation, as mentioned above. Furthermore, activation of substantia nigra neurons with intracranial self-stimulation-inducing patterns enhances learning and striatal synaptic plasticity [132]. An elegant series of studies by the Palmiter laboratory indicates a key role for dorsal striatal dopamine in instrumental learning and performance. Using dopamine restored in the dorsal striatum of mice that have been engineered to lack the neurotransmitter, these investigators have shown that food-seeking and instrumental learning/performance were rescued [136, 137]. Thus, full neurochemical integration within the dorsal striatum is all that is needed for proper motivational signaling and instrumental performance. This is not to say that the limbic circuitry does not have reward-related functions, but rather that an intact limbic circuit may not be necessary for proper learning and performance of a purely instrumental task.

In recent years researchers have also focused on the circuitry involved in generating undesirable effects that contribute to drug taking and relapse, and the effects of the drugs themselves on this circuitry (reviewed in [84, 86]). There is evidence for reduction in the positive hedonic effects of drugs after sustained self-administration, and negative consequences of drug use and withdrawal increase with repeated use and withdrawal [48, 81, 84, 86, 92, 102]. The amygdala and associated structures appear to have prominent roles in this scenario. The amygdala has generally been thought of as a brain region involved in the processing of information related to emotion, and the role of the amygdala in anxiety and responses to stress is widely known [90]. However, one can also view the role of the amygdala as providing a neural index of

the incentive value of a particular stimulus or event [10, 144, 176]. In this context, the amygdala plays roles in both reward and reinforcement processes as defined above. Furthermore, it is now clear that the structure we call the amygdala can be subdivided based on cytoarchitecture and afferent/efferent connections. Two well characterized amygdalar subregions are the basolateral and central nuclei. The basolateral amygdala is an archicortical structure containing mainly glutamatergic projection neurons and a small number of GABAergic interneurons. The basolateral amygdala innervates other structures within the amygdala, but also has connections with parts of the prefrontal cortex, and the dorsomedial and ventral regions of the striatum [143]. Input to the basolateral amygdala from areas such as the ventral tegmental area and the locus coeruleus provides information about arousal and motivational state [128]; thus, one possible role for this brain region is to integrate information necessary for a reward signal and relay that information to the associative circuit involved in action-outcome learning. The central amygdala is similar in cytoarchitecture to the striatum, having a large proportion of GABAergic projection neurons [143]. This structure receives excitatory input from the basolateral amygdala, neocortical and paleocortical regions, as well as information about motivational state via neuromodulatory regions such as the hypothalamus [143]. Output from the central amygdala is sent to the bed nucleus of the stria terminalis, hypothalamus, and other subcortical regions as well as to the substantia nigra and ventral tegmental area, where it can influence the circuitry involved in stimulus-response and stimulus-outcome learning [128, 143]. The amygdala has also emerged as a brain region with important roles in conditioned responses related to the rewarding effects of drugs studied using the conditioned place preference task described in the following section [20, 55]. The amygdala interconnections with the bed nucleus of the stria terminalis, a subcortical nucleus with a striatal-like organization (i.e., populated predominantly by GABAergic projection neurons) have generated a great deal of interest, as the bed nucleus of the stria terminalis has been implicated in the actions of drugs of abuse as well as in drug self-administration and relapse [5, 57, 179].

Clearly, a better understanding of the brain regions in involved in learning and control of behavior involving reward and reinforcement is emerging. In addition, methodology is emerging that will help us define the roles of brain circuitry and circuit physiology in behavior, and help us to refine our behavioral models based on neuroscientific findings. One of the challenges in addiction research in the coming years will be to determine how the function of these brain circuits contributes to responses to drugs of abuse, maladaptive use of the drugs, and addiction.

Models of Drug Use and Drug Addiction

Examination of the neural basis of drug actions, drug use, and addiction has relied to a great extent on development of laboratory animal models. A great deal of progress has been made with this approach. However, it has proven difficult to model all aspects of drug actions and addiction. For example, how does one assess "euphoria" or "craving" in an animal that is incapable of verbal self-report. Progress was slow at times for development of reasonable models of self-administration for drugs such as alcohol, cannabinoids, and nicotine [95, 147, 158]. Agreeing on a universal definition of addiction and developing an animal model thereof has also proven to be difficult. Nonetheless, several decades of research have led to the development of a variety of behavioral tests that assay various aspects of drug action, drug use, and addiction (Table 1). These techniques continue to be refined and combined with new techniques for neuroscientific investigation to provide more complete information about relevant neural mechanisms. The following discussion will describe some of these animal models with the emphasis on models of drug reward, reinforcement, and addiction.

Table 1 Models of drug reward and reinforcement: relation to phenotypes of human drug use, dependence, and addiction

Model	Human drug use phenotype
Simple operant self-administration	Hedonic value, liking/wanting
Devaluation	Goal-directed vs. habitual responding
Intracranial self-stimulation threshold changes	Hedonic value, anhedonia
Conditioned place preference/aversion	Reinforcement, craving, incentive sensitization, resistance to negative outcome
Progressive ratio breakpoint	Hedonic value, compulsivity
Behavioral "cost"	Hedonic value, compulsivity
Response persistence without drug	Compulsivity
Punished responding/pairing with undesirable tastant	Compulsivity, resistance to negative outcome
Cue-induced reinstatement	Craving, incentive sensitization
Secondary reinforcement	Craving, habitual responding
Psychomotor stimulation/sensitization	Incentive sensitization

A seemingly direct way to measure the reinforcing effects of a substance is to determine whether delivery of the drug itself will support learning or continued performance of a particular action or set of actions. This so-called self-administration paradigm has been used to examine the reinforcing actions of many drugs of abuse in a variety of animal models, and in general all of these drugs have been found to support self-administration under at least one schedule of drug administration [50]. Comparisons of self-administration in humans and laboratory animals have indicated similarities that auger well for the experimental use of these procedures [120]. The general procedure is to train the animal to press a lever or nosepoke an object in order to receive the drug either by oral, intravenous, or intracranial routes of administration. Using the basic instrumental training schedule, animals can also be tested in a final short "extinction" session in which no drug is available to see if they perform the operant behavior. This helps to assess the drug-seeking behavior without any interference from neural actions of the drug itself (e.g., depressant effects that reduce rate of responding). Variations of this basic procedure include the use of secondary reinforcers (e.g., stimuli paired with the opportunity for drug self-administration that come to elicit behavior themselves) [13, 41], and use of a progressive ratio schedule in which animals must increase their responses exponentially [133] with each trial in order to continue drug delivery. In this latter procedure, the investigator assesses the "breakpoint", which is the response requirement beyond which the subject will no longer work for the drug. This procedure can be used to determine the relative reinforcing efficacy of a particular drug. This approach has the advantage of direct measurement of the animal's willingness to use the drug. However, there are some drawbacks to self-administration techniques. For example, self-administration leading to high levels of drug in the brain that impair subsequent performance of the actions needed for further drug taking (reviewed in [60]). Oral self-administration of drugs such as ethanol brings into play factors such as taste that affect the willingness of certain animals to ingest the desired drug [54]. Use of instrumental self-administration procedures also necessitates consideration of separate neural control of drug seeking and drug taking [14, 139, 147]. Nonetheless, self-administration procedures are arguably the most direct measure of use and abuse, particularly given the variety of procedures that have been developed using instrumental paradigms. Self-administration procedures also allow investigators to examine the effects of treatments on drug use in preclinical assays.

In light of the previous discussion of reinforcement and reward, or action-outcome and habit learning, it seems important to evaluate which of these modes of behavior actually drives drug self-administration. As mentioned above investigators are just beginning to examine this

issue with interesting early results [38, 106, 122], but see also [146]. Another common variant of the drug self-administration procedure is cue-induced drug-related responding and reinstatement of this responding and/or drug taking. It has clearly been demonstrated that cues signaling the opportunity to respond instrumentally and obtain a drug can come to elicit responding in the absence of the drug, and especially robustly when the drug has been omitted for long periods of time [17, 77, 151]. This procedure involves a component of stimulus-outcome learning or Pavlovian-instrumental transfer with the cue serving as the Pavlovian conditioned stimulus. Indeed, this type of conditioning has become pretty much the standard in instrumental self-administration procedures as some explicitly paired cue, most often a light, is included in most such studies. This may be one reason for the large number of studies implicating the aforementioned limbic circuitry in drug-seeking behavior, as this circuitry appears to have important roles in stimulus-outcome learning. There is certainly some heuristic value to such studies in the context of human addiction, as it is easy to imaging how environmental stimuli that signal drug availability might trigger drug seeking and relapse.

Other surrogate measures of the rewarding effects of drugs of abuse have been developed. Drawing on the intracranial self-stimulation paradigm discussed above, investigators have examined the ability of drugs of abuse to shift the threshold stimulus intensities needed to support self-stimulation. Several abused drugs produce a leftward shift in the stimulus-response curve or increase rates of responding, indicating that they enhance the reinforcing properties of intracranial self-stimulation (see [187] for review). Drugs with this sort of action include those that are strongly self-administered such as cocaine and amphetamine, as well as other drugs of abuse, although studies of ethanol have yielded mixed results that might be explained by variables such as route of drug administration [9, 87, 107]. This technique can reveal indirectly the rewarding or reinforcing effects of drugs, but thus far the emphasis has mainly been on the effects of investigator-administered drugs and involvement of the limbic circuitry. It would be interesting to see this line of research extended to include more self-administration/intracranial self-stimulation studies and examination of different circuitry and component brain regions.

Recent studies have focused on identifying behaviors that might be indicative of an "addictive" phenotype in experimental animals. One approach has been to develop a battery of tests designed to measure continued drug seeking and taking under conditions where these behaviors become increasingly difficult and costly. Deroche-Gamonet et al. [36] have develop a three-test battery consisting of: (1) measuring the progressive ratio breakpoint mentioned above; (2) measuring the persistence of instrumental responding on a previously cocaine-associated manipulandum even when a signal indicates no drug availability, and (3) determining whether cocaine self-administration will continue even when associated with electric footshock (a paradigm also used in [122, 173]). Interestingly, Wolffgramm and Heyne [189] and Petry and Heyman [123] have used a conceptually similar approach with alcohol. Wolffgramm and Heyne [189] provided the alcohol in a solution with a normally aversive tastant, and found that this procedure decreased drinking in animals that had short-term alcohol drinking experience while drinking was maintained at much higher levels in animals that had been drinking alcohol for a long time period (at least 9 months). Petry and Heyman [123] steadily increased the behavioral "cost" necessary to obtain an alcohol-containing solution and found that rats with experience drinking alcohol maintained their drinking despite the increasing cost, while similar effects were not observed with palatable nutrient-containing solutions. These sorts of techniques are now being used to examine factors that predispose animals to uncontrolled/compulsive drug self-administration. Everitt and coworkers have determined that what appears to be impulsive responding in a 5-choice serial reaction time test is predictive of later abusive drug use in

this paradigm [13]. This paradigm has now been used by investigators to identify subgroups of rats that are especially vulnerable to what might be termed addiction. Interestingly, only a relatively modest subgroup of rats given extensive self-administration experience show maintained responding in the second and third tests and also show high breakpoints in test one [36]. It is hoped that this approach will provide a powerful tool for identifying genetic, neuronal and circuit differences that contribute to enhanced susceptibility to drug addiction.

Investigators have also taken advantage of Pavlovian conditioning to examine whether drug administration can be used to produce a conditioned place preference in an animal [172]. In this paradigm, the animal is given the drug paired with one of 2 or 3 chambers in an apparatus, and then tested later for location preference. In a final drug-free test, the animal is then free to choose a location in which to spend the trial. If more time is spent in a particular location, this is thought to indicate that the drug paired with this location has a preferred or reinforcing effect. This technique has the advantage that the animals are not subjected to drug intoxication at the time of testing, so there is little chance of impairment of the behavior by the drug itself. However, it must be stressed that the location is a conditioned stimulus and not a reward or reinforcer of any kind in this paradigm. Thus, the technique does not measure these functions per se, i.e., the animal does not have to repeat an action in order to obtain an outcome, and thus, it is at best a surrogate measure of the underlying construct and one that may be subject to influence by properties of the environment or drug that are not directly related to its reinforcing effects.

The "psychomotor" stimulant effects of drugs have also been proposed to provide a measure of drug reinforcement, reward, and addiction [188]. Administration of many drugs will produce forward locomotion and it has been theorized that this represents an operant approach response indicative of positive reinforcement by the drug [188]. The fact that forward locomotion is elicited by stimulation of the medial forebrain bundle, the site where stimulation yields intracranial self-stimulation, was also advanced as evidence that the mechanisms underlying this locomotion are linked to positive reinforcement. However, it is possible that sensitization is merely an adjunct consequence of drug taking and medial forebrain bundle stimulation. The circuitry that controls performance of voluntary actions overlaps extensively with that involved in reinforcement, reward, habit formation and addiction. Thus, it is possible that drug actions produce separate effects that both influence locomotion and drug reward or drug seeking, but that these effects are separable. Indeed, elegant recent studies showed just such a separation for regions of the ventral tegmental area and nucleus accumbens implicated in cocaine- and opiate-induced locomotor stimulation and conditioned place preference or self-administration [152, 153]. In addition, mice that lack dopamine show a nearly complete loss of morphine-stimulated locomotion, but continue to show morphine-induced conditioned place preference [63]. Locomotor stimulation and reward/reinforcement can also be separated pharmacologically. In the case of alcohol, stimulation of forward locomotion is inconsistent in rats and locomotor depressant effects are most often observed [46, 97], but rats clearly show other signs of ethanol reward and reinforcement (see [83, 84] for examples). Furthermore, Risinger et al. [134] and Sanchez et al. [148] found that genetic factors underlying ethanol-induced locomotor stimulation and conditioned place preference or ethanol drinking differ. Thus, it is not clear that forward locomotion is a good proxy for the actual reinforcing effects of the drug.

The idea of sensitization, an increase in frequency and intensity of a behavior elicited by a stimulus or treatment, has also figured prominently in models of drug abuse and addiction. Repeated administration of certain drugs of abuse, psychostimulants in particular, elicits successively larger increases in locomotor activity in rodents. It has been speculated that this locomotor sensitization is a result of the underlying neuroadaptive processes that contribute to addiction following repeated drug exposure.

However, it is still not clear that the locomotor-stimulating effects are related to reward or reinforcement per se, as discussed above. In one sense, however, drug seeking and self-administration must involve some form of sensitization, as these behaviors involve increases in responding elicited by the drug or drug-related environments or cues. One theory advanced to account for this aspect of drug-related behavior is the incentive-sensitization model [139]. This theory provides a reasonable explanation for the willingness of addicts to expend a great deal of energy and engage in new behaviors to obtain drugs, and also can explain the greater motivation of animals to work for previously used drugs in tasks such as the progressive ratio/breakpoint paradigm mentioned above. Other behavioral measures in laboratory animals provide evidence for enhanced incentive to seek and use drugs. For example, conditioned place-preference and cue-induced reinstatement of drug seeking indicate that the motivational value of previously neutral stimuli is enhanced when these stimuli are associated with drugs of abuse (reviewed in [139]). Thus, while simple locomotor sensitization may provide only limited information about drug effects on the brain reward/reinforcement system, the concept of sensitization is important within this context.

A role for negative reinforcement in addiction is also easily conceptualized, and experimental models of addiction based on this idea have been developed. Drugs such as benzodiazepines have known anxiolytic properties [21], and thus reduce an aversive state. The psychostimulants produce acute mood elevation that may provide temporary relief from negative affect (although these drugs are by no means effective antidepressants). Thus, negative reinforcement may be a strong driving force for acute drug use.

Relief of the negative symptoms encountered during drug withdrawal can also be characterized as a negative reinforcing component of addiction. Withdrawal following chronic use of different drugs of abuse produces symptoms ranging from heightened anxiety and irritability (benzodiazepines, alcohol) and dysphoria and depression (psychostimulants) to severe physiological symptoms such as abdominal cramps (heroin) [21, 102]. Withdrawal from drugs is associated with higher thresholds for intracranial self-stimulation in experimental animals, indicating dysphoria associated with this state [86, 154]. Relief from these symptoms has been postulated to drive relapse to drug use [84, 86]. Indeed, animals made dependent on drugs will increase self-administration and drug-related instrumental responding following drug withdrawal (reviewed in [86]). This sort of "reinstatement responding" has also been observed in alcohol-dependent animals and is referred to as the "alcohol deprivation effect" (reviewed in [163]). Animals that have undergone "conditioned aversion" in which withdrawal is rapidly induced and paired with previously neutral stimuli show reinstatement of heroin self-administration and elevation of intracranial self-stimulation thresholds, as if the aversive effects of withdrawal were reducing rewarding drug effects while driving relapse [81]. It is easy to imagine how this withdrawal-relief model can explain relapse after full-blown symptoms have begun. However, it is not so clear that this model can explain continuous drug use in the absence of withdrawal sufficient to produce symptoms. The ability of this model to explain relapse long after the cessation of withdrawal symptoms is also not as clear. However, lasting recruitment of drug effects on brain systems involved in stress responding has been suggested to underlie the long-term susceptibility to relapse [86].

The concept of negative reinforcement is also built into addiction theories based on Opponent-Process theories [86, 161]. These theories essentially propose that net emotional state is the result of competition between emotions (e.g., elation vs. fear), and that changes in the competitive balance over time can lead to changes in net emotion and behavior. Within the context of addiction one can easily envision that the euphoric "high" achieved just after administration of a drug like cocaine can dissipate and be replaced by depression as the neurochemical effects of the drug wear off [177]. With repeated drug use, the euphoria becomes less pronounced as the depression is

enhanced, and the user ends up taking the drug to relieve the depression, which could be termed a negative reinforcement model. This process has been modeled with cocaine and heroin self-administration, and it was found that both intracranial self-stimulation thresholds and cocaine or heroin self-administration escalated after several cycles of self-administration and withdrawal [2, 81]. Koob, LeMoal, and coworkers have extended these ideas to include the concept of "allostasis" [101, 185] in which the emotional "set-point" resulting from the new balance of opponent processes is altered toward a more depressed level with repeated drug use [84, 86]. The addict ends up using the drug to maintain this new set-point, often relieving more adverse emotional symptoms. Experimental models such as withdrawal-induced excessive self-administration have been used in conjunction with neurochemical approaches to implicate the amygdala and associated brain regions in these allostatic changes and the accompanying negative reinforcement driving drug taking and relapse (reviewed in [84, 86]). Brain systems for responding to environmental stress and internal anxiety may provide the aversive effects that interact with brain reward/ reinforcement circuitry to drive drug use in these models [85].

Actions of Addictive Drugs Within the Reinforcement and Reward Circuitry

The majority of abused substances act on specific molecular targets within the brain. These drug actions influence mechanisms thought to be involved in addiction, usually by producing a direct reinforcing or rewarding effect. Using the aforementioned addiction models combined with neurochemical and pharmacological techniques, investigators have discovered a number of molecular interactions produced by acute and chronic drug exposure that underlie the rewarding and reinforcing effects of drugs of abuse. Perhaps the mechanisms that are easiest to appreciate are those triggered by the so-called psychostimulant drugs, such as cocaine and amphetamine. These compounds act directly on the protein known as the dopamine transporter to enhance the concentration of dopamine present in the synaptic cleft following release of the neurotransmitter [88]. Cocaine is a competitive inhibitor of dopamine transporter that reduces the reuptake of dopamine into neurons, while amphetamine can also increase release of dopamine directly through the dopamine transporter [76]. It is easy to see how these molecular actions have rewarding and reinforcing consequences, given that dopamine has an important role in both of these processes, and these drugs will enhance dopamine signaling.

Given that cocaine is thought to act primarily on the dopamine transporter, it is surprising that evidence has emerged for actions of drugs of abuse that could be construed as indicating reinforcing effects of cocaine even in the absence of the transporter [140, 162]. However, it appears that blockade of serotonin reuptake indirectly mediates this effect. Even more surprising is the finding that serotonin mediates cocaine conditioned place preference in dopamine deficient mice [64]. These mice show a conditioned place preference for morphine [63]. Thus, dopamine itself may not be necessary for this drug-related learning. However, evidence that manipulations that decrease the firing of dopaminergic neurons reduces conditioned place preference in these dopamine-deficient mice suggest that another factor released by these neurons may have important roles in drug-related reward [64].

The actions of many other drugs of abuse have also been suggested to involve dopamine, but in a less direct manner. For example, opiates, nicotine and alcohol all increase dopamine levels in regions of the brain such as the ventral and dorsal striatum, and appear to do so by increasing the firing activity of the dopaminergic neurons themselves (reviewed in [125]). Hypotheses about the mechanisms underlying the reinforcing effects of these drugs of abuse have generally centered on the idea that enhancement of dopaminergic transmission leads to reward or reinforcement,

and that all drugs of abuse work through this mechanism in one way or another. However, this idea is undoubtedly too simplistic given the evidence discussed above that dopamine is not necessary for reward-related learning. Furthermore, dopamine does not appear to be necessary for self-administration and reinforcing effects of all drugs of abuse, particularly for drugs with indirect effects on the dopaminergic system. Studies of the effects of dopaminergic lesions and dopamine receptor antagonists on ethanol self-administration have yielded mixed results in a variety of self-administration and operant paradigms. D2 receptor antagonists and D1 antagonists and knockout of D1 and D2 reduce self-administration in some paradigms, but alcohol intake is not abolished after lesions of the dopaminergic system of by other dopamine receptor antagonists [125, 130, 145]. The evidence for dopamine involvement in opiate self-administration and opiate-related reward/reinforcement is likewise mixed, including evidence for lack of effect of dopaminergic lesions [124, 125]. Thus, it appears that dopaminergic transmission is not strictly necessary for alcohol and opiate intake. Dopamine is probably not the final common pathway for drug reward, reinforcement, and self-administration as was once imagined, and the focus has now shifted to the importance of the circuitry that is influenced by dopamine.

The primary targets of almost all drugs of abuse are cell surface proteins that regulate synaptic transmission. The role of neurotransmitter transporters as targets for psychostimulants has already been discussed. Drugs such as nicotine, benzodiazepines, barbiturates, and, to some extent, alcohol produce their actions by altering the neurotransmitter receptors known as ligand-gated ion channels [21]. These receptors mediated fast synaptic transmission in the brain and can directly influence the activity of neurons within the brain reward/reinforcement circuitry. An assortment of other psychoactive and addictive drugs, including opiates, cannabinoids, and hallucinogens, produce their actions via G protein-coupled receptors [21]. This class of receptors mediates the neuromodulatory actions of neurotransmitters by initiating or influencing intracellular molecular signaling pathways [21, 79]. The subtle changes in neuronal activity and gene expression produced by drug actions at these receptors can have profound acute and long-lasting effects on the brain reward and reinforcement systems.

Opiate drugs produce their intoxicating and rewarding effects through activation of mu, and to a lesser extent delta and kappa, opiate receptors [30, 98]. Opioid peptides and their receptors have also been implicated in the rewarding effects of drugs of abuse, including effects of nicotine, cannabinoids and alcohol (reviewed in [30, 47]). There is also considerable evidence that opiate receptor blockade reduces rewarding and reinforcing effects of a variety of drugs of abuse, as well as drug seeking and taking in animal models of addiction (see [18] for review). The opiate receptor antagonist naltrexone can also produce lower sensitivity to intracranial self-stimulation, but this is mainly seen with stimulation in the ventral striatum and not with ventral tegmental area stimulation [182]. Thus, there is reason to believe that opioid peptides can mediate reinforcing and rewarding effects of drugs of abuse, perhaps independent of the actions of dopamine.

As mentioned above, the cannabinoid drugs produce their intoxicating actions mainly via brain cannabinoid-1 receptors. Delta-9-tetrahydrocannabinol, the main psychoactive ingredient in cannabis-derived drugs, is a partial agonist of the cannabinoid-1 receptor. Several synthetic delta-9-tetrahydrocannabinol analogs and other cannabinoid-1 agonists also produce intoxicating effects. Emerging evidence indicates an important role for endocannabinoids and the cannabinoid-1 receptor in drug self-administration. Antagonist blockade or gene-targeted knockout of cannabinoid-1 receptors decreases self-administration of a variety of drugs of abuse in animal models [96], and the cannabinoid-1 antagonist rimonabant shows some effectiveness in reducing cigarette smoking in humans [91]. Blockade of the receptor decreases intake of ethanol and self-administration [27, 180]. Antagonists of the

cannabinoid-1 receptor also reduce increases in extracellular dopamine produced by several drugs of abuse [24], and thus, endocannabinoids may alter the rewarding *or* reinforcing actions of drugs of abuse via this mechanism.

Chronic exposure to drugs of abuse is thought to bring about neuroadaptive changes that alter the brain reinforcement/reward circuitry. Recent studies have focused on changes in the efficacy of synaptic transmission and alterations in dendritic morphology in neurons within the ventral tegmental area and nucleus accumbens. Cocaine exposure has been demonstrated to produce changes in the ratio of excitatory synaptic responses mediated by AMPA and N-methyl-D-aspartate-type glutamate receptors, a change thought to reflect long-term plasticity of glutamatergic synapses [4, 169, 175]. This sort of synaptic plasticity has been observed in recordings from both nucleus accumbens medium spiny neurons and ventral tegmental area dopaminergic neurons [169, 175]. Even a single dose of cocaine appears to produce this plastic change in excitatory transmission [175]. Other drugs of abuse, including ethanol, alter efficacy of both excitatory and inhibitory transmission in the ventral tegmental area [103, 164]. Synaptic plasticity produced by drug exposure may condition synapses within the reinforcement/reward circuits to enhance responses to subsequent exposure to drugs or drug-related stimuli. This could occur at the expense of using this circuitry to learn other, more adaptive, responses to environmental stimuli.

Chronic drug exposure also alters long-term synaptic depression mediated by endocannabinoids and the cannabinoid-1 receptor. Repeated exposure to delta-9-tetrahydrocannabinol for days eliminates this form of long-term synaptic depression in the hippocampus and nucleus accumbens [65, 100], and this adaptation appears to involve decreases in the presynaptic actions of cannabinoid-1 receptors. Even a single exposure to delta-9-tetrahydrocannabinol produces a similar action [99]. A single treatment with cocaine also eliminates endocannabinoid-dependent long-term synaptic depression [44], and chronic ethanol exposure has been reported to have a similar action in the striatum [190]. Given the role of cannabinoid-1 receptors in responses to drugs of abuse mentioned previously, it is possible that adaptations in endocannabinoid/cannabinoid-1 function underlie neuroadaptations that lead to altered reinforcing and rewarding properties of many drugs of abuse.

Repeated exposure to cocaine, amphetamine and other drugs of abuse alters the dendritic structure of neurons in the prefrontal cortex, nucleus accumbens, and dorsal striatum [73, 108, 138]. Changes in spine density and dendritic branching are seen, with differential effects in different brain regions. These morphological changes are thought to lead to alterations in the ability of neurons within this circuitry to respond to normal levels of synaptic input. Ultimately, this dendritic rearrangement could lead to less plasticity within the circuitry and help to rigidify behaviors related to the addictive drug.

There are also a host of cellular and molecular changes within the reinforcement/reward circuitry that have been related to drugs of abuse (see [110] for review), and there is simply not space within this review to cover all of these changes. However, interesting information is emerging from examination of drug-induced changes in glutamatergic synaptic transmission within the circuitry of interest. Glutamate signaling through G protein-coupled receptors called "metabotropic" glutamate receptors is one system implicated in these drug-induced changes [58, 168]. The metabotropic glutamate receptors come in a variety of subtypes [29]. The different metabotropic glutamate receptor subtypes produce diverse cellular actions including inhibition and stimulation of neurotransmitter release and activation of intracellular signaling pathways that contribute to changes in neuronal excitability and long-lasting plasticity of synaptic transmission [29]. An emerging line of research has implicated group I metabotropic glutamate receptors in neuroadaptations to abused drugs, as well as drug self-administration [58, 168]. The expression and function of metabotropic glutamate receptor-5

is down-regulated following chronic administration of cocaine and withdrawal, but up-regulated by alcohol exposure (reviewed in [168]). At the same time, expression of the Homer protein that interacts with this receptor and changes its signaling functions undergoes similar drug-related up-regulation [165, 167, 168]. The group I metabotropic glutamate receptors are implicated in forms of synaptic plasticity throughout the brain reward/reinforcement circuitry, including endocannabinoid-dependent long-term synaptic depression [58]. Thus, cocaine-induced down-regulation of metabotropic glutamate receptor-5 in brain regions such as the nucleus accumbens following chronic drug exposure enhances could underlie loss of metabotropic glutamate receptor-mediated synaptic plasticity [44, 58]. In the case of alcohol, increased metabotropic glutamate receptor/Homer expression may be part of a general increase in glutamatergic signaling after repeated drug administration and withdrawal, contributing to plastic changes in the circuitry that ultimately foster increased drug seeking and self-administration [168]. This idea is consistent with the finding that a metabotropic glutamate receptor-5 antagonist decreases alcohol seeking and relapse in animals with self-administration experience [8].

However, despite this wealth of knowledge, it is still not clear how the cellular and molecular changes brought about by drugs of abuse contribute to overall changes in circuit function that ultimately lead to addiction. Addressing this topic will require more sophisticated analysis of neuronal and circuit function in vivo, combined with continued work at the molecular, cellular and behavioral levels. Clearly, this is a key direction for future research on the neural basis of drug reinforcement and reward.

What Drives Drug Use, Abuse, and Addiction: The Direction of Future Research

Ultimately, the goals of research on drugs and addiction are to gain a better understanding of how drugs act on the brain, and to develop better approaches for minimizing and treating drug abuse and drug addiction. The neurobiological mechanisms discussed in the present paper indicate that brain mechanisms of reward and reinforcement are more complicated than most of us previously imagined in terms of both the circuitry involved and the underlying neurochemistry.

The interactions of drugs of abuse with these systems are likewise complex. It is likely that drugs engage multiple aspects of the different circuits during the initial phases of exposure. Drug actions on dopaminergic transmission and other aspects of the associative circuit will signal the positive hedonic value of the drug and establish the motivation to continue to take the drug. At the same time, drug-associated cues and environmental connections to drug availability will be signaled and learned through the limbic circuitry, likely contributing to the sensitized incentive described by Robinson and Berridge [139]. It is currently thought that the role of the sensorimotor circuitry in drug seeking and taking develops rather slowly during the course of experience with drugs [41, 50]. However, the rate of recruitment of this system may depend on the schedule and contingencies of drug availability, especially in relation to instrumental behaviors. Furthermore, engagement of the sensorimotor circuitry may develop in series or in parallel with activation of the other circuits, and there may be competition between the different circuits for control of behavior. Ultimately the involvement of the systems will likely depend on the pattern of recruitment of different circuit elements. However, there is emerging evidence that reinforcing effects of drugs ultimately lead to involvement of the sensorimotor circuitry and establishment of drug-related "habits" [12, 41, 50, 191]. One intriguing scenario is a shift from a purely stimulus-outcome based mode of responding to one that also includes stimulus-response-based actions. Thus, a drug user may initially come to associate certain cues with the rewarding effects of a drug, and this may initially drive drug seeking. With continued drug exposure, the stimulus-response circuitry becomes progressively more engaged as drugs reinforce

the stimulus/environment control of drug seeking and use. Indeed, the work of Everitt and colleagues appears to support such a transition from limbic to sensorimotor circuit control of drug-related actions [12, 41]. It remains to be seen how action-outcome-based learning plays a role in this scenario, but this form of learning will almost certainly play a role in drug use and abuse in humans. One possibility is that action-outcome learning may drive the acquisition of new behaviors that are designed to locate and obtain drugs of abuse, providing another mechanism through which incentive sensitization takes over brain function to promote drug seeking and use. Brain mechanisms involved in stress responsivity and production of aversive responses to drug withdrawal also become progressively more involved as drug use and abuse continues, and these circuits likely interact with mechanisms of reward and reinforcement to promote relapse to drug use (Fig. 1).

The effects of stress on the prefrontal cortex are of interest in this regard. Recent studies showing that exposure to acute or chronic stress and corticosterone treatment stunts the dendritic morphology of neurons in the medial prefrontal cortex [23, 72, 129] suggest that the circuitry involving this brain region is impaired during stress. These dendritic stunting effects have been postulated to impair "executive" decision-making capabilities [139]. One result of this neurotoxic stress effect may be to drive behavior away from goal-directed actions and toward habitual responding [43]. Thus, stress may act on the reward/reinforcement circuitry at a number of levels to promote inflexible drug seeking and use. Ultimately, drug use and abuse is initiated and sustained by a number of intrinsic neural mechanisms including goal-directed behavior, environmentally stimulated instrumental behavior, habitization of drug-related responses, and negative reinforcement/allostasis that promotes a return to drug usage.

Determining the relative roles of these different neural mechanisms and neural circuits in drug use, abuse, and addiction will require new avenues of research at the molecular, cellular, systems and behavioral levels. Ultimately, an integrative approach that incorporates all of these levels of analysis is needed. Behavioral models of different aspect of drug reward, reinforcement, and addiction need to be used with an eye to determining the roles of the underlying changes in circuits, cells and molecules. In using these models it will be necessary to bear in mind all of the possible processes that contribute to drug use, relapse, and addiction, including goal-directed behavior, cue-related conditioning, avoidance of aversive consequences and development of habitual actions. The development of models that allow investigators to select animals that are highly sensitive to compulsive drug use should provide the opportunity to examine genetic, epigenetic and environmental factors that have predispositional effects in these animals. However, the generality of these models to multiple drugs of abuse needs to be demonstrated, and it will be important to determine if the same factors play a role in development of compulsive use of different drugs. It is quite possible that no one model will be able to tell us all that we need to know to understand maladaptive drug use and addiction. Thus, it is important to continue to cultivate useful models and develop new ones, always with an eye to determining the underlying neurobiology.

In considering the role of neural circuitry in drug reward, reinforcement, and addiction a more inclusive approach will likely be needed. Basic neuroscientific research is now revealing multiple parallel brain systems for control of different aspects of action production and action learning. Movement beyond the monolithic concept of a single neural reward/reinforcement system is necessary. It is likely that these systems will have similar roles in behavior directed toward drugs of abuse, and this must be considered in designing experiments aimed at determining the neural basis of drug seeking and use.

At the cellular and molecular levels a number of changes brought about by drug exposure and related conditioning have been described. However, little is known about the role of most of these changes in the development of maladaptive drug use and/or addiction. Consideration of the wide variety of neurotransmitters and

receptors that participate in normal and abnormal functioning of the relevant brain circuitry is especially important. Experimental approaches designed to manipulate particular molecules within given cell types and circuits (e.g., local drug application, disconnection analyses, and the use of sophisticated genetically manipulated mice) will play an ever increasing role in our quest to determine which molecular and cellular changes are important and which are merely epiphenomena or secondary to the truly causal changes. The powerful tools for genetic manipulation, molecular analysis, examination of neurophysiology and neurochemistry at the in vitro and in vivo levels, and ever more sophisticated behavioral analysis in a variety of organisms should allow investigators to make rapid progress in this area in the coming years.

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Neurobehavioral Toxicology of Substances of Abuse

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Contents

Ethanol (Alcohol)

History

Ethanol is surely the oldest known substance of abuse. The details of the original discovery of fermented beverages have been lost to time because of the unavailability of the written word. Thus, no one really knows exactly when humans started drinking fermented beverages. Animals such as birds, insects, and elephants have shown

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_14,

signs of drunkenness by purposefully eating ripened fruit in which yeast produced ethanol [76]. It is known that intentionally fermented beverages existed as early as 10,000 B.C. [188]. Aristotle, the founding father of the scientific method, showed in the third century B.C. that boiled wine lost its intoxicating character, but he never took the next step of condensing the ethanol [76]. The distillation of ethanol from wine was discovered by a Muslim chemist in the eighth century A.D. There are a myriad of accounts of the incorporation of alcoholic beverages into the daily life of every society. As with all substances of abuse, ethanol was probably not used abusively at first. For example, early versions of beer were used as food. Alcoholic beverages such as beer and wine were used in ritualistic religious exercises, and evidence of the use of beer and wine as medicinal remedies exist at least 2,000 years before the birth of Christ.

A recently published book describes in detail the cultural history of alcohol [76]. The use of alcoholic beverages in most societies is certainly evident. It has produced social and health benefits as well as significant detrimental forensic and health problems. For example, light to moderate alcohol intake is probably associated with lower risk of cardiovascular mortality in hypertensive men [149, 161]. On the other hand, excessive ethanol consumption is closely associated with abnormal elevation of blood pressure in normotensive and hypertensive individuals [161]. Despite its social and possible health benefits, excessive ethanol consumption is a major medical health problem. In 1995, it was reported that about 10 million Americans were considered to be alcoholic [9].

Chemical Properties

Ethanol is a relatively simple molecule (C_2H_6O) with a molecular weight of 46 and density of 0.789 g/cm^3. At ambient temperatures, it is a clear, colorless liquid that is highly volatile, flammable, and miscible with water and many other organic solvents. Its lipid:water partition coefficient is 0.096, which indicates that the distribution of ethanol favors an aqueous versus a lipid phase [177]. In humans, this solubility ratio explains the distribution of ethanol in total body water.

Ethanol concentration is expressed in a variety of ways depending on the application. For example, a blood alcohol concentration of 0.1% (w/v) is the upper limit of the legal range while driving a car in many states. This concentration can also be expressed as 100 mg%, 100 mg/deciliter, 1 g/L, and 21.7 mM. The concentration of ethanol in commercially available forms of consumable, distilled alcoholic beverages is expressed in terms of proof, which is a number that is approximately double the percentage of ethanol (200 proof = 100% ethanol). The term proof was used in the nineteenth century by English sailors who developed a test for the minimal concentration of ethanol in rum. If the sailor could successfully ignite gun powder soaked in the rum, it was "proof" that the rum was acceptably potent and had not been diluted with water. At least 50% (v/v) of ethanol is necessary to ignite gun powder. This simple test was important because the sailors were given rum as part of their pay.

Pharmacokinetics

Routes of Administration

Alcohol is one of the drugs of abuse that can be legally purchased with age as the only restriction. Humans self-administer ethanol by the oral route exclusively. There are many forms of commercially available alcoholic beverages with widely varying percentages by volume, including beer (~5%), malt liquor (~7%), wine (~12%), sherry or port (~17%), cordials or liqueur (~24%), brandy (~40%), and distilled spirits (~40–50%).

Absorption and Distribution

After oral administration, ethanol is rapidly absorbed into the blood principally from the small intestine, but also from the stomach and

colon [46, 71, 115]. It is known that food, ethanol concentration, and liquid volume affect the gastric emptying rate and gastric absorption of ethanol, but once ethanol reaches the small intestine, its absorption is rapid and complete [251]. For example, when a non-intoxicating dose of ethanol (~0.5 g/kg) is ingested over a relatively short period of time (~30 min) on an empty stomach, ethanol reaches its maximal concentration in the blood within 15–30 min [16]. In fact, intravenous administration of ethanol combined with quantification of either breath or blood ethanol concentration has been used to estimate total body water [177].

Metabolism

The metabolism of ethanol occurs mainly in the liver by oxidation of ethanol to acetaldehyde by alcohol dehydrogenase and conversion of nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide hydrate. A secondary pathway of oxidative ethanol metabolism occurs in liver microsomal tissue in the smooth endoplasmic reticulum [139]. Chronic consumption of ethanol increases the capacity of the liver microsomal ethanol oxidizing system with a rise in several cytochromes P-450, especially a nicotinamide adenine dinucleotide phosphate-requiring enzyme (CYP2E1). This system provides a higher rate of ethanol oxidation and is important to the development of tolerance to alcohol [139]. Both of these mechanisms produce acetaldehyde which is then converted to acetate by the action of aldehyde dehydrogenase.

Elimination/Excretion

The disappearance of ethanol from the blood or breath was originally thought to be a linear, zero order function, i.e., independent of the blood ethanol concentration and probably due to saturation of alcohol dehydrogenase [155]. However, it has been shown more recently that the elimination profile is more accurately described by Michaelis–Menten kinetics [250]. Nevertheless, at higher doses of ethanol, there is an apparent linear phase (15 mg%/h) that starts at the completion of the absorption-distribution phases and extends to a blood ethanol concentration of about 20 mg%. Below this concentration, the elimination becomes curvilinear. The elimination half-life of ethanol is about 2–4 h. Between 90 and 95% of ingested ethanol is converted to acetaldehyde and acetate and then eliminated in the urine. About 3–5% of a dose of ethanol is eliminated unchanged in the urine, breath, or through the skin [250]. Less than 2% of ethanol is metabolized non-oxidatively to ethyl glucuronide, ethyl sulfate, phosphatidylethanol, and fatty acid methyl esters. Interestingly, these "direct metabolites" of ethanol are measurable as markers for ethanol consumption.

Pharmacodynamics

The small size and simplicity of ethanol's structure (Fig. 1) is in contrast to its significant and complicated pharmacodynamic effects. When compared with most other drugs, very high concentrations of ethanol, in the millimolar range, are required to produce biological effects. Because of its simple chemical structure and the concentrations required for physiological effects, ethanol binding sites with high affinity (μM or nM range) most likely do not exist. It has been proposed that an ethanol binding site exists on gamma-aminobutyric acid-A ($GABA_A$) receptors that contain a combination of α4 (or α6), β3, and δ subunits, making them sensitive to concentrations of ethanol as low as 3 mM [90, 243]. Furthermore, relatively recent reports indicate that a certain domain of the

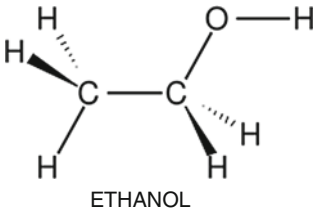


Fig. 1 Structure of ethanol

enzyme adenylyl cyclase is responsible for sensitivity to ethanol [90]. Amino acid mutations of target proteins designed to modify ethanol's effects have suggested that specific groups of amino acid residues in transmembrane regions of proteins may be binding sites for ethanol [159]. The results of these relatively recent studies suggest that ethanol situates itself into tiny pockets in protein structures to produce significant changes in biochemical, physiological, and behavioral functions.

Neuropharmacological Effects

The neuropharmacological effects of ethanol have been identified and measured at biological levels from the molecular to the behavioral.

At the cellular/molecular level, it has been shown that acute, physiologically relevant concentrations of ethanol (5–50 mM) affect the function of numerous different receptor types [236]. Ethanol inhibits *N*-methyl-*D*-aspartate receptors [100, 145] and L-type Ca^{2+} channels [244], and enhances the function of gamma-aminobutyric acid-A receptors [8], glycine receptors [159], serotonin-3 receptors [144], and neuronal nicotinic acetylcholine receptors [5, 172].

Effects of ethanol on the aforementioned receptor systems (e.g., a neurotransmitter receptor or ion channel) can often be demonstrated using electrophysiological techniques, thereby showing effects on neurons or neuronal systems. If ethanol affects the rate of neuronal firing, membrane potential, or other cellular parameters, then the effects of ethanol on receptor systems and perhaps specific brain areas can sometimes be linked to certain behaviors [53]. Electrophysiological studies have shown that ethanol affects the firing rate of neurons in several brain areas, including the cerebellum, inferior olivary nucleus, locus coeruleus, ventral tegmental area, substantia nigra, hippocampus, and septal area [53]. Furthermore, these effects of ethanol on single cells are thought to mediate neurotransmission in the mammalian central nervous system, especially in the hippocampus, locus coeruleus, cerebellum, spinal cord, and cortex via pre- and post-synaptic effects [53].

From the behavioral perspective, acute low doses of ethanol are anxiolytic and can enhance mood and produce euphoric feelings in humans. In fact, the use of ethanol as a disinhibitor in social settings is well known and widespread throughout recorded history [76]. For those who have the ability to limit ethanol intake, there appear to be social and health benefits. On the other hand, higher acute doses cause intoxication, sedation, sleep, and "hangover," and very high acute doses can induce coma and possibly death as a result of respiratory depression. Studies with laboratory rodents showed effects of ethanol to produce hypothermia, analgesia, motor activation, and, at higher doses, motor incoordination. Chronic, heavy alcohol consumption produces a myriad of problems as discussed below.

The behavioral consequences of acutely administered, lower doses (<30 mM) of ethanol may be linked to certain receptor systems. For example, intoxication, sedation, and motor incoordination are probably mediated via certain subunit configurations of the gamma-aminobutyric acid-A receptor [53, 243]. Also, there is thought to be differential sensitivity among presynaptic, postsynaptic, and extrasynaptic gamma-aminobutyric acid-A receptors with the extrasynaptic types being the most sensitive [67]. Ethanol-induced hypothermia and analgesia are not thought to be mediated by gamma-aminobutyric acid-A receptors, but by inwardly rectifying G protein-gated K^+ channels [18, 108, 123]. The concentration of ethanol required to affect other receptors is very high (>50 mM), so the involvement of these receptors at physiological concentrations is not clear.

A discussion of the neuropharmacology of ethanol would not be complete without comments about acetaldehyde. Acetaldehyde is the first metabolic product of ethanol in vivo and is produced by the action of alcohol dehydrogenase. Acetaldehyde may be responsible for some of the effects of ethanol, probably mostly the unpleasant and chronic side effects [53, 243]. The mechanism whereby these effects of

acetaldehyde occur may be due to aldehyde-amine condensation products of amino acid side chains on proteins [53]. Humans who carry a certain inactive form of mitochondrial aldehyde dehydrogenase do not metabolize acetaldehyde and have an uncomfortable facial flushing reaction after drinking alcohol [162]. Also, the hangover that occurs after a bout of heavy drinking is probably caused by high concentrations of acetaldehyde [243].

Toxicology

Whether ethanol produces an acute, satisfying, possibly beneficial effect versus an acute or chronic, unhealthy toxic effect is related to the concentration of ethanol, the dose of ethanol, and the length of exposure to ethanol. From a medical perspective, ethanol consumption of less than two standard drinks per day ($\leq\sim$30 g) by humans appears to decrease mortality [11] and the mechanism is probably related to a reduction of coronary heart disease [47]. Thus, low or moderate levels of ethanol consumption are thought to be healthful. On the other hand, chronic heavy ethanol consumption of 5 standard drinks per day ($\sim$75 g) or more for men and 4 standard drinks per day ($\sim$60 g) or more for women or frequent binging can cause severe, detrimental health problems [138]. These health problems result from direct toxic effects of ethanol on the liver, heart, brain, kidneys, and stomach. Indirectly, the replacement of calories from food by calories from ethanol (malnutrition) can cause additional negative effects on these organ systems [138]. These serious effects of ethanol abuse can eventually result in alcoholism, a pathology that includes very serious medical and behavioral difficulties.

Cocaine

History

Cocaine is a derivative of the coca plant *Erythroxylon coca* native to the mountains of South America. Traditionally, South American natives have chewed coca leaves as a stimulant to fend off fatigue, especially at relatively hypoxic elevations of the Andes Mountains. In 1574, the Spanish physician Nicolas Bautista Alfaro (1493–1588) published a description of the plant, its use and its effects [32]. In 1862, the German chemist Albert Neiman (Gottingen, Germany, 1834–1861) isolated the active component of the coca plant and called it cocaine. He was also the first to report the local anesthetic properties of cocaine, noting its numbing effects on his own tongue. In 1880, pharmacologist Basil Von Anrep of the University of Leipzig proposed use of cocaine as a surgical anesthetic in humans [240]. Canadian surgeon William S. Halsted became the first physician to use cocaine for a nerve block during surgery and subsequently became the first known physician to develop a cocaine addiction. In 1884, psychiatrist Sigmund Freud published a cocaine monograph entitled "Uber Coca" in which he advocated for the use of cocaine to treat a variety of conditions including asthma, wasting diseases and syphilis [74]. Freud also eventually became addicted to cocaine. In the late 1800s, cocaine was added to a number of beverages including the "medicinal" wine Vin Mariani in France. In 1895, The Lancet published a report of six cocaine associated deaths underscoring the significant potential toxicity of this drug. Cocaine was an ingredient in the original version of John Pemberton's Coca Cola; cocaine was removed from the popular soft drink in 1906. With passage of the Harrison Narcotic Act in 1914, nonprescription use of cocaine was made illegal. In 1970 cocaine was classified as a Schedule II drug (Comprehensive Drug Abuse Prevention and Control Act).

Pharmacodynamics

The cocaine is a tropane (aminoester) alkaloid with a $p\mathrm{K}_a$ of 8.6. "Crack" cocaine (free-base) is produced by combining cocaine HCl with an alkali. Crack cocaine is more heat-stable than is cocaine HCl and therefore can be smoked [63].

Cocaine interacts primarily with these central nervous system biogenic amine systems. Cocaine blocks the in vitro reuptake of norepinephrine, dopamine, and serotonin [111]. Saturable, high-affinity Na^+-independent and Na^+-dependent [^{3}H]-cocaine binding has been associated with sites for serotonin and for dopamine reuptake, respectively, in the central nervous system [200]. With acute or low-dose administration of cocaine, this reuptake inhibition leads to increased aminergic concentrations within aminergic synapses and increased binding both to pre- and postsynaptic aminergic receptors. Chronic cocaine administration is generally believed to result in aminergic depletion for the duration of drug exposure [111]. However, unlike high doses of methamphetamine [107], chronic cocaine does not produce dopamine nerve terminal degeneration, at least in the prefrontal and frontal cortex or dorsal raphe [50].

Various addictive drugs such as cocaine that act as positive reinforcers increase synaptic dopaminergic concentrations in selected areas such as the nucleus accumbens. Homologous recombination targeting the dopamine transporter results in an absence of cocaine- or amphetamine-induced behavioral activation [84]. The ventral tegmental area, nucleus accumbens, and caudate nucleus, areas rich in the neurotransmitter dopamine, are collectively considered the "reward pathway" [126, 127]. Cocaine antagonism of presynaptic dopamine transport results in elevated dopamine levels in mesolimbic synapses with resultant drug reinforcement. Maintenance of higher dopamine levels in "reward pathway" synapses leads to feelings of euphoria and a "cocaine high". The increased availability of synaptic dopamine is thought to act on D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors in the mesocorticolimbic synapses. The effects of cocaine acting on the dopamine D1 receptor in the nucleus accumbens and ventral tegmental area are thought to be responsible, at least in part, for the reinforcing properties associated with long-term exposure to this drug [218].

Long-term cocaine use is associated with a selective decrease in D1 receptors in striatal reward areas both in rodents [29, 30, 33] and in non-human primates [167]. Dopamine depletion using the neurotoxin 6-hydroxydopamine infused into either the nucleus accumbens or the ventral tegmental area results in an attenuation of the reinforcing effects of cocaine self-administration. Similarly, dopamine D1 receptor knockout mice demonstrated a lack of reinforcing effect of cocaine in contrast to wild-type controls [31]. D1 and D2 receptors have opposing intracellular and behavioral effects and thus may differentially affect drug-reinforcing behaviors. David Self and colleagues [218] demonstrated that cocaine self-administration behavior was mediated by dopamine D1 and not by dopamine D2 receptors and that this behavior progressively diminished in rats when cocaine was replaced with saline ("extinction behavior").

Cocaine also blocks voltage-gated sodium channels and thus reversibly attenuates conduction of nerve impulses, which accounts for the local anesthetic properties of the drug [200]. Depending on the relative distribution of the drug, a relatively selective depression of inhibitory neurons can produce cerebral excitation at lower concentrations of the drug, and this in turn can lead to generalized convulsions. At high concentrations, cocaine could produce more profound depression of brain function and ultimately coma, cardiorespiratory arrest, and death.

Pharmacokinetics

Distribution

Cocaine is rapidly absorbed across nasal, trachea and laryngeal epithelial membranes within minutes of its administration. Peak plasma concentrations of 120–474 ng/ml are reached within 30–60 min of intranasal administration and remain detectable up to 6 h after administration [15, 234]. Cocaine may limit its own absorption due to its activity as a potent vasoconstrictor [250]. Bioavailability of intranasal cocaine (i.e., area under the plasma concentration-time curve) is approximately 5

times less than that for equivalent intravenous dosing (0.19–2.0 mg/kg). The biological half-life for cocaine is 0.5–1.5 h with a volume of distribution of 2.0 L/kg and a systemic clearance of 2.0 L/min [111].

Metabolism/Elimination

Cocaine metabolism is catalyzed by esterase activity, principally within plasma and liver. Liver esterase activity accounts for 30–50% of the metabolism of cocaine to ecgonine methyl ester. Another 30–40% of cocaine is non-enzymatically hydrolyzed into benzoylecgonine (Fig. 2). The elimination half-lives of these major metabolites of cocaine are 6 and 4 h, respectively. These metabolites can be detected in urine samples up to 60 h after cocaine administration. A small amount (1–5%) of cocaine is excreted unchanged in urine within 8 h of administration [111]. Individuals with liver dysfunction or malnutrition, or who are being treated with plasmapheresis, who are pregnant or who have taken anticholinesterase medication (e.g., echothiophate eye drops, neostigmine) are relatively esterase-deficient, resulting in reduced capacity to degrade cocaine and thus elevated circulating levels of the drug with the potential for increased toxicity.

Cocaine metabolism demonstrates first-order kinetics over a wide range of doses. Within 4–5 h, almost all of a dose of cocaine has been metabolized, with metabolites present in urine for 4–8 h following intranasal dosing [111]. Measurable levels of the metabolite benzoylecgonine may be detected in urine as long as 60 h after a single dose of cocaine and for up to 3 weeks after heavy use of cocaine.

Less than 10% of cocaine is *N*-methylated into the active metabolite norcocaine. Liver *N*-methylation activity is increased by progesterone. *N*-methylation of cocaine into norcocaine is thus enhanced under conditions of elevated progesterone, e.g., during pregnancy. This may account for the reported increased cocaine-associated cardiotoxicity during pregnancy.

Concurrent use of cocaine and alcohol results in the production of the active metabolite cocaethylene (ethylbenzoylecgonine) (Fig. 3) [220]. Cocaethylene has a significantly longer elimination half-life than cocaine and may be more cardiotoxic than cocaine [209].

Toxicology

Cocaine-induced antagonism of nigrostriatal dopamine activity may result in extrapyramidal motor dysfunction including bradykinesia,

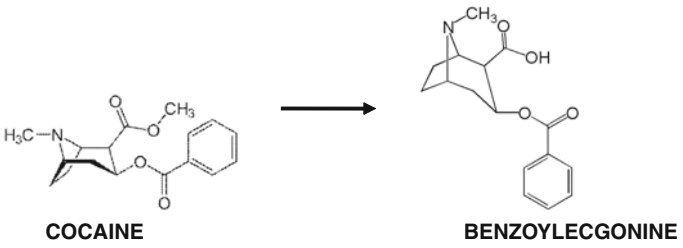


Fig. 2 Structures of cocaine and its metabolite benzoylecgonine

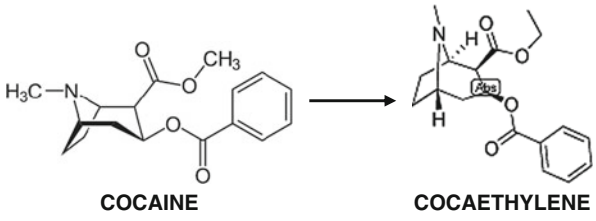


Fig. 3 Structures of cocaine and cocaethylene

akinesia, akathisia, catalepsy and dystonic reactions [72]. In a study conducted between 1979 and 1990 by the Medical Examiner's Office for Dade County, Florida, excited delirium was associated with approximately 1 in every 6 cocaine-related deaths. These victims were described as having experienced an immediate onset of bizarre and sometimes violent behavior, including extreme paranoia, ending in cardiorespiratory collapse and death.

Cocaine abuse is also associated with both acute and long-term cardiotoxicity [207, 232, 237]. Acutely, cocaine acts as a vasoconstrictor reducing blood flow to myocardium with an increased risk for cardiac ischemia and infarction. Cocaine-inhibited reuptake of norepinephrine also leads to increased intracellular concentrations of calcium within cardiocytes which through membrane depolarization can trigger sustained action potentials, extra systolic contractions and tachycardia. Long-term effects of cocaine on cardiac function can include a depression in contractility, in part related to the activity of cocaine as a local anesthetic. Cardiomyopathy associated with long-term cocaine abuse may be a result of oxidative stress to the myocardium [109]. Systemic effects include peripheral vascular constriction with resultant ischemic compromise of various organs.

Long-term use of cocaine is also associated with elevated circulating levels of muscle enzymes such as creatine kinase, suggesting muscle degradation or rhabdomyolysis [210]. Thirty-three percent of the participants in a study of cocaine-induced rhabdomyolysis experienced acute renal failure, severe liver dysfunction, and disseminated intravascular coagulation; six of them died.

Cocaine has been shown repeatedly to affect adversely reproductive function in female rats [118, 119], male and female non-human primates [156] and male [41] and female [24] humans. In the rat, cocaine administration produces loss of estrous cyclicity which at higher doses of cocaine may become permanent [119]. Maternal cocaine use during gestation has also been associated with numerous adverse effects on the developing fetus, including growth retardation, dysmorphic features, seizures and strokes and numerous postnatal behavioral abnormalities [239]. Because such fetuses are typically exposed to various confounding variables, such as a lack of prenatal care, poor maternal nutrition and polydrug exposures, the idea of a specific cocaine teratophilia (or "cocaine baby") syndrome has been called into question [125].

Amphetamine and Amphetamine-Analogs

History

The Chinese plant ma hung (*Ephedra vulgaris*) has been used traditionally to treat asthma. In the 1920s the active ingredient in extracts of this plant was identified as ephedrine. In 1887, the Romanian chemist Lazar Edeleanu (1861–1941) first synthesized alpha-methylphenethylamine [62], now more commonly known as amphetamine (**a**lpha-**m**ethyl**ph**en**e**thyl**amine**). Originally named phenylisopropylamine, amphetamine was largely forgotten for the next four decades. In the late 1930s, amphetamine was prescribed for narcolepsy as well as hyperactivity syndromes. In 1932, the pharmaceutical company Smith, Kline and French marketed the racemic amphetamine (dl-amphetamine) mixture benzedrine as an over-the-counter medication for treating congestion by inhalation of the drug. Benzedrine was typically administered via inhalers. From its introduction in the 1930s until 1954, ephedrine was available without prescription (i.e., "over-the-counter"). By the 1940s and 1950s, reported abuse of these inhalers began to emerge. Benzedrine inhalers as well as other preparations of the drug could be used to produce a stimulant effect and were sometimes abused as "bennies". With passage of the Comprehensive Drug Abuse Prevention and Control Act in 1970, amphetamine was classified as a Schedule III drug. The following

year, the classification of amphetamine was changed to Schedule II.

The term "amphetamines" also refers to a class of drugs derived from amphetamine, the substituted amphetamines. In recent years, the easily synthesized *N*-methylated form of amphetamine, methamphetamine, has become readily available and one of the most commonly abused stimulants in the United States. However, methamphetamine is not a recent addition to the list of amphetamine-related drugs. In 1885, the Japanese physician-chemist Nagayoshi Nagai (1844–1929) isolated ephedrine from the plant Ephedra vulgaris and, in 1893, synthesized methamphetamine by reduction of ephedrine using red phosphorus and iodine [141]. In 1929, he was the first to synthesize and elucidate the structure of ephedrine. In 1919, the Japanese chemist Akira Ogata (1887–1978) synthesized crystallized methamphetamine. In the 1980s, methamphetamine became increasingly more popular as a street drug. In 1996, the Methamphetamine Control Act was enacted to regulate the key ingredients (e.g., ephedrine, pseudoephedrine, phenylpropanolamine) in manufacturing methamphetamine and to increase criminal penalties for possession, distribution and manufacturing of the drug. The price of methamphetamine is largely determined by the availability of ephedrine, a key ingredient. Regulation of ephedrine, and its resulting unavailability, has increased its wholesale price. As a result, drug traffickers have switched to a less regulated and more economic substitute, pseudoephedrine. However, the Combat Methamphetamine Epidemic Act of 2005, a part of HR 3199 bill was enacted regulating over-the-counter sales of cold medicines containing pseudoephedrine. Methamphetamine can be smoked, snorted or injected, has significantly longer lasting stimulant effects than cocaine, and is generally much less expensive to purchase than cocaine [157]. Methamphetamine is considered highly addictive. Methamphetamine users typically develop tolerance to the drug that leads to higher and more frequent use.

Amphetamine is a homologue of phenethylamine and a weak base with a chemical structure very similar to dopamine and norepinephrine. Amphetamine is the parent compound for a class of similar psychoactive drugs including the *N*-methylated form of amphetamine, methamphetamine and the methylenedioxy analog of methamphetamine, 3,4-methylenedioxy-N-methylamphetamine ("Ecstacy;" MDMA; Fig. 4). Typically, formulated as a racemic mixture (D- and L-amphetamine), D-amphetamine is thought to act primarily on the dopaminergic systems, while L-amphetamine is comparatively norepinephrinergic (noradrenergic). Amphetamine and related drugs are lipid soluble in non-ionized form and as such are readily absorbed across the gastrointestinal tract lining as well as across the blood-brain barrier. Amphetamines can thus be taken effectively either by oral or parenteral routes of administration.

Pharmacologist David E. Nichols formulated the term "enactogen" to describe a class of synthetic drugs similar in structure to the stimulant 3,4-methylenedioxy-*N*-methylamphetamine (Ecstasy) but which exibit hallucinogenic properties [174, 176]. The term "entactogen" is a combination of the roots "en" (Greek: *within*), "tactus" (Latin: *touch*) and "gen" (Greek: *produce*) [176]. Enactogens are characterized by a substituted amphetamine core thus belonging to the phenethylamine class of psychoactive drugs. Enactogens include 3,4-

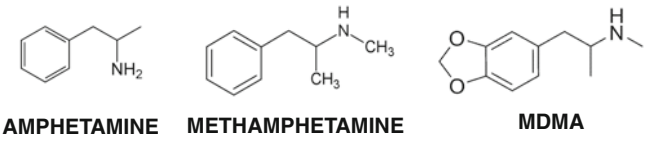


Fig. 4 Structures of amphetamine and structurally related drugs. MDMA = 3,4-methylenedioxy-*N*-methylamphetamine

methylenedioxyamphetamine (Tenamfetamine), 4-methylenedioxy-*N*-ethylamphetamine, 3,4-methylenedioxy-alpha-ethyl-*N*-methylphenethylamine ("EDEN" or "Methyl-J"), α-ethyltryptamine ("etryptamine"), and 4-bromo-2,5-dimethyphenethylamine. 3,4-Methyle-nedioxy-*N*-methylamphetamine is also often considered a member of the entactogen family.

4-Bromo-2,5-dimethyphenethylamine was first synthesized from 2,5-dimethoxybenzaldehyde by Russian-American pharmacologist Alexander Shulgin in 1974. In the late 1970s, the German pharmaceutical company Drittewelle began manufacturing and marketing the drug as an aphrodisiac called Eros. Shortly after its introduction to clinical psychiatry, 4-bromo-2,5-dimethyphenethylamine made its way into the recreational drug scene. 4-Bromo-2,5-dimethyphenethylamine remains popular within the rave subculture but is often confused with 3,4-methylenedioxy-*N*-methylamphetamine (Ecstasy). 4-Bromo-2,5-dimethyphenethylamine and related entactogens are now classified as Schedule I drugs in the United States.

Based on the known mechanisms of action of 3,4-methylenedioxy-*N*-methylamphetamine, entactogens are thought to act by increasing synaptic levels of dopamine, norepinephrine, and serotonin. However, there have been very few research studies to examine the pharmacology of entactogens in humans or experimental animal models.

Pharmacodynamics

Amphetamines are central nervous system and sympathetic nervous system stimulants, acting on biogenic amine pathways [157]. Physical effects include reduced appetite, hyperactivity, restlessness and insomnia, tachycardia and increased blood pressure and constipation. Behavioral effects include anxiety and generalized excitability, a perception of increased energy, repetitive actions, increased alertness, emotional liability and, with higher or long-term dosing, occasional psychosis. These effects are similar to those of other stimulants such as cocaine. The amount of releasable as well as previously released dopamine at dopaminergic nerve terminals is closely regulated by two selective membrane-bound transporters [114, 166, 205, 211]. Dopamine is moved via vesicular monoamine transporter-2 into synaptic vesicles for storage and eventual release. Without vesicular transport, dopamine remains within the cytoplasm where it is subject to degradation including oxidation and reactive free radicals which are potentially neurotoxic. Extracellular dopamine is moved back into the presynapse via the dopamine transporter. Dopamine transporter inhibition or blockade results in increased levels of extracellular dopamine. Amphetamines induce presynaptic dopamine release, block dopamine reuptake, inhibit dopamine storage within presynaptic vesicles and block enzyme-catalyzed dopamine metabolism. Shortly after amphetamine administration, reversal of the dopamine transporter results in non-vesicular dopamine efflux [128, 227]. In addition, the movement of dopamine into synaptic vesicles is blocked by amphetamine, resulting in increased dopamine release into the synapse and the potential for dopamine oxidation and damaging free radical formation within the presynapse. Although also acting through similar mechanisms on norepinephrine and, to a lesser extent, serotonin terminals, amphetamine's reinforcing and behavioral-stimulant effects are associated with enhanced dopaminergic activity, primarily within the mesolimbic dopamine system [54, 166]. The targeted effects of amphetamine on dopaminergic activity in caudate nucleus, nucleus accumbens and ventral striatum correlate well with stereotypic onset of euphoria associated with this drug [61, 113]. Amphetamine also acts to increase glutamate release in selected brain areas such as the nucleus accumbens, striatum and prefrontal cortex [54]. These areas are implicated in reward pathways.

Similar to its effects on the dopamine transporter, amphetamine can also reverse the direction of serotonin movement via the serotonin transporter [228]. Amphetamine

interacts with the serotoninergic system in selected brain regions such as the mesocorticolimbic pathway [97]. Similar to amphetamine, methamphetamine induces release of serotonin, dopamine, and norepinephrine as well as blockade of serotonin, dopamine, and norepinephrine transporters within the central nervous system, leading to increased synaptic activities of these biogenic amines.

Formation of free radicals including oxygen and nitrogen species is particularly characteristic of methamphetamine administration [83, 133, 258]. An amphetamine analog, methamphetamine, induces selective degeneration of dopamine neuron terminals without cell body loss. Methamphetamine-induced terminal degeneration may be mediated in part by excitatory amino acid (e.g., glutamate) activity [49]. Methamphetamine also induces rapid and reversible decreases in the rate-limiting enzyme for serotonin (5-hydroxytryptamine) synthesis, leading to reduced levels of this biogenic amine within various central nervous system areas [12, 104, 191].

Amphetamine, 3,4-methylenedioxy-*N*-methylamphetamine, and other psychotropic agents may also interact with a relatively new class of receptors called the trace amine-associated receptors [21]. Trace amine-associated receptors represent a class of G protein-coupled binding sites for endogenous trace amines, metabolic products of the better know biogenic amines such as norepinephrine, dopamine, serotonin, and histamine. Trace amines are normally present in very low (nanomolar) concentrations and include ρ-tyramine, octomaine, tryptamine and β-phenylethylamine. Trace amines such as β-phenylethylamine may function to modulate biogenic amine synaptic activities in selected brain areas related to affective states and thus in maintaining levels of excitement and alertness [227]. Branchek and Blackburn [25] have hypothesized a role for trace amines in substance abuse, depression, attention deficit hyperactivity disorder, eating disorders, schizophrenia, and other neuropsychiatric diseases.

Pharmacokinetics

Metabolism/Elimination

Metabolism of amphetamine is almost exclusively hepatic. In the liver, amphetamine can be hydroxylated (phenyl ring), deaminated or conjugated [254]. Methamphetamine is N-demethylated. In a study of human subjects given measured doses of amphetamine orally, 34% of the drug was excreted unchanged in urine [189]. Metabolites of the drug included benzoic acid and parahydroxy-amphetamine. These metabolites were themselves further converted into hippuric acid and parahydroxynorefedron, respectively.

Toxicity

The toxic effects of amphetamine and related drugs can be very serious and potentially fatal [56]. Short-term effects of amphetamine include increased heart rate and blood pressure, decreased appetite, feelings of elation and self-assuredness, and reduced fatigue. Long-term, repetitive amphetamine use has been associated with insomnia and restlessness, significant weight loss, hallucinations and paranoid psychosis. Amphetamine use can also include psychic dependence and tolerance, as well as psychotic episodes in some individuals [45]. Continuous high dose amphetamine use has been associated with a state of paranoid (“amphetamine”) psychosis closely resembling the symptoms of paranoid schizophrenia. Symptoms include hyperactivity, anxiety, paranoid delusions and auditory-tactile hallucinations in a setting of clear consciousness with little if any disorientation.

Use of amphetamines and related stimulants is particularly dangerous in individuals with a history of heart disease or underlying hypertension as well as those with glaucoma [56]. Amphetamines and stimulants should also be avoided by anorexic individuals because of the appetite suppressing properties of these drugs.

Amphetamines can cause life-threatening hypertensive crisis and possibly neurotoxic reactions when taken with monoamine oxidase inhibitors for clinical depression. Amphetamine-associated death is considered to be a direct consequence of excessive sympathomimetic activity. Amphetamine toxicity includes hypertension, hyperpyrexia, delirium, convulsions and severe tachycardia leading to cardiovascular collapse. Amphetamine also increases sympathetic tone regulating smooth muscle contraction and thus can affect adversely the functions of the gastrointestinal tract, uterus, urinary bladder and other organs dependent on smooth muscle activity.

3,4-Methylenedioxy-*N*-methylamphetamine has been associated with serotoninergic depletion and neuronal degeneration in rodent and non-human primate models [93, 201, 202, 222]. These neurotoxic effects were more pronounced in non-human primates than in rodents [222]. Within 3 weeks of 3,4-methylenedioxy-*N*-methylamphetamine administration, profound serotoninergic neurodegeneration was seen in non-human primates in most brain areas [203]. Some central nervous system areas showed evidence of partial recovery, i.e., hippocampus, caudate nucleus and frontal cortex; however, the partial recoveries appeared to be short-term, with a return to the dramatic patterns of serotoninergic losses seen 2 weeks after drug exposure.

Colado and colleagues [42] reported that 3,4-methylenedioxy-*N*-methylamphetamine administration to pregnant rats does not produce damage to serotonin nerve terminals in the brains of the fetuses, in contrast to the serotoninergic neurodegeneration seen in the central nervous system of the mothers. They hypothesized that this contrast in maternal versus fetal effects may be due to 3,4-methylenedioxy-*N*-methylamphetamine converted into free radical associated metabolites in the adult brain but not in the immature brain. Alternatively, the developing central nervous system may have more effective or more active free radical scavenging mechanisms than the mature adult central nervous system.

Therapeutic administration of amphetamines is usually by oral route. When used recreationally, amphetamines are taken orally, snorted, smoked, or injected intravenously [65]. Methamphetamine's methyl group is lipid soluble and easily transported across the blood-brain barrier as well as relatively resistant to enzymatic degradation catalyzed by monoamine oxidase. After oral administration (4 × 10 mg), methamphetamine is initially detected in plasma samples within 15 min–2 h. Maximal plasma concentrations (14.5–33.8 μg/L) are achieved within 2–12 h and the drug remains measurable for 36–72 h after administration [215]. Methamphetamine has an elimination half-life of 9–15 h primarily via urinary excretion. Methamphetamine elimination half-life varies with differences in urinary pH. One of the metabolites of methamphetamine is amphetamine.

Amphetamine and amphetamine-like derivatives are potent central nervous system stimulants affecting regulatory centers for heart rate, body temperature, blood pressure, appetite, attention, mood and responses associated with alertness or alarm responses [56]. Physiological and psychological responses to amphetamines closely resemble the sympathetic nervous system induced fight-or-flight responses, including increased heart rate and blood pressure, vasoconstriction, bronchodilation, and hyperglycemia. Users report increased ability to focus on tasks, an overall increase in mental alertness, avoidance of fatigue and decrease in appetite.

Drug tolerance develops rapidly in amphetamine abuse [135]. Tolerance to the drug's effects results in increasing amounts of the drug needed to obtain similar rewarding effects. However, chronic amphetamine use can produce so-called "reverse tolerance", or sensitization to some of the psychological effects of the drug. Amphetamine users will often take more of the drug during withdrawal periods and may use other drugs such as benzodiazepines or less commonly barbiturates to lessen the effects of withdrawal [38, 135].

Methamphetamine administration is associated with both dopaminergic and serotoninergic neurodegeneration. The generation of free radicals as a by-product of increased dopamine and serotonin metabolism is postulated to play a key role in this neurodegeneration [83, 258]. Blocking increases in methamphetamine-induced release of dopamine or serotonin reduce the neurodegeneration seen with administration of this drug. Additionally, pretreating with multiple injections of escalating doses of methamphetamine produces tolerance to the long-term neurotoxic effects of methamphetamine on striatal dopamine neurons [225]. Though not yet well defined, the mechanism for this tolerance may be related to aberrant vesicular monoamine transporter-2 and dopamine transporter function in these neurons.

Opiates

History

Crude opium is a component of the opaque, milky-white sap obtained from the seedpods of the poppy plant (*Papaver somniferum*) [27]. This plant and its product opium was likely cultivated in the Mediterranean region as early as 5000 B.C. by ancient Egyptians and Greeks and later by the ancient Romans. Opium was introduced into China around 800 A.D. and, with the arrival of European explorers to China, to Europe by the seventeenth century. In 1680, a famous English physician named Thomas Syndenham introduced opium to the medical field. In the seventeenth century, many people in Europe were treated for a variety of health problems with opium. In 1729, opium smoking was made illegal in China and soon the importation of opium was banned. This ban upset the British who were in charge of trading this valuable product. Opium was still smuggled into China and is considered the underlying cause of the so-called "Opium Wars" (1839–1842 and 1856–1860) between the British and the Chinese. In the United States, opium was used to treat soldiers during the Civil War (1861–1865). During the late 1800s, doctors prescribed "tonics" containing opiates for many conditions. Typically, these medicines failed to list opiates as one of the ingredients.

Opium represents a complex of sugars, proteins, fats, water, meconic acid, plant wax, latex, gums, ammonia, sulphuric and lactic acids, and numerous alkaloids. Alkaloids present in opium include morphine (10–15%), codeine (1–3%), noscapine (4–8%), papaverine (1–3%), and thebaine (1–2%). Narceine and approximately 25 other alkaloids are also present but have little to no effect on the central nervous system, and are not usually considered to be opiates. Thebaine is considered highly toxic and thus not used therapeutically [3]. Thebaine acts as a potent stimulant rather than as a depressant, at higher concentrations causing strychnine-like convulsions. Thebaine can be used to produce the semi-synthetic morphine analogues oxycodone, dihydromorphenone, hydrocodone, and etorphine.

In 1805 the German pharmacist Frederick Serturner isolated morphine from opium. He named this new-found compound after Morpheus, the Greek god of dreams. Morphine-related analogues include the diphenylpropylamines (e.g., methadone), the 4-phenylpiperidines (e.g., meperidine), the morphinans (e.g., levorphanol) and 6,7-benzomorphans (e.g., metazocine), each of which has in common a piperidine ring or a key component of that ring structure. Heroin was first synthesized in 1874 by the British chemist C. Adler Wright. Heroin is synthesized from morphine. Heroin is the 3, 6-diacetyl ester of morphine, i.e., diacetylmorphine (Fig. 5). Heroin became widely accepted within the medical community in the early 1900s. The high risk for addiction was not initially recognized by physicians at that time. With a better understanding for its abuse potential, heroin was later regulated with passage of the Harrison Narcotic Act of 1914. The drug is now classified as a Schedule I substance with significant abuse potential but no accepted medical use.

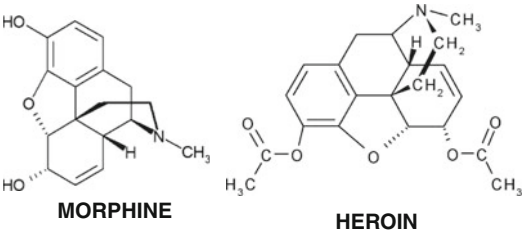


Fig. 5 Structures of morphine and heroin

The term "opiate" refers to morphine-like alkaloids (e.g., morphine itself, heroin, codeine, thebane and papaverine) derived from opium as well as a number of semisynthetic and synthetic opiates. "Opioid" refers to endogenous substances with morphine-like activity. Endogenous opioids include dynorphins, enkephalins, endorphins, endomorphins and nociceptin/orphanin FQ. The term "endorphin" was first used in the mid-1970s to describe any endogenous morphine-like substance, now classified as endogenous opioidergic peptides. We now recognize several classes of endogenous opioidergic peptides including enkephalins, endorphins, dynorphins and endomorphins. Opiates like morphine and heroin bind to and activate the same receptors used by endogenous opioidergic peptides, namely mu, kappa, and delta receptors. Opioidergic receptors are expressed only in the central nervous system, gastrointestinal tract and vas deferens. Most opioid receptors are linked to an inhibitory G protein (G_i). Thus endogenous opioidergic peptide receptor binding is associated with inhibition of adenylate/cyclic AMP second messenger systems and inhibition of the target neuron.

Endogenous opioidergic peptides are generally involved with homeostasis or regulation of basic physiologic functions including respiration, endocrine functions and nociception (pain). Endogenous opioidergic peptides may also play important roles in mood and affect. The greatest density of opioidergic receptors is found in the limbic system (emotions and affect) and in the dorsal horn of the spinal cord (nociception). Thus, it should not be surprising that endogenous opioidergic peptides are thought to integrate euphoric and emotional components of pain relief.

According to the 2006 National Survey on Drug Use and Health, heroin accounts for nearly 90% of opiate abuse in the United States though some opiates with medicinal use such as morphine, oxycodone, meperidine, and codeine are also subject to abuse. Reflecting greater worldwide availability as well as an interest among drug dealers to reach a wider market with an aversion to the risks associated with use of hypodermic needles, heroin purity has risen from 10% as recently as the 1980s to current purity of 50–60% and greater. Heroin is rarely sold in pure form on the street but rather is routinely diluted with cutting agents such as sugar, starch, baking soda, quinine, or other substances. A typical street unit or "bag" of heroin contains 30–50 mg of cut drug.

Pharmacodynamics

Opiate agonists and antagonists bind to stereospecific, saturable receptors in the brain and other tissues. Central nervous system opioidergic receptors are widely but unevenly distributed. These receptors were originally classified according to their affinity for binding agonists: mu receptors preferentially bind morphine, kappa receptors preferentially bind ketocyclazocine, and delta receptors bind deltorphin II. Morphine also binds to both kappa and delta receptors though with lesser affinity than to mu receptors. In 2000, these receptors were reclassified as OP_1 (delta), OP_2 (kappa), and OP_3 (mu) by a subcommittee of the International Union of Basic and Clinical Pharmacology (IUPHAR Compendium of Receptor Characterization and Classification, 2nd Edition, London: IUPHAR Media, pp. 321–333, 2000). Mu receptors are located widely throughout the central nervous system, especially in the limbic system (frontal and temporal cortex, amygdala, and hippocampus), thalamus, striatum, hypothalamus, and midbrain. Kappa receptors are located primarily

in the spinal cord, periaqueductal grey area and cerebral cortex. Delta receptors are located primarily in pontine nuclei, amygdala, olfactory bulbs and deep cerebral cortex. Opiate receptors are G protein coupled and function as modulators, both positive and negative, of synaptic transmission. Most known opiates exhibit no ceiling effect for analgesia with the exception of codeine for which a ceiling effect is estimated as 7 mg/kg. Mu-receptor activation can result in analgesia, euphoria, respiratory depression, miosis, decreased gastrointestinal motility, and physical dependence. Kappa-receptor stimulation also produces analgesia, miosis, respiratory depression, as well as, dysphoria and some psychomimetic effects (i.e., disorientation and/or depersonalization). Delta-receptor activation produces dysphoria, respiratory depression at high doses and cardiac stimulation. Opiates working primarily through mu receptors also suppress cough reflex. The antitussive effects of codeine are mediated through direct action on receptors in the cough center of the medulla.

Heroin is rapidly transported across the blood-brain barrier and metabolized into morphine and related compounds. It is generally assumed that heroin itself has only minor pharmacological effects. Most of the pharmacological effects associated with heroin are actually caused by morphine as well as, to some degree, the other two major metabolites 6-acetylmorphine and morphine-6-glucuronide [246]. Morphine-6-glucuronide possesses analgesic properties though morphine-3-glucuronide does not seem to have any agonistic effect either in vivo or in cell cultures [95].

Most opiates such as heroin and morphine produces a profound sense of euphoria in most users though this effect diminishes with development of tolerance to the drug. Heroin and morphine share in common the ability to induce euphoria and relaxation as well as, with time, drowsiness and sleepiness. Short-term studies among users suggest that heroin tolerance develops no more rapidly than tolerance to morphine [233]. This is perhaps not surprising given the physiochemical properties of heroin and morphine and the metabolism of heroin metabolism of heroin to morphine.

Pharmacokinetics

Routes of Administration/Metabolism

Heroin represents the diacetyl derivative of morphine. The usual route of administration is intravenous though other routes of administration include intramuscular, subcutaneous, rectal and intranasal. After absorption, it is rapidly converted into either morphine or monoacetylmorphine which is highly lipid soluble and thus easily crosses the blood-brain barrier with rapid induction of euphoria (NIDA Research Report—Heroin Abuse and Addiction: NIH Publication No. 05-4165, Printed October 1997, Reprinted September, 2000, Revised May 2005). When taken orally, heroin undergoes extensive first-pass metabolism via deacetylation into morphine in the liver. Thus heroin can be considered a prodrug [214]. In contrast, intravenous injection of the drug essentially bypasses first pass metabolism with rapid distribution across the blood-brain barrier due to the presence of acetyl groups which make the drug more lipid soluble than morphine [122]. Within the brain, heroin is deacetylated into 3- and 6-monoacetylmorphine and morphine, which bind to μ-opioid receptors. Most of the morphine is further converted to morphine-3-glucuronide (approximately 50%) and morphine-6-glucuronide (approximately 10%) [4]. Recent studies have demonstrated that the brain, pancreas, and myocardium can also produce morphine [19].

Morphine is metabolized primarily into morphine-3-glucuronide and morphine-6-glucuronide via glucuronidation catalyzed by the liver enzyme UDP glucuronosyl transferase 2B7 (UGT2B7) [117]. Morphine is similarly metabolized in brain and kidneys. At least in studies using rodent models, morphine-6-glucuronide is far more potent an analgesic than morphine itself. However, this morphine metabolite crosses the blood-brain barrier poorly in contrast to morphine.

Toxicology

The psychological dependence associated with opioidergic addiction is both protracted and complex. Well beyond the recovery from the physical need for the drug, the opiate addict may obsess about use of the drug and feel an inability to deal with daily activities without use of the drug. These individuals are at high risk for relapse assuming that neither the physical environment nor the behavioral motivators associated with the abuse have been altered.

Opiate withdrawal symptoms in opiate users can be seen as early as 2–3 h after last dose of drug (National Institute on Drug Abuse, InfoFacts: Heroin, May 2006). Major withdrawal signs peak between 48 and 72 h after last dose and subside within 9–12 days. Initial signs of withdrawal include dilated pupils, profuse sweating and anxiety. These individuals also experience progressively stronger drug craving, severe abdominal distress, diarrhea, nausea and vomiting, restlessness, muscle and bone pain, insomnia, cold flashes with goose bumps ("cold turkey") alternating with high temperature spiking ("hot flashes"), and kicking movements ("kicking the habit"). Severe depression is a common manifestation. Opiate withdrawal is rarely fatal though sudden withdrawal by heavily dependent users in poor health may be fatal. Opiate withdrawal is considered less risky than alcohol, benzodiazepine, or barbiturate withdrawal.

Following intravenous infusion of heroin, the user experiences a surge of euphoria ("rush") along with dry mouth, a warm flushing of the skin and a heaviness of the extremities [151]. The user then becomes alternately somnolent and alert ("on the nod"), shifting between wakeful and drowsy states. Mental functioning declines. Tolerance to the effects of the drug develops over time and regular usage. In effect, the user must use more heroin to achieve the same intensity of effect. Eventually, drug-induced neural plasticity within reward pathways of the brain results in addiction to the drug.

It is very difficult to establish a median lethal dose for heroin among regular users. Individuals have overdosed on as little as 1 mg/kg of heroin. A median lethal dose for non-addicts has been suggested as 1–5 mg/kg. However, there may be no easily identifiable upper limit to the amount of heroin a heavily addicted individual can take. Research studies conducted in the 1920s among opiate addicts described administering heroin in doses of 1,600–1,800 mg with no obvious adverse side effects. These results are supported by studies in rats showing that 14 days of pretreatment with morphine or heroin reduced mortalities associated with subsequent morphine administration [226]. Thus, long-term opiate abuse is typically associated with development of highly significant drug tolerance.

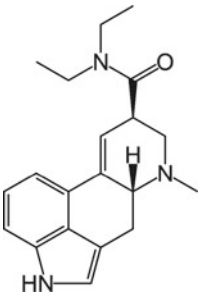
Neurologic complications associated with heroin use include peripheral neuropathies, nerve pressure palsies, hypoxic encephalopathy, seizures, rhabdomyolysis and transverse myelopathies. Spongiform leukoencephalopathy is a relatively rare complication of heroin use with only 70 reported cases from the first reported case in 1984 through 2004 [89]. This complication is typically seen among users who inhale fumes generated by heating heroin, a practice called "chasing the dragon" [98]. The typical lesions include abnormal white matter with patchy spongiform change and prominent reactive fibrous gliosis consisting of glial fibrillary acidic protein-positive fibrous astrocytes. Symptoms vary according to the brain regions involved but often include cognitive dysfunction, cerebellar ataxia, dysarthria, and motor restlessness, with an estimated mortality rate of approximately 25%.

Heroin-related death has been associated with the phenomenon of place tolerance and overdose as a result of using the drug in an unaccustomed environment [79]. The mechanism for fatal overdosing in this situation was described as an overriding of conditioned or place tolerance. Because heroin use is such a highly ritualized behavior, longtime users exhibit increased tolerance to the drug in locations in which they have

repeatedly administered heroin. When the drug is used in a different location, this environment-conditioned tolerance does not occur, which produces enhanced effects of the drug. In response to this decrease in tolerance, the user increases the typical dose of the drug. If extreme in self-dosing, the result can be a fatal overdose.

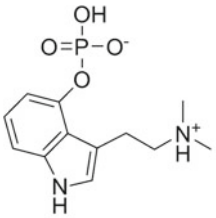
Morphine also affects immune system function via interactions with dendritic cells [158]. Dendritic cells, a type of antigen presenting cell, express opiate receptors. Dendritic cells exposed to morphine during their maturation produce increased levels of interleukin-12, a cytokine responsible for promoting the proliferation, growth, and differentiation of T lymphocytes which are active in adaptive immune responses, and less so, interleukin-10, a cytokine responsible for promoting B lymphocyte responsiveness.

Fig. 6 Structure of lysergic acid diethylamide (LSD)



LSD

Fig. 7 Structure of psilocybin



PSILOCYBIN

Hallucinogens: Lysergic Acid Diethylamide, Psilocybin, Mescaline

History

Hallucinogens comprise a class of drugs defined by their ability to induce changes in the user's perception of reality. Users describe seemingly real images, sounds and sensations which do not in fact exist (National Institute on Drug Abuse, Research Report: Hallucinogens and Dissociative Drugs, March 2001). Traditionally, these drugs were derived from plant sources but are now synthetic with resultant greater purity of product (Drug Enforcement Administration, Drug Descriptions: Hallucinogens). Commonly used hallucinogens include lysergic acid diethylamide (Fig. 6) and psilocybin (Fig. 7).

Lysergic acid is a component of ergot alkaloids found in the ergot fungus (*Claviceps purpurea*) which infects cereal grains including rye (National Institute on Drug Abuse, InfoFacts: LSD, May 2006). Ergot alkaloids are very potent compounds responsible for ergotism (also known as ergotoxicosis, ergot poisoning and St. Anthony's Fire) characterized by convulsive and vasoconstrictive symptoms including gangrene and hallucinations, mania, and psychoses.

Lysergic acid diethylamide was first synthesized in 1938 by Swiss chemist Albert Hofmann (1905–2008) [101]. The hallucinogenic effects of lysergic acid diethylamide were not immediately recognized and the drug was ignored over the next several years. But in 1943, Hofmann accidentally absorbed a very small amount of lysergic acid diethylamide and experienced firsthand the psychogenic effects of the drug. He then followed up with an additional self-administration of lysergic acid diethylamide, later reporting the intensely psychedelic effects associated with the drug. The abbreviation "LSD" is derived from its early codename *LSD-25* (German "lysergsäure-diethylamid" followed by a sequential development number). Lysergic acid diethylamide was initially marketed by Sandoz Laboratories as a therapeutic drug with numerous potentially useful psychiatric applications. However, the drug's entry into

the illicit, recreational environment with ensuing political repercussions eventually precluded further interest in the drug among pharmaceutical companies and physicians. The substance was eventually banned for any use other than research as a Drug Enforcement Administration schedule I substance.

For a time during the 1950s and early 1960s, intelligence agencies in the United States and other countries had an interest in the use of lysergic acid diethylamide to facilitate interrogations and mind control (U.S. Congress: The Select Committee to Study Governmental Operations with Respect to Intelligence Activities, Foreign and Military Intelligence [Church Committee report], Report no. 94–755, 94th Congress, 2nd Session, Washington, D.C.: GPO, 1976). The Central Intelligence Agency conducted such studies through the Office of Scientific Intelligence largely in response to similar studies employed by the Soviet Union and China in the early 1950s. One such study involved the use of United States soldiers dosed with lysergic acid diethylamide to study the effects of panic. By the late 1960s, the Central Intelligence Agency had ended these lysergic acid diethylamide studies, the results of which were considered too unpredictable.

The principal psychoactive component of so-called "magic mushrooms" is an indole related to tryptamine, psilocybin. Use of hallucinogenic mushrooms (*Psilocybe cubensis* and *Psilocybe semilanceata*) may go back as far as prehistoric humans though conclusive evidence for this is lacking. Their early use was probably associated with religious communing, divination and healing just as they are among some present-day Native Americans. Bernardino de Sahagún (1499–1590), a Franciscan missionary, described the ritualistic use of teonanácatl or "flesh of the gods" among the Central American Aztecs. In the 1960s, recreational use of hallucinogenic mushrooms was promoted by R. Gordon and Valentina Wasson, Timothy Leary, and others which led to the popularization of a number of psychoactive *Psilocybe* species found in North America, Europe, and Asia.

In 1958, Hofmann had identified psilocin and psilocybin as the active compounds in psychoactive mushrooms. By the early 1970s, a number of psychoactive *Psilocybe* species were described, these variants being found in North America, Europe and Asia. These mushrooms may also contain small amounts of other psychoactive tryptamines. Psilocybin and psilocin are listed as Schedule I drugs in the United States and many other countries.

Mushroom concentrations of psilocybin and psilocin vary significantly among varieties of psychoactive mushrooms but averages 0.5–2.0% of the dry weight of the average mushroom. The more common species *Psilocybe cubensis* contains approximately 10–25 mg psilocybin and psilocin. When psilocybin is ingested, it is broken down to produce psilocin, which is responsible for the hallucinogenic effects. About 25–50 mg of psilocybin and/or psilocin is generally thought to be a heavy psychoactive dose of these drugs.

Pharmacodynamics

The hallucinogenic effects of lysergic acid diethylamide and phenethylamine hallucinogens are thought to be mediated by the binding of these drugs to the serotonin-2A receptor [150]. Lysergic acid diethylamide administered in so-called "recreational doses" has been shown to interact with serotonin-1A, serotonin-2A, serotonin-2C, serotonin-5A, serotonin-5B, and serotonin-6 receptors. More specifically, the hallucinogenic effects of lysergic acid diethylamide have been attributed to the drug's strong partial agonist effects at serotonin-2A receptors [150]; selective serotonin-2A specific antagonists block the psychotropic activity of lysergic acid diethylamide [175]. With the exception of the ligand-gated ion channel serotonin-3 receptor, serotonin receptors are G protein coupled, seven-transmembrane receptors that activate intracellular second messenger pathways. The exact sites and mechanisms of action are not yet known.

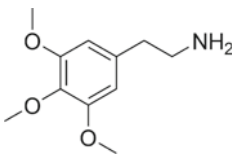
In addition to the drug's effects on serotonin-2A receptors, lysergic acid diethylamide has also been shown to affect glutaminergic systems within the central nervous system. Systemic lysergic acid diethylamide (0.1 mg/kg, intraperitoneally) or direct lysergic acid diethylamide infusion (10 μM) into prefrontal cortex has been associated with elevated levels of glutamate release in this brain region, an effect blocked by administration of the serotonin-2A antagonist M100907 (0.05 mg/kg, intraperitoneally) [171]. Chronically, lysergic acid diethylamide may activate dopamine- and cyclic AMP-regulated phosphoprotein with molecular weight 32 kDa (DARPP-32)-related pathways—a mechanism of action shared by numerous other psychoactive drugs, including cocaine, amphetamine, methamphetamine, nicotine, caffeine, phencyclidine, ethanol, and morphine [229].

Typical doses of lysergic acid diethylamide are measured in microgram amounts rather than the more typical milligram amounts associated with other drugs of abuse. Hofmann determined that an active dose of mescaline, roughly 0.2–0.5 g, has effects comparable to 100 μg or less of lysergic acid diethylamide [101]. A single dose of lysergic acid diethylamide is typically 100–500 μg; threshold psychotropic effects of the drug are experienced with as little as 25 μg [87]. The median lethal dose for lysergic acid diethylamide has been estimated to range from 200 μg/kg to >1 mg/kg though there are no known deaths attributed directly to the use of lysergic acid diethylamide. Lysergic acid diethylamide users do not exhibit the typical features of drug addiction and dependence though tolerance to the drug can develop rapidly. Users demonstrate cross-tolerance between lysergic acid diethylamide and psilocybin [110]. Attenuation of tolerance to lysergic acid diethylamide is thought to be related to drug-induced down-regulation of serotonin-2A receptors in as yet undefined central nervous system areas.

Adverse reactions to lysergic acid diethylamide have been treated using fast-acting benzodiazepines such as diazepam or triazolam. These serve as anxiolytics, calming the individual but without directly blocking lysergic acid diethylamide binding at serotonin-2A sites. Theoretically, specific serotonin-2A receptor antagonists, e.g., the atypical antipsychotic quetiapine fumarate, would act to block lysergic acid diethylamide binding at these receptors, thus attenuating the psychoactive effects of lysergic acid diethylamide.

Mescaline (3,4,5-trimethoxyphenethylamine) (Fig. 8) is a naturally occurring hallucinogenic phenethylamine. Mescaline is one of several psychoactive alkaloids produced by several species of cactus including the peyote cactus (*Lophophora williamsii*), the San Pedro cactus (*Echinopsis pachanoi*), and the Peruvian Torch cactus (*Echinopsis peruviana*) [129]. The peyote cacti are primarily subterranean, with underground roots and a relatively small above-ground crown consisting of several disk-shaped "buttons". These buttons are cut from the cactus and dried. Peyote includes a number of alkaloids including mescaline. Peyote has been used as a part of religious rites by Native American Indians of the arid northern Mexico and southwest United States for thousands of years. Peyote buttons with measurable levels of mescaline were found within prehistoric native Indian ruins and traced back to 3780–3660 B.C. by radiocarbon dating [64]. Mescaline was first isolated and identified in 1897 by German chemist Arthur Heffter and first synthesized in 1919 by Ernst Späth.

Fig. 8 Structure of mescaline



Mescaline is rapidly absorbed after oral ingestion by rats [184]. The hallucinogenic effects of associated with ingestion of mescaline are seen in doses of 300–600 mg, the equivalent of 9–20 small peyote cactus tops. Mescaline is 1,000 to 3,000 times less potent than lysergic acid diethylamide, and 30 times less potent than psilocybin. The median lethal dose has been estimated as 212 mg/kg intraperitoneally for mice, 132 mg/kg intraperitoneally for rats

and 328 mg/kg intraperitoneally for guinea pigs. About half the initial dosage is excreted by 6 h, but the effects of mescaline can last up to 12 h. Tolerance to mescaline increases with repeated administration. Mescaline may exhibit cross-tolerance with either lysergic acid diethylamide or psilocin. Equipotent doses of mescaline and lysergic acid diethylamide have been described as all but indistinguishable in psychoactivity [216]. A significant amount (20–50%) of an ingested dose of mescaline is excreted in the urine unchanged in canine experimental models [40]. Lesser amounts (7%) are excreted in urine by humans [55]. Mescaline is primarily metabolized via oxidative deamination. Excreted metabolites include 3,4,5-trimethoxyphenylacetic acid and 3,4,5-trimethoxybezoic acid.

In contrast to lysergic acid diethylamide-induced hallucinations, those associated with mescaline use are described as being consistent with actual experiences but are typically intensified through visual and auditory inputs [58, 192]. Mescaline elicits a pattern of sympathetic arousal, with the peripheral nervous system being a major target for this drug. Similar to lysergic acid diethylamide, mescaline binds to and activates brain serotonin serotonin-2A receptors with a high nanomolar affinity [164].

Pharmacokinetics

Routes of Administration

Lysergic acid diethylamide is typically administered orally. Often absorbent paper, sugar cubes or gelatin cubes are used as vehicles to deliver very small amounts of the drug. Unlike most other medicinal or illicit drugs which are dosed in milligram concentrations, psychoactive doses are measured in microgram concentrations. Liquid forms of the drug can be administered either intramuscularly or intravenously. About 20–30 μg is thought to be a threshold dose to experience psychoactive effects [87]. The psychoactive effects of a threshold dose (20–30 μg) of lysergic acid diethylamide typically last from 6 to 12 h depending on tolerance, body weight and age. These effects do not last longer than measurable blood levels of lysergic acid diethylamide as was once thought. Aghajanian and Bing [80] reported that lysergic acid diethylamide had an elimination half-life of 175 min. In a case study involving a single adult male, a 1 μg/kg dose of lysergic acid diethylamide orally had a plasma half-life of 5.1 h, with a peak plasma concentration of 5 ng/mL 3 h after drug administration [185]. These investigators also reported a close correlation between measurable blood concentrations of lysergic acid diethylamide and the time course of the subject's difficulties with simple arithmetic problems.

Following ingestion, psilocybin is rapidly absorbed and dephosphorylated to psilocin [91]. Similar to lysergic acid diethylamide, psilocin is a highly potent serotonin-1A, serotonin-2A, and serotonin-2C receptor agonist. The receptor binding potency of psilocin correlates strongly with its potency as a hallucinogen [186]. The psychoactive effects of psilocin can be highly variable among individuals. Effects reported by many individuals include strong visual and auditory components. Ingestion of psilocybin and/or psilocin is associated with an increase in the ability to concentrate on memories, feelings of time expansion, abstract and distractive thought patterns as well as indecisiveness, phonetic experimentation (glossolalia) and epiphanies about life [186, 256].

Psilocybin has a reported onset of action of 15–30 min following ingestion, with psychoactive effects lasting 5–8 h [208]. The duration of psychoactive effects correlate with dosage, which is a function of mushroom preparation and storage, and with variations in metabolism among users.

Toxicology

Lysergic acid diethylamide has been shown to bind to and induce conformational changes in

the structure of the DNA helix [59], and though reported to be mutagenic at higher doses in animal models, no detectable DNA damage or increased incidence of cancers has been seen with lysergic acid diethylamide use in humans. In fact, most hallucinogens are not known to have long-term toxicities. However, an important caveat is the potential for 3,4-methylenedioxy-*N*-methylamphetamine to produce free radicals as a side reaction to the effects of this drug on biogenic amine systems in the central nervous system. These free radicals may induce neurodegeneration within various brain areas with resultant disease states. Hallucinogen persisting perception disorder (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition diagnosis: diagnostic code 292.89) represents a condition in which the vision system-related effects of this drug persist over a long period of time [68]. Hallucinogen persisting perception disorder is distinctly different from so-called "flashbacks" in being persistent. The mechanism for this disorder has not been defined.

To date no significant toxicities have been associated with ingestion of psilocybin mushrooms, and a lethal dose in humans has not been established. The oral median lethal dose in rats is 280 mg/kg [186]. Psilocybin represents approximately 1% of the dried weight of the *Psilocybe cubensis* mushroom. An adult weighing 60 kg would have to ingest 1.7 kg of dried mushrooms to reach a dosage equivalent to the oral median lethal dose in rats. Psilocybin and psilocin are not considered addictive although both can induce short-term increases in tolerance of users.

Cannabis

History

In 1378, the Emir of the Joneima in Arabia, Soudoun Sheikouni, issued the first recorded edict prohibiting cannabis use [137]. He ordered all cannabis plants in the region destroyed and that those convicted of ingesting the plant have all of their teeth removed. Less than 20 years later, in 1393, use of cannabis in Arabia had increased [137]. And so it goes even today with the allure of this unique plant. Despite centuries of government edicts from all corners of the globe, cannabis remains the most popular psychoactive substance on the planet with the exception of caffeine, tobacco, and ethanol.

Cannabis has been used in China for over 5,000 years [152]. Its use in the Middle East is probably similarly ancient. The translation of the ingredients of the holy oil used by Aaron and his sons to anoint the tabernacle of Moses consisted of myrrh, cinnamon, cassia (commonly used as cinnamon in North America) and calamus extracted into olive oil. However, in the original Hebrew text, the last ingredient is "kanah bosm" which some contend is actually the Scythian etymological root of cannabis [152]. Indeed, the Greek historian Herodatus describes recreational use of cannabis among the Scythians 2,500–3,000 years ago [152].

Cannabis is the genus name given to several strains of the plant commonly called hemp [241]. As early as 1855, it was recognized that hemp carefully cultivated in the gardens of the near and far east had vastly different properties when consumed than the hemp grown as a large scale crop in Europe which was used in the production of fibers for rope, paper, and fabric [241]. For thousands of years in the near and far East, preparations of cannabis were smoked, eaten, or prepared in beverages [137]. Thus, while improvements in refining and distilling capabilities over the past 200 years have led to drastic increases in the potency and portability of drugs such as cocaine, morphine, and even ethanol, cannabis users continue to employ the same methods practiced by prehistoric peoples.

Chemical Properties

Raw cannabis contains 483 distinct chemical constituants, most of which are common to other plants [66]. However, the genus *Cannabis* alone produces the 66 known chemicals that constitude the cannabinoids [66]. Cannabinoids are

terpenes joined to an alkyl-substituted resorcinol [194]. Several of the cannabinoids are psychoactive, most notably Δ^9-tetrahydrocannabinol (Fig. 9). Δ^9-Tetrahydrocannabinol is regarded as the principal psychoactive constituent of cannabis and can produce discriminative stimulus effects in experienced cannabis users [35]. Other constituents of cannabis are also psychoactive, or may be metabolized into psychoactive or may be metabolized into psychoactive chemicals after ingestion; however, most of the research on psychoactive effects of cannabis focus on properties of Δ^9-tetrahydrocannabinol.

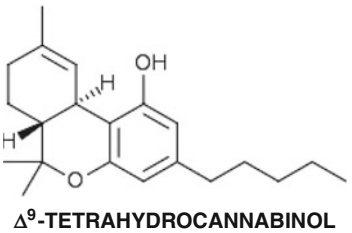


Fig. 9 Structure of Δ^9-tetrahydrocannabinol

Δ^9-Tetrahydrocannabinol has a molecular weight of 314. It is insoluble in water, and experimental preparations commonly employ the use of an emulsifier such as vegetable oil to allow an injectable solution. The concentration of Δ^9-tetrahydrocannabinol in cannabis depends upon the source, with levels ranging from 0.007% to almost 4.0% [194]. Although official reports released by the United States Department of Justice assert that the concentration of Δ^9-tetrahydrocannabinol in cannabis is increasing both in the United States and abroad (http://www.usdoj.gov/ndic/pubs11/18862/marijuan.htm; http://www.whitehousedrugpolicy.gov/news/press07/042507_2.html), others, including the director of the University of Mississippi Marijuana Potency Monitoring Project, Mohammed ElSohly, dispute this claim (http://www.slate.com/?id=2074151). While selective breeding techniques have undoubtedly resulted in enriched Δ^9-tetrahydrocannabinol-containing strains, notably in Canada and the Netherlands, after several generations in the United States, the Δ^9-tetrahydrocannabinol content of these strains recedes to levels common to American plants [194]. Climate, light, soil, humidity, and stress during the growing season all affect Δ^9-tetrahydrocannabinol content [194].

Pharmacokinetics

Routes of Administration

Marijuana is most commonly smoked. The plant material is macerated and rolled into cigarettes or loaded into a pipe. Some people utilize a water pipe in which the smoke is drawn through water with the intent of removing toxic compounds resulting from pyrolosis. This method does appear to effectively reduce the ingestion of pyrolytic toxins [213]. However, a study funded by the Multidisciplinary Association for Psychedelic Studies and the California chapter of the National Organization to Reform Marijuana Laws showed that while water pipes filter out tar, the water also traps substantial amounts of Δ^9-tetrahydrocannabinol, which leads the user to ingest more smoke, offsetting the benefits of water filtration [81]. An alternative to smoking that is growing in popularity is vaporization. This technique requires specialized equipment that heats the plant material up to 200°C, the vaporization temperature of Δ^9-tetrahydrocannabinol (MSDS, 2008; CRC Handbook) and related compounds, but not hot enough to result in combustion. This method has been shown to result in similar subjective effects (almost 90% of the vaporized substance is Δ^9-tetrahydrocannabinol), yet almost completely eliminates combustion byproducts in the inhaled product [2, 82, 94].

Δ^9-Tetrahydrocannabinol can also be eaten. Typically, fat-soluble cannabinoids are extracted into butter or some other oil which is filtered and used to make foods. Although this method eliminates any byproducts of combustion, the onset of psychoactive effects is slower and more difficult for the user to titrate [26, 194]. Alternatively, cannabinoids can be extracted from the plant

material with ethanol. The ethanol can then be consumed or used as a tincture. Again, this method eliminates harmful byproducts resulting from combustion, but makes dose titration more difficult. Further, impairment due to cannabis is enhanced by ethanol, possibly due to pharmacokinetic or pharmacodynamic interactions [103, 154]. Oral and topical preparations were the most commonly used medicinal applications in the late nineteenth and early twenieth centuries [69].

Distribution/Bioavailability

Inhalation of Δ^9-tetrahydrocannabinol results in rapid absorption, similar to other inhaled drugs. Further, smoking and vaporization produce very similar pharmacokinetic profiles in plasma of human volunteers [236]. Depending on the experience of the individual, 15–50% of the Δ^9-tetrahydrocannabinol in the raw plant matter reaches systemic circulation [181]. Oral consumption of cannabis leads to much slower and more variable absorption of Δ^9-tetrahydrocannabinol, which may depend in part on the vehicle.

The volume of distribution for Δ^9-tetrahydrocannabinol is about 10 L and is primarily distributed to body fat, and internal organs with fatty compositions such as the liver, heart, mammary tissue, and brain. Δ^9-Tetrahydrocannabinol in plasma is almost entirely bound to lipoproteins, albumin, and red blood cells. Only about 3% of free Δ^9-tetrahydrocannabinol is found in plasma [181].

Metabolism/Elimination

Metabolism of Δ^9-tetrahydrocannabinol is primarily achieved by the liver, though other organs are also able to metabolize Δ^9-tetrahydrocannabinol. Δ^9-Tetrahydrocannabinol is hydroxylated into 11-OH-Δ^9-tetrahydrocannabinol by mitochondrial cytochrome P-450, which maintains pharmacological activity [181]. Further metabolism by the same enzyme results in the inactive 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol [181]. One recent report determined the half-life of Δ^9-tetrahydrocannabinol to be 1.4 h, though this period is shorter than the results previously reported by others [9]. Determination of the half-life of Δ^9-tetrahydrocannabinol can be difficult, due to the slow development of equilibrium between plasma and fat-bound Δ^9-tetrahydrocannabinol.

Pharmacodynamics

Pharmacology

There are two types of cannabinoid receptors that have been definitively identified. Cannabinoid-1 receptors are widely expressed in the central nervous system, particularly in the hippocampus, cortex, cerebellum, and mesolimbic dopamine system. Cannabinoid-2 receptors were first identified on immune cells and thought to exist only in the periphery, but have recently been shown to be expressed by neurons and glial cells in the brain. http://www.ncbi.nlm.nih.gov.libproxy.uthscsa.edu/pubmed/18654765.

Cellular Effects

Both cannabinoid-1 and cannabinoid-2 receptors are G protein-linked receptors with a homologous structure to other, similar receptor proteins. These receptors contain seven transmembrane spanning domains with an extracellular head and intracellular tail [196]. Cannabinoid receptors are thought to associate primarily with the G_i/G_o family of G proteins, resulting in inhibition of adenylate cyclase and inhibition of calcium channels upon receptor activation [180]. However, more recent evidence suggests that at least the cannabinoid-1 receptor may associate with alternative second messenger systems depending on the agonist or tissue preparation [78].

Tissue Effects

Due to the activated receptor complex coupling with inhibitory G proteins, cannabinoid agonists tend to have inhibitory effects. Cannabinoid-1 receptors are enriched in brain and are generally thought to function as inhibitory feedback modulators of pre-synaptic neurons [235]. Stimulation of post-synaptic neurons results in liberation of membrane-bound endogenous cannabinoid agonists which migrate back across the synapse to the pre-synaptic membrane. Stimulation of cannabinoid-1 receptors then inhibits further production or release of neurotransmitter [235].

Both cannabinoid-1 and cannabinoid-2 receptors appear to promote neurogenesis, particularly in the hippocampus [112, 183]. However, the progenitor cells that result from the application of cannabinoid agonists remain undifferentiated, awaiting further signaling by other molecules. It remains unclear whether the levels of Δ^9-tetrahydrocannabinol and other cannabinoid agonists ingested by cannabis users are able to produce these effects.

Immune Effects

Generally, cannabinoids consumed during moderate marijuana use have little effect on immune system function; however, immune function can be suppressed in cells directly exposed to smoke [121]. Consequences of heavy use on immune function remain unclear. Immune cells express cannabinoid-2 receptors, with expression levels in B cells > natural killer cells > monocytes > neutrophils > T cells. Cannabinoid signaling is involved in migration of immune cells. Immune cells migrate up the concentration gradient toward the endogenous cannabinoid 2-arachidonoylglycerol. Agonists (including the partial agonist Δ^9-tetrahydrocannabinol) interfere with this chemotaxis, and this inhibition of cell migration is antagonized by cannabinoid-2 receptor antagonists [160]. Studies leading to this conclusion were performed in vitro with levels of cannabinoids unlikely to be found in recreational cannabis users. Indeed, recreational use of cannabis by immunocompromised individuals does not appear to result in increased HIV viral load or reduce the circulating T lymphoctes [1, 37].

Systemic Effects

Cannabinoid-1 receptors are highly enriched in the central nervous system, particularly in the hippocampus, cerebellum, cortex, and mesolimbic dopmaine system [196]. Cannabinoid-1- specific agonists produce characteristic effects associated with cannabinoids, including hypothermia, antinociception, locomotor depression, and ataxia [44]. Cannabis intoxication in humans produces sedation, euphoria, time dilation, dry mouth, and perceptual disturbances [173].

Therapeutic Effects

Recently, Western medicine has rediscovered potential therapeutic uses for cannabis. Because Δ^9-tetrahydrocannabinol simulates appetite and inhibits emesis, it has been used as a treatment for wasting due to chemotherapy in cancer patients as well as in HIV patients [1, 124]. Because Δ^9-tetrahydrocannabinol produces antinociception, it has been used as an adjunct to treat peripheral neuropathic pain in HIV and other patients [193]. The anti-spastic properties of cannabis have led to its use in individuals with multiple sclerosis, and its intraoptic pressure-lowering properties have led to its use in glaucoma [43, 124]. Clearly, the endogenous cannabinoid system is a rich target for therapeutic agents; however, promoting smoking as a delivery system is generally frowned upon. Thus, other delivery systems have gained traction in recent years [82, 94, 193].

Toxicology

Apoptosis

Application of Δ^9-tetrahydrocannabinol to cultured hippocampal neurons can result in cell death due to apoptosis. Chan et al. [36] treated

hippocampal slices from adult female rats with Δ^9-tetrahydrocannabinol (0.2, 0.38, 0.5, 1, and 2 μM) daily and assessed cell viability over 10 days. Δ^9-Tetrahydrocannabinol concentrations of ≥0.5 μM resulted in dose- and time-dependent decreases in cell viability over the first 6 days. The apoptotic effect of Δ^9-tetrahydrocannabinol appears to be mediated by cannabinoid-1 receptor mediated activation of c-Jun N-terminal kinase, initiating the caspase-3 programmed cell death pathway. However, in aggregating brain cell cultures consisting primarily of neurons, glia, or a mixture of the two, repeated treatment with 1 and 2 μM did not result in cell death, though GABAergic, cholinergic, and astrocytic markers were reduced following treatment [163].

It is important to note that these concentrations of Δ^9-tetrahydrocannabinol are likely higher than those achieved in vivo. Postmortem brain samples in cannabis users revealed Δ^9-tetrahydrocannabinol levels ranging from 3 nM to 0.1 μM, well below concentrations used in in vitro studies [169]. Blood levels were lower than brain levels in every subject. Consumption of a marijuana cigarette (3.55% Δ^9-tetrahydrocannabinol) resulted in Δ^9-tetrahydrocannabinol levels up to 0.85 μM; however, peak levels were rapid in onset and dissipated rapidly [105]. Thus, the relevance of apoptosis due to concentrations of Δ^9-tetrahydrocannabinol at or above 0.5 μM remains unclear. Further studies designed to examine apoptosis following systemic Δ^9-tetrahydrocannabinol administration would help clarify the impact of Δ^9-tetrahydrocannabinol on neuronal cell death.

Lung Cancer

Because smoked cannabis delivers comparable or even higher levels of tar than tobacco cigarettes, there is some interest in the relative risk of developing cancer due to chronic use [204, 231, 257]. Such studies are difficult to undertake as many cannabis users also use other recreational substances, especially tobacco [6]. To date, studies have reported mixed results [212, 238]. Recently, a case-control study was reported using adults identified by the New Zealand Cancer Registry [6]. Age-matched controls were randomly selected from the electoral roll. In this study, cannabis use, broadly defined, did not increase the relative risk for the development of lung cancer. However, heavy cannabis use (>10.5 cigarettes/day/year) did significantly increase the risk for developing lung cancer after adjusting for age, ethnicity, tobacco use, and family history of lung cancer. Thus, smoking cannabis does appear to pose a risk for subsequent development of lung cancer, but only if used at extremely high levels.

Head and Neck Cancer

While heavy cannabis use may lead to the development of lung cancer, cannabis use is not linked to increased incidence of head and neck cancer [6]. Although heavy use of cannabis (>8.3 cigarettes/day/year) resulted in a slight increase in the prevalence of head and neck cancers, this increase was non-significant. In contrast, alcohol or tobacco use significantly increased the risk of developing head and neck cancer in this study.

Mental Disorders-Psychosis

Perhaps the most controversial, potentially toxic effect of cannabis at present is a link between cannabis use in adolescence and subsequent development of psychosis. Cannabis use can result in acute psychotic episodes [140]. More recent studies have suggested that prolonged cannabis use during adolescence can increase the likelihood of psychotic symptoms at age 26.

Depression

Few studies have investigated links between cannabis use and major depressive disorder. Wilcox et al. [248] and Lynskey et al. [148]

found that initiation of cannabis use during adolescence increased the risk of subsequent depressive disorder. However, these studies were not conclusive. Further, basic research has demonstrated an anti-depressive effect of indirect cannabinoid agonists [22, 86]. Thus, a causal link between cannabis use and depression has not been decisively established.

Drug Addiction

Perhaps the most contentious debate over possible psychiatric sequelae of cannabis use relates to the "gateway" theory. That is, that use of cannabis leads to an increased likelihood of subsequent addiction to other illicit substances [170]. Currently, the most widely held opinion is the correlated vulnerabilities theory which posits a predisposition toward illicit substance use. Thus those who use cannabis could have a more permissive attitude toward illicit substances in general and may be more willing to try other illicit substances. Further, because cannabis is only available on the black market, it is often purchased from sellers who also deal in other illicit substances.

The alternative theory is that cannabis use changes the neurobiology of the initiate in ways that promote subsequent addictions. Lynskey et al. [148] report that cannabis use increases the risk of subsequent drug use in twins independent of early-onset alcohol and tobacco use or other behavioral or environmental factors. Cannabis is often the first illicit drug used by those who proceed on to addictions to other illicit substances (although it should be noted that alcohol and tobacco, which are typically used prior to cannabis, are technically illegal for adolescents in the United States). Indeed, tobacco use appears to precede and predict cannabis use [116]. However, more recently, Patton et al. [190] reported that cannabis use precedes and predicts tobacco use. Thus, it does not appear that the "gateway" phenomenon is specific to cannabis, and these results support the correlated vulnerabilities theory.

Treatment of Cannabis Addiction

No pharmacotherapy is presently approved for use in cannabis dependence. The development of cannabinoid-1 receptor antagonists such as rimonabant has provided a potential candidate, though approval for clinical use of rimonabant in the United States was recently denied due to safety concerns [134]. At present, the only treatments shown to be effective for cannabis addiction or dependence are behavioral therapies, including cognitive behavioral therapy, motivational enhancement therapy, and contingency management or some combination of these three [28]. Due to the controversy surrounding the clinical relevance of cannabis dependence and addiction, potential treatments for the disorder have not been as widely researched as for other substance use disorders such as alcohol or cocaine.

Nicotine

History

Tobacco is a plant native to the Americas. Prior to domestication, only one strain was probably existant; however, propagation of tobacco use across the world under widely varying conditions has produced up to 40 unique species [242]. Likely for thousands of years, tobacco was used by pre-Columbian Americans in religious ceremonies. Shamans used tobacco in combination with other substances to simulate near-death experiences [242].

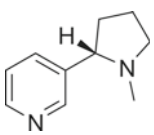
Tobacco was introduced to Europe by Christopher Columbus's crew in the late 1400s from the Bahamas. The natives they encountered smoked cigars which they called *tabacos*. Tobacco was rolled into maize leaves and smoked. Natives of Hispanola burned tobacco over open coals and inhaled the smoke through the nose. The Aztecs smoked tobacco mixed with fragrant herbs and resins from clay pipes, but also insufflated dried, crushed leaves (snuff), and chewed leaves mixed with lime. However,

pre-Colombian tobacco use appears to have been confined to North and Central America as the people of South America (with the notable exception of Peru) did not produce pipes or other smoking devices, nor was tobacco part of their folklore or culture before the arrival of Spaniards [242]. In 1559, Jean Nicot visited a pharmacy in Lisbon and brought tobacco products back to France [195]. Very soon afterward, the use of snuff (kept in sufficiently impressive boxes) was widespread among the nobility of France. For introducing this plant to greater Europe, the genus of tobacco (*Nicotiana*) and its primary psychoactive constituent (nicotine) bear the name of Nicot [195].

The United States was established, in part, to produce tobacco to meet the growing demand in Europe. From the 1600s on, tobacco use spread widely and quickly around the world. Only within the past 40 years, as the serious health concerns arising from tobacco use have become generally accepted have smoking rates begun to decline. From 1965 to 2006, smoking prevalence among adults in the United States has declined from between 40 and 50% to between 20 and 30% (Centers for Disease Control and Prevention's Office on Smoking and Health).

Chemical Properties

The primary active ingredient in tobacco is nicotine. The structure of nicotine is shown in Fig. 10. Nicotine has a molecular weight of 162.26 g/mol and is soluble in water. Nicotine extracted from tobacco in water has been used as an insecticide since 1746 [195].



NICOTINE

Fig. 10 Structure of nicotine

Pharmacokinetics

Routes of Administration

Tobacco is most commonly rolled into cigarettes and smoked. This hasn't always been the case. Until the twentieth century, tobacco was most commonly chewed, insufflated as snuff, or smoked in pipes [178, 242]. The advent of cigarette rolling machines led to increased production capacity and ultimately increased consumption of cigarettes. During the 1900s, cigarette manufacturers expended enormous resources on developing improvements in the paper, filters, flavorings, and even the tobacco blends used in cigarettes in order to produce brand-specific cigarette qualities and to increase consumer desire and demand [178].

Inhalation of cigarette smoke results in a rapid transfer of nicotine from the lungs into the blood and then into the brain. Nicotine migration from inhaled smoke to lung to brain within 10 s has been linked to its high abuse and addiction liability [96], though this has recently been questioned [52]. Because nicotine is a polar compound (weak base with pKa = 8), the use of ammonia during the production process results in a free-base form of the compound which speeds the transfer from lung to blood. Tobacco manufacturers insist that ammonia is used in the production of cigarettes to enhance the flavor of the product, rather than to enhance the psychopharmacological effects of nicotine. However, industry documents show that tobacco companies have known that the use of ammonia enhances nicotine delivery for several decades [252].

Tobacco can also be smoked loose in a pipe, or rolled into tobacco leaves as a cigar. Many users perceive that such use is less harmful that smoking tobacco in cigarettes. Reasons for these beliefs include the notion that nicotine is an additive in cigarettes but is not present in cigar or pipe tobacco, that cigar or pipe tobacco is less processed or "more organic", and that cigar or pipe smoking behavior is typically more moderate than cigarette smoking [230]. In fact,

smoking tobacco in any formulation presents a similar health risk of developing lung, larnyngeal, or oral cancers as well as other diseases that increase morbidity and mortality [230].

Smokeless tobacco includes snuff, which is insufflated, dip or chew which is kept in the mouth in contact with the buccal lining, as well as several newer formulations including snus, a Scandinavian snuff product which is held in the mouth inside a pouch. While these forms do not expose the user or bystanders to harmful smoke, smokeless tobacco contains known carcinogens. Exposure to nitrosoamines is extremely high in users of smokeless tobacco, and over a 20-year period of use, exposure levels can reach those known to produce tumors in rodents [20]. Although results are mixed and at times difficult to interpret due to differences in socioeconomic status, diet, and genetic background, use of smokeless tobacco generally increases the risk developing cancer (especially oral, esophageal, and pancreatic cancers), though not as much as use of smoked tobacco.

More recently, electronic cigarettes and other novel nicotine delivery devices have been manufactured [245]. These cigarettes contain no tobacco and do not burn. Rather, a battery powered atomizer heats a nicotine formulation contained in a disposable filter pack. Users puff on the device just as they would puff on a tobacco cigarette and the tip glows red to simulate the smoking experience. Because the user and bystanders are not exposed to smoke or tobacco, these products are touted as safer than other tobacco formulations. However, the cost is more prohibitive than tobacco products, and no long-term data on the potential health consequences or maintenance of use are yet available on these devices.

Distribution/Bioavailability

A dose of 60 mg of free-base nicotine is considered lethal in humans [195]. Even a dose as low as 4 mg can produce symptoms consistent with acetylcholinesterase inhibitor poisoning, including salivation, vomiting, muscle weakness, convulsions, and fibrillation. Smoke from modern cigarettes yields between 1 and 2 mg of nicotine per cigarette. Nicotine replacement gum is sold in 2 and 4 mg formulations, with the higher dose recommended for heavy (>25 cigarettes/day) smokers who presumably have developed tolerance to nicotine (Nicorette web site).

Metabolism/Elimination

In animals, only a small portion of administered nicotine is eliminated unchanged. Nicotine and its metabolic products are largely excreted in urine, with a single dose requiring 16 h for complete elimination [253]. Nicotine is metabolized to cotinine primarily by the liver, specifically by CYP2A6, CYP2B6, and CYP2E1 [17]. Cotinine has a longer half-life than nicotine (16 h vs. 2 h, respectively) and thus is increasingly used as a clinical biomarker of recent (2–3 days) nicotine use [17].

Pharmacodynamics

Generally, nicotine has a biphasic dose-effect curve, with low doses producing tachycardia, hypertension, and general arousal and higher doses producing bradycardia, hypotension and sedation [17]. Still higher doses can produce salivation, emesis, and convulsions. All of these effects of nicotine are subject to rapid and dramatic tolerance upon continued use. Tolerance to central nervous system and cardiovascular effects can occur within a day of use (with a return to morning levels due to abstinence imposed by sleep).

Pharmacological Effects

Nicotine binds to nicotinic acetylcholine receptors. These receptors are located in the central nervous system and distributed pre-synaptically, post-synaptically, and on the cell soma [197].

The nicotinic receptors consist of pentomers composed of either five alpha (α2–α10) subunits or a combinations of alpha and beta (β2–β4) subunits [17, 197]. The most abundant subunits are the α4 and β2, and receptors comprised of these subunits may account for 90% of all nicotine binding sites in the brain [17]. When acetylcholine or nicotine binds to the recognition site at the interface between an alpha subunit and an adjacent (alpha or beta) subunit, the conformation of the receptor changes which opens a channel to allow sodium and calcium to enter the cell [197]. This, in turn, facilitates the release of neurotransmitters—particularly dopamine in the midbrain region but also norepinephrine, gamma-aminobutyric acid, glutamate, and endorphins [17]. Because midbrain dopamine appears to be a common pathway activated by drugs of abuse and other pleasurable events, it is this action that is believed to be central to the addictive nature of tobacco [17].

Tissue Effects

In brain, acute administration of nicotine leads to a complex pattern of effects. As noted above, nicotine has a direct effect on neurons, facilitating release of neurotransmitters including norepiniephrine. The release of norepinephrine from the adrenal cortex as well as stimulation of the reticular formation results in increased arousal reflected by a decrease in alpha activity of an electroencephalagram [153]. Respiration is increased due to direct stimulation of the medulla [153]. Nicotine also stimulates the brain region responsible for emesis, leading to vomiting following high doses or in inexperienced users [153].

In the periphery, nicotine receptors are found primarily in the neuromuscular junction of voluntary muscles [153]. Nicotinic stimulation of these receptors can lead to tremor. In the cardiovascular system, nicotine increases heart rate and constricts capillaries in the skin, which lead to increased blood pressure [153]. Nicotine also inhibits stomach secretion and stimulates bowel activity [153].

Systemic Effects

Because nicotine produces rapid and profound tolerance, systemic effects of nicotine differ between smokers and non-smokers. In smokers, nicotine improves motor performance (in simulated driving tasks) and learning but impairs fine motor control due to the voluntary muscle tremor it produces [153]. While nicotine administration results in heightened arousal, most smokers report that nicotine is relaxing. This paradoxical effect on mood has been widely studied and may owe more to the other trappings of smoking (holding the cigarette, lighting it, and stopping other activities to focus on the act of smoking) rather than to a direct effect of nicotine [153]. Clearly, nicotine is reinforcing and promotes subsequent seeking and consumption of the substance, as evidenced by the high rates of addiction to nicotine [153].

Toxicology

Acute

High doses of nicotine can lead to respiratory depression and increased secretion of saliva and mucus similar to the effects of a cholinesterase inhibitor. As previously noted, nicotine can increase blood pressure and induce vomiting.

Withdrawal

Tobacco use leads to profound tolerance [17]. Abrupt cessation of nicotine leads to a wide array of withdrawal signs and symptoms including anxiety, dizziness, nausea, constipation, inability to concentrate, weight gain, and sleep disturbances [153]. The use of nicotine replacement or varenicline can minimize these problems [136].

Cardiopulmonary System

Toxic effects of tobacco use on the lungs are due to the inhalation of smoke rather than to direct

effects of nicotine. Ash and tar are deposited in the lungs and pyrolytic compounds in the smoke, particularly benzo[a]pyrine, which is metabolized into a carcinogenic compound by P-450 enzymes in lung tissue [195, 219]. Nicotine inhibits the action of cilia in the lungs which normally would move the tar up and out of the lungs and into the esophagus, leading to increased exposure to these toxic chemicals [120, 153]. Ultimately, this repeated insult to the lining of the lungs can lead to emphysema and lung cancer [187, 245].

Tobacco use is clearly linked to an increased risk of heart disease. Direct effects of nicotine on the heart and vasculature are compounded by effects of carbon monoxide and other pyrolytic compounds derived from the accompanying smoke [153]. Reduced systemic oxygen perfusion further taxes the heart and brain. Additionally, smoking contributes to the deposition of cholesterol on the vascular walls causing atherosclerosis [153]. This also reduces blood perfusion and increases the circulatory pressure.

Stroke

Because smoking is clearly linked to vascular disease, one might assume that smoking could be causally linked to acute cerebral ischemic events (stroke). However, such a relationship has been difficult to demonstrate. In a literature review, Giroud and Dumas [85] concluded that smoking increases the risk of stroke by a factor of 1.7–5.7. Despite the relative lack of data demonstrating a causal link, tobacco use is contraindicated in those at risk or recovering from stroke primarily due to its hypertensive effects [51, 73].

Cancer

While the link between some cancers and smoking is debated [153], the link between smoking and lung cancer is clear. By one estimate, 90% of all lung cancer is attributable to exposure to tobacco smoke [245]. A major constituent of smoke produced by burning tobacco is benzo[a]pyrene, which is oxidized by a P-450 enzyme to trans-7, 8-diol-9, 10-epoxide, a potent carcinogen [195]. While the use of smokeless tobacco can certainly reduce the risk of lung cancer, smokeless tobacco may lead to an increase in oral, esophageal, and pancreatic cancer [20]. Nitrosoamines that naturally occur in tobacco at extremely high levels are likely the causative element in these cancers, though carcinogenic effects of nicotine itself may also play a role by promoting the growth of cancer cells [20, 34].

Therapeutic Effects

Nicotine can improve cognitive function, especially in those afflicted with neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. The use of nicotinic agonists in such individuals has recently been suggested [39]. However, due to the known perils of smoking and even smokeless nicotine delivery, such therapeutic use awaits the development of novel nicotinic agonists as well as improved delivery methods.

Treatment for Cessation of Smoking

A vast array of drugs have been tested as pharmacotherapeutics for smoking cessation [136], yet, few of these treatments have proven success over placebo. Presently, the best candidates for pharmacotherapy of smoking include bupropion and nicotine (delivered via gum or a transdermal patch formulation). Varenicline is an exciting new development currently approved as a smoking cessation therapy. Additionally, recent studies suggest that contingency management may be an effective means to reduce smoking in those who wish to stop as well as those who do not.

Bupropion appears to be effective in some individuals [249]. It works by blocking reuptake of synaptic dopamine and norepinephrine, which are thought to be important in the reinforcing and conditioned aspects of nicotine effects, respectively [136]. Nicotine replacement therapy has

been shown to be effective in some individuals. Nicotine is provided in chewing gum or on a transdermal patch. Smokers can use the gum as desired while the patch is applied and remains continuously affixed. Nicotine replacement reduces the urge to smoke by providing an alternative means of administration. However, due to potential teratogenic effects of nicotine, its use in pregnant and nursing mothers has been debated [223]. Varenicline is a nicotinic receptor partial agonist. By occupying nicotine binding sites, it can blunt or block receptor activation by nicotine yet, due to its low efficacy agonist effects, provides a low level of nicotinic signalling on its own. This compound is approved for use, yet some questions remain over its long-term safety, particularly regarding potential for development of depression, especially during smoking cessation [106, 198]. Taken together, several promising pharmacotherapies (including bupropion, nicotine replacement and varenicline) exist for treatment of tobacco addiction, each of which is more effective than placebo [63].

In addition to pharmacotherapies, behavioral therapies for smoking have been shown to be effective [131]. Most promising is contingency management. In this procedure, reducing tobacco use is reinforced, usually with a monetary payout contingent on reduced carbon monoxide or salivary cotinine levels. Even those not wishing to stop smoking reduce their consumption of cigarettes when subjected to contingency management [132]. Combining pharmacotherapy with behavioral therapy may be more effective than either alone, though this has yet to be definitively confirmed [165].

Inhalants

History

Probably the first wave of inhalant abuse was launched by the discovery of the euphoric properties of ether. During a short-lived prohibition on alcohol in Ireland during the late nineteenth century, the ethanol-like properties of ether made it an attractive alternative [194]. Volatile substance abuse was first described in 1951, and reports of "sudden sniffing deaths" began appearing in the 1960s [142]. It was at this time that amyl nitrate became widely available [14]. After over-the-counter sales of amyl nitrate were curtailed, other related nitrates were substituted, as was nitrous oxide in the form of small canisters used as whipped cream propellant and solvents such as those found in fuels, paints, and other industrial products. The median age of first inhalant use is 13 years [142]. The lifetime prevalence of use is similar in girls and boys [142]. Sniffing is inhalation directly from a container, huffing is pouring the volatile liquid directly on fabric and placing the fabric over the nose or mouth, and bagging is when the solvent is sprayed into a bag and rebreathed [142].

Mechanism of Action

Inhalants are generally grouped into three categories. The most commonly used are volatile hydrocarbons, which includes fuels such as gasoline and solvents such as toluene [142]. Volatile alkyl nitrites have distinct pharmacologic and behavioral effects and are considered a unique class of inhalant [142]. Finally, nitrous oxide is not a hydrocarbon but is widely abused as an inhalant [142].

Historically, the Meyer-Overton hypothesis was invoked to explain inhalant action. Inhalants are highly lipophilic, and the Meyer-Overton hypothesis posits that anesthetic action is related to the disruption of the orientation of membrane-bound proteins by perturbing the lipid membrane, especially in the central nervous system. This hypothesis was also used for many years to explain the actions of ethanol. However, as with ethanol, more recent evidence suggests that specific alterations in proteins responsible for neurotransmission, particularly glutamatergic, GABAergic and opioidergic pathways.

Smooth Muscle Relaxation

Although other volatile hydrocarbon effects are apparent at specific proteins in the central nervous system, the alkyl nitrites have not been shown to specifically alter proteins involved in neurotransmission. Rather, these compounds are thought to produce smooth muscle relaxation, perhaps by liberating nitrous oxide [142]. Alternatively, effects due to these drugs could be indirect, resulting from biotransformation into other pharmacologically active chemicals, such as isobutyl alcohol [142].

N-Methyl-D-Aspartate

The first evidence that inhalants could alter ion channel function specifically, rather than non-specifically by inserting in the lipid bilayer, came from Cruz et al. [48]. In that study, toluene dose-dependently inhibited inward cationic currents through recombinant Xenopus *N*-methyl-*D*-aspartate receptors. The site of action appeared to be in the NR1/NR2B subunit combination, though other combinations were also affected to a lesser extent. Addition of glycine or *N*-methyl-*D*-aspartate did not alter the inhibitory effect of toluene, which would be expected if toluene was acting as an antagonist at the *N*-methyl-*D*-aspartate or glycine site. It is important to note that *N*-methyl-*D*-aspartate function was inhibited at concentrations well below those that altered the conductance of the membrane, indicating that the effects were not due to general disruption of the membrane. α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptors were not similarly affected. Subsequently, Bale [13] replicated these findings in primary neuronal cultures. Additional evidence for specific action of inhalants at *N*-methyl-*D*-aspartate receptors is the upregulation of *N*-methyl-*D*-aspartate receptors following chronic exposure [23]. Like the volatile hydrocarbons, nitrous oxide also inhibits *N*-methyl-*D*-aspartate receptors [142].

Gamma-Aminobutyric Acid

Volatile hydrocarbons increase gamma-aminobutyric acid-A receptor function [142]. The site of action on gamma-aminobutyric acid-A receptors appears to be the α1β1 subunit [23]. One volatile convulsant solvent, flurothyl, inhibits recombinant gamma-aminobutyric acid-A receptor. Nitrous oxide does not influence GABAergic signalling [142]. Taken together, volatile hydrocarbon inhalants (excepting alkyl nitrites) share similar pharmacological effects with ethanol; namely inhibition of *N*-methyl-*D*-aspartate receptors and enhancement of GABAergic signalling.

Dopamine

Based on the widespread abuse of inhalants, and the involvement of the dopaminergic system in reinforcing actions of many abused drugs, one might expect inhalants to enhance dopaminergic signalling. Indeed, brief exposure to toluene increases dopaminergic firing from the ventral tegmental area and increases extracellular dopamine in the nucleus accumbens [23]. Although this evidence is consistent with dopaminergic effects of other abused drugs, it is likely that these effects are due to indirect actions of solvents at gamma-aminobutyric acid receptors, rather than to a direct effect on dopamine receptors [23].

Other Receptors and Ion Channels

There is some evidence of opioidergic involvement in the effects of inhalants. The antinociceptive effects of nitrous oxide are antagonized by naloxone, though the anesthetic effects are not [142]. Acute toluene exposure increases μ-opiod receptor protein levels in the brainstem [146]. There is also evidence of volatile organic solvents affecting serotonin-3 receptors, P2X receptors, and voltage-gated ion channels, though the relationship between these effects and behavioral effects remains murky [23].

Pharmocokinetics

Generally, inhalants are highly lipophilic, and are rapidly absorbed and eliminated. Inhalants are eliminated unchanged by respiration, are metabolized in the liver, or both [142]. Nitrous oxide is eliminated unchanged by respiration while aromatic hydrocarbons are largely metabolized by hepatic mechanisms. Alkyl nitrites may be converted to alcohols as well as nitric oxide donors. Metabolism of aromatic hydrocarbons in the liver occurs via the cytochrome P450 system. The CYP2E1 enzyme appears to be the primary enzyme recruited [142]. Extrahepatic metabolism of aromatic hydrocarbons occurs to a lesser extent and may result in organ-specific toxicity [142].

Pharmacodynamics

Toluene produces a biphasic effect on locomotion, similar to ethanol. Low doses result in hyperlocomotion, with higher doses progressing from sedation to motor impairment to anesthesia [23]. Inhalants can protect against seizures in animals, though convulsions have also been seen. In humans, inhalants rarely produce convulsions [23]. Toluene exerts anxiolytic effects in animal models, which might be expected due to activity at gamma-aminobutyric acid-A receptors [23]. Rats exposed to toluene chronically show deficits in learning and memory as assessed by the Morris-water maze [23]. This finding is mirrored by clinical evidence of learning and memory deficits in habitual inhalant abusers [142].

Operant work with inhalants is sparse. One major impediment is producing consistent exposure conditions inside of the chamber typically used for such studies. However, operant responding for food is diminished by acute exposure to inhalants, regardless of the schedule of reinforcement employed [23]. Toluene and other solvents share discriminative stimulus effects with other classic central nervous system depressants such as ethanol. This is not surprising considering the effects on gamma-aminobutyric acid-A and *N*-methyl-*D*-aspartate receptors common to these drug classes. While some have reported success at training rodents to self-administer solvents intravenously, establishing inhalant self-administration has yet to be reported [23]. Proper containment of the volatilized solvent and consistent delivery contingent upon an appropriate response will be required to perform such procedures.

Toxicology

Each class of inhalants presents its own unique toxicology. Chronic use of any inhalant can lead to neuropathy. Volatile organic solvents present the most overt and widespread toxicological effects, including cardio, renal, and hepatic toxicities. Amyl nitrites also produce direct toxic effects, while toxic effects of nitrous oxide are indirect.

Volatile organic solvent abuse leads to an array of toxic effects. Most common are neuropathies. Neurological damage is generally not dose-related. However, there may be a relationship between neurological damage and duration of use [146]. Chronic abuse of n-hexane (found in glues and fuel) is associated with peripheral neuropathy, while toluene is associated with cerebellar disease [146]. Neuropathy related to volatile organic solvent use can present as euphoria, hallucinations, headache, and dizziness progressing to slurred speech, confusion, tremor, and weakness [142]. Transient cranial nerve palsy can also occur [142]. Heavy use of these agents leads to white matter degeneration and demyelination evidenced by perivascular macrophages containing coarse or laminar myelin debris [142].

Pulmonary effects are due to either direct damage to lung tissue or by asphyxiation [146]. Hypoxia causes pulmonary toxicity that is usually due to the method of administration (mask/rebreathing) rather than overabundance of hydrocarbons [142]. Also inadvertent aspiration of liquid hydrocarbon can injure tissue [142].

Acute cardiotoxicity is usually the cause of "sudden sniffing death." It is thought that the inhalant sensitizes the myocardium by blocking the potassium current, prolonging repolarization [142]. Chronic use can result in chronic myocarditis with fibrosis and present as palpitations, shortness of breath, syncope and electrocardiographic abnormalities [142]. Renal disorders are especially associated with toluene abuse. In particular, chronic toluene exposure is considered causal for tubular acidosis, urinary calculi, glomerulonephritis, and renal failure [146]. Distal renal tubular acidosis can result in hypokalemia and muscle weakness [142]. Hepatic failure has also been observed, primarily following halogenated hydrocarbon use, such as carbon tetrachloride or refrigerants, probably due to a reactive metabolite [142]. Use during pregnancy increases the risk of premature labor or spontaneous abortion, and neonates can exhibit withdrawal symptoms [146]. Further, use of inhalants during pregnancy is associated with premature, low birth weight and length, small head, developmental delay and reduced neuronal density in rodent studies [142].

Volatile alkyl nitrite use is associated with methemoglobinemia [142]. This may be a result of the ability of these strong oxidants to change the charge on the ferrous ion from $Fe^{2+}$to Fe^{3+}[142]. The most prominent toxic effects of nitrous oxide are due to asphyxiation and auto accidents, rather than to a direct effect of the agent [142]. Chronic abuse can lead to irreversible oxidation of cobalamin (vitamin B12), which leads to aberrations in the myelin sheath [142].

Barbiturates

History

Among classes of abused drugs, barbiturates are relative newcomers with a history of just over 100 years of use and abuse. The primary reason for this rather short history is that, unlike drugs from other pharmacological classes, barbiturates have not been found in nature and had to be developed in the laboratory. In 1864, Adolf von Baeyer synthesized the first barbiturate, malonylurea, which was later named barbituric acid [143]. With the perfection of the synthetic process by Edouard Grimaux in 1879, derivatives of barbituric acid could be widely developed, including diethyl-barbituric acid or barbital, which became the first barbiturate on the market in 1904 [143]. The clinical success of barbiturates led to the synthesis of more than 2,500 different compounds with 50 of them available clinically.

Barbiturates were initially introduced as hypnotics, although other effects became evident with their continued development and clinical use. For example, the anticonvulsant effects were discovered in 1912, the same year that phenobarbital was first available commercially [102, 143]. Systematic use of barbiturates in intravenous anesthesia did not occur until 1927, with pentobarbital introduced in anesthesia in 1930, and thiopental and methohexital introduced later (1936 and 1956, respectively). These therapeutic effects led to the huge popularity and widespread use of the barbiturates, which peaked during the 1930s and 1940s [102]. In addition to the therapeutic effects of barbiturates, adverse effects were also increasing evident. One effect that took very little time to emerge was the development of dependence. Evidence that dependence developed with repeated barbiturate administration appeared in the literature in 1905, 1 year after the introduction of barbital [143]. Another problem associated with the use of barbiturates was fatal overdose. In fact, the two scientists who were responsible for the introduction of barbital in 1904, Josef von Mering and Emil Fischer, are thought to have been dependent on barbiturates and to have died of a possible overdose [143]. The abuse potential of these drugs was not reliably documented until the 1950s [102]. Together, these adverse effects led to the decline of the clinical use of barbiturates, which was further exacerbated by the introduction of the benzodiazepines in the 1960s. This new class of drugs produced similar therapeutic effects with a greater margin of safety. Today, barbiturates

are used clinically for some indications, mostly for certain types of seizures and for induction of anesthesia.

Chemical Properties

Barbituric acid is 2,4,6-trioxohexahydropyrimidine (Fig. 11). Clinically useful barbiturates are formed by the addition of alkyl or aryl groups at position 5 [99]. Salts can result when the carbonyl group on position 2 takes on an acidic character, thereby improving solubility in water and increasing absorption [99]. Thus, sodium salts are more amenable to intravenous administration and are the form of barbiturates used in anesthesia. Although barbiturates are highly lipid soluble, replacing the oxygen at C2 with sulfur decreases partition coefficients, resulting in drugs with shorter onsets and durations of action [99]. These barbiturates, which include thiopental, have been used extensively to induce anesthesia.

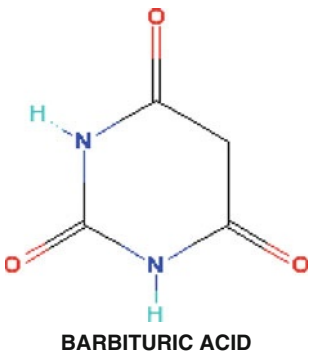


Fig. 11 Structure of barbituric acid. From http://pubchem.ncbi.nlm.nih.gov

Pharmacokinetics

Routes of Administration

Because mechanism of action does not vary among barbiturates, these drugs are generally classified according to their pharmacokinetics, specifically by their duration of action [57]. Differences in formulations, therapeutic use and abuse of barbiturates are due to differences in their duration of action. For example, ultrashort-acting barbiturates, such as methohexital and thiopental, are only available for intravenous use and are used exclusively for induction of anesthesia. Short- to intermediate-acting barbiturates, such as pentobarbital, are available in capsules, suppositories or in solution for intravenous or intramuscular administration. Long-acting barbiturates, such as phenobarbital, are only available for oral use.

Absorption and Distribution

After oral administration, barbiturates are rapidly and completely absorbed from the upper part of the small intestine. Long-acting barbiturates are absorbed more slowly than shorter-acting drugs [255]. Barbiturates are widely distributed, beginning with highly vascularized areas like the brain. For the highly lipid-soluble, ultra-short-acting drugs, these initially high concentrations of barbiturates in the central nervous system decline as the drug distributes to less vascularized areas like muscle and fat [99]. This redistribution of barbiturates from the brain to other tissues contributes to the very short duration of action of these drugs.

Metabolism/Excretion

Barbiturates are almost completely metabolized in the liver before renal excretion, and unchanged barbiturates infrequently appear in urine [255]. Microsomal enzymes oxidate the larger of the two substituent groups at position 5, forming alcohols, phenols, ketones or carboxylic acids [99]. Repeated administration of barbiturates results in the induction of the hepatic enzymes responsible for their inactivation. This metabolic tolerance shortens the half-life of barbiturates as well as that of any other drugs metabolized through the same enzymes.

Pharmacodynamics

Mechanism of Action

Barbiturates act at gamma-aminobutyric acid-A receptors. The gamma-aminobutyric acid-A receptor complex is a transmembrane protein complex that is formed by five subunits with multiple binding sites on each gamma-aminobutyric acid-A receptor. When gamma-aminobutyric acid binds to its distinct sites on this protein complex, channels open and Cl^- enters the cell. Other sites on the gamma-aminobutyric acid-A receptor complex are modulatory sites, and drugs acting at these sites can alter the effects of gamma-aminobutyric acid. Barbiturates act at distinct modulatory sites to facilitate the actions of gamma-aminobutyric acid, thereby increasing Cl^- flux [7]. At large concentrations, barbiturates can activate channels even in the absence of gamma-aminobutyric acid [7, 70, 206].

Pharmacological Effects

The primary pharmacological effect of barbiturates is to decrease activity of the central nervous system. The most prominent effects of barbiturates are their sedative effects, which vary with dose from mild sedation to general anesthesia. These drugs decrease sleep latency and the number of awakenings and can also affect the stages of sleep by decreasing time spent in rapid-eye-movement and slow-wave sleep [99]. Barbiturates can also reduce anxiety, although sometimes this effect is difficult to dissociate from sedative effects. The ability of barbiturates to prevent and reverse convulsions continues to be exploited clinically.

Toxicology

In addition to these therapeutic effects, depression of the central nervous system also accounts for the most serious acute toxicological effect of barbiturates. When central nervous system activity is reduced, there is a concomitant decrease in ventilation. Barbiturates affect both respiratory drive and its rhythmic characteristics, and at large doses, these effects can be severe enough to eliminate respiration. Thus, acute barbiturate overdose can be fatal. The respiratory-depressant effects of barbiturates can also be exacerbated by other drugs, particularly those with actions at gamma-aminobutyric acid-A receptors. Combinations of sublethal doses of barbiturates with drugs like ethanol or benzodiazepines can result in life-threatening decreases in ventilation.

In addition to their respiratory-depressant effects, barbiturates produce several other adverse effects that ultimately led to the decline of their clinical use. Perhaps the most serious problems occur when the drugs are administered repeatedly. Chronic use or abuse of sedative doses of barbiturates can result in the development of tolerance or dependence. In addition to pharmacokinetic tolerance that occurs when hepatic microsomal enzymes are induced, pharmacodynamic tolerance can also develop, which likely involves changes in gamma-aminobutyric acid-A receptor structure or function. One change that occurs in gamma-aminobutyric acid-A receptors during chronic barbiturate treatment is a functional uncoupling of binding sites [259]. Regardless of the mechanism, the development of tolerance has multiple consequences. First, a larger dose or more frequent administration is needed to maintain the desired effect. Because pharmacokinetic tolerance shortens the duration of action of a drug without altering the amount of drug needed to produce an effect, use of larger doses could lead to overdose [255]. Even if overdose is avoided by increasing frequency rather than dose, the escalating intake is more likely to result in the development of dependence and the emergence of a more robust withdrawal syndrome.

A second important consequence of chronic barbiturate treatment is the development of dependence, which is evident when withdrawal signs emerge following abrupt discontinuation of treatment. Signs begin to appear 24 h after the last dose of the barbiturate, peak within 2–3 days

and subside slowly over the next 10–14 days [75, 247]. The withdrawal syndrome has been classified based on the severity of signs and symptoms. For example, mild signs include apprehension, muscle weakness, tremors, twitches, orthostatic hypotension, anorexia, insomnia, anxiety and profuse sweating whereas severe withdrawal includes clonic-tonic seizures and psychosis which usually resembles delirium tremens that are observed when alcohol use is discontinued [247]. Increasing the dose, frequency or duration of chronic barbiturate treatment will increase the severity of the withdrawal syndrome that emerges when treatment is terminated. Because the most serious signs of barbiturate withdrawal can be life threatening, one approach that has been used to decrease barbiturate use while avoiding severe withdrawal signs has been to substitute an equivalent dose of a longer-acting barbiturate, such as phenobarbital, for the drug administered chronically [224]. The slow offset of the longer-acting drug results in the maintenance of more constant blood levels of the barbiturate, thereby preventing the emergence of severe withdrawal; the dose of phenobarbital can be slowly decreased over time until the individual can safely stop taking barbiturates altogether.

Although barbiturate abuse has declined over the last 40 years along with the decline of their clinical use, they have been abused more frequently than other central nervous system depressants except for alcohol. Some people abuse barbiturates exclusively. Often, use of barbiturates began when they were prescribed for the treatment of some disorder. With continued use and possibly escalating intake due to the development of tolerance, dependence also developed leading to the emergence of withdrawal when treatment was discontinued. These abusers continue to take barbiturates to avoid withdrawal, as opposed to taking the drug to treat the condition that prompted the initial use of barbiturates [57]. In contrast, other abusers take barbiturates in small doses, infrequently or for short periods so that dependence does not develop. These abusers often use barbiturates in combination with other drugs of abuse, including ethanol, opioids, and psychoactive stimulants.

Benzodiazepines

History

The history of the benzodiazepines is even shorter than that of the barbiturates. In the 1930s, Dr. Leo Sternbach was working on a chemical group called heptoxdiazines, which did not seem to have biological activity [130]. He moved from Poland to the United States to work for Hoffmann-LaRoche where he resumed his study of these compounds. In 1957, pharmacological effects, including sedative effects, were observed for one of his compounds (Ro#5-0690); the chemists later found that the compound had undergone a molecular rearrangement to become a 1,4-benzodiazepine [130]. Initially, the compound was called methaminodiazepoxide, although the name was later changed to chlordiazepoxide. The clinical effectiveness of chlordiazepoxide was not immediately evident. In fact, chlordiazepoxide was nearly discarded because a large dose was given to geriatric patients, resulting in ataxia [130]. Eventually, more appropriate doses were used and its clinical utility and safety were established. It was introduced in 1960 with the more successful benzodiazepine diazepam introduced in 1963. More than 3000 benzodiazepines have been synthesized, with as many as 35 in clinical use around the world. Because benzodiazepines have a larger margin of safety, as compared with the barbiturates, they quickly became the drugs of choice to reduce anxiety, promote sleep and reverse convulsions. They are still widely used today.

Chemical Properties

Benzodiazepine refers to the chemical structure of the drug, which has a benzene ring fused to a seven-member diazepine ring; benzodiazepines

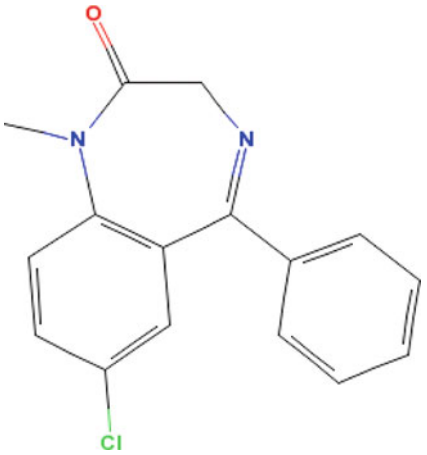


Fig. 12 Structure of diazepam. From http://pubchem.ncbi.nlm.nih.gov

that are used clinically have 1,4-diazepine rings [99]. Substituent groups at positions 1 and 3 can vary widely. Unlike diazepam (see Fig. 12), some benzodiazepines have triazolo (e.g., triazolam, alprazolam) or imidazolo (e.g., midazolam) rings fused at positions 1 and 2 [99]. Another drug with a fused imidazolo ring at positions 1 and 2 also has a methyl group at position 4 and a keto group replacing the ring at position 5; these structural variations dramatically change the pharmacology, resulting in the benzodiazepine antagonist flumazenil [99]. Like barbiturates, benzodiazepines have high lipid:water distribution coefficients; unfortunately, benzodiazepines do not form salts as readily as barbiturates. With exception of midazolam and chlordiazepoxide, which can form hydrochloride salts, benzodiazepines are insoluble in water.

Pharmacokinetics

Routes of Administration

Another similarity between barbiturates and benzodiazepines is that, within each class of compounds, the mechanism of action does not vary. Consequently, benzodiazepines are also generally classified according to their pharmacokinetics, specifically by their duration of action. Short-acting benzodiazepines generally have a half-life of minutes to a few hours; these drugs, which include midazolam, are primarily used for conscious sedation or the induction of anesthesia and are, therefore, available in commercially prepared solutions for intravenous administration. Intermediate-acting benzodiazepines, such as alprazolam or lorazepam, are used orally for anxiety and insomnia, although lorazepam is also available for parenteral administration primarily to reverse convulsions. Long-acting drugs, such as diazepam, are generally used orally.

Absorption and Distribution

The benzodiazepines that are currently used clinically are completely absorbed after oral administration. Once in the systemic circulation, they bind to plasma proteins with the extent of binding varying with lipid solubility from 70% for alprazolam to 99% for diazepam [99]. Redistribution can occur for drugs with the highest lipid solubility.

Metabolism/Excretion

Benzodiazepines are extensively metabolized by several hepatic microsomal systems. The most important aspect of the pharmacokinetics of benzodiazepines is the formation of active metabolites. Although a few benzodiazepines (e.g., lorazepam) are inactivated by the initial metabolic reaction, most are converted to metabolites that have the same mechanism of action as the parent compound. For some drugs, more than one biotransformation reaction is needed to inactivate the drug and often the subsequent reactions occur more slowly than the initial reaction. Consequently, the duration of action of most benzodiazepines has little to do with its half-life in plasma. The hepatic enzymes responsible for metabolism of benzodiazepines are not induced by chronic benzodiazepine treatment.

Pharmacodynamics

Mechanism of Action

Like barbiturates, benzodiazepines act at their own distinct sites on gamma-aminobutyric acid-A receptors where they facilitate the actions of gamma-aminobutyric acid [179]. One distinct difference between benzodiazepines and barbiturates is that benzodiazepines do not activate the channel directly and their actions are dependent on the presence of gamma-aminobutyric acid [92, 221]. Gamma-aminobutyric acid-A receptors are formed by 5 protein subunits which form the ion channel. Based on their amino acid sequence, several classes of subunits have been identified with multiple variants within each class [147]. The large number of subunits that can be combined to form gamma-aminobutyric acid-A receptor complexes indicates that many variations of this complex are possible. The subunit composition of gamma-aminobutyric acid-A receptors is clearly important in forming modulatory sites, particularly benzodiazepine sites. The gamma-aminobutyric acid-A receptor complex often includes 2α, 1β, and 2γ subunits. Benzodiazepine binding sites are formed when a γ_2 subunit is coexpressed with any α and any β [147] with the subtype of the α subunit conferring selectivity to benzodiazepine ligands [60]. Generally, 1,4-benzodiazepines bind with high affinity to benzodiazepine receptors containing an α_1, α_2, α_3, or α_5 subunit and do not bind, or bind with very low affinity, to receptors containing an α_4 subunits [147]. Three non-benzodiazepine drugs (zolpidem, zaleplon, and eszopiclone) have been introduced clinically in the last 15 years that are selective benzodiazepine receptors containing α_1 subunits and they have been used extensively in place of benzodiazepines for the treatment of insomnia.

Pharmacological Effects

The pharmacological effects of benzodiazepines are similar to those of the barbiturates; the primary effect is central nervous system depression. The most prominent effects of benzodiazepines are their anxiolytic, sedative, and anticonvulsant effects, although other therapeutic uses include their use as muscle relaxants or to induce anesthesia. In terms of clinical utility, benzodiazepines are similar to barbiturates in many ways. For example, drugs from these pharmacological classes promote sleep by decreasing sleep latency, the number of awakenings and the time spent in rapid-eye-movement and slow-wave sleep while increasing the time spent in stage 2 sleep [99]. One way in which drugs from these classes differ is their ability to relieve anxiety; the anxiolytic effects of benzodiazepines are evident at doses that do not produce sedation whereas doses of barbiturates that produce anxiolytic effects also produce sedation.

Toxicology

Benzodiazepines are relatively safe drugs. Although central nervous system depression by benzodiazepines results in decreased ventilation, these respiratory-depressant effects are mild. Even when the dose of benzodiazepines is increased, the effects on respiration are not severe enough to be life-threatening. From a clinical perspective, benzodiazepines are much safer than barbiturates because of differences in the severity of respiratory-depressant effects; this larger margin of safety of benzodiazepines has resulted in their widespread use and contributed to the decline of the clinical use of barbiturates. When administered alone, benzodiazepine overdose does not result in life-threatening respiratory depression; however, these effects can be exacerbated by other drugs. Ventilation can be dramatically decreased when benzodiazepines are administered in combination with ethanol, other positive gamma-aminobutyric acid-A modulators or drugs with primary mechanisms of action at receptors other than gamma-aminobutyric acid-A receptors, such as opioids.

Although overdose of benzodiazepines does not result in severe acute effects, their use is limited by other adverse effects, particularly by

effects that occur during chronic treatment. For example, the use of sedative doses of benzodiazepines for 2 weeks can result in the development of tolerance. Escalating intake to maintain the therapeutic effect can exacerbate the development of dependence. In order to avoid both phenomena, physicians generally limit the duration of benzodiazepine use to less than 2 weeks. Because drugs selective for benzodiazepine receptors containing α_1 subunits have sedative effects and are less likely to produce tolerance, the introduction of these drugs has led to a decline in the use of benzodiazepines for insomnia. Tolerance is less problematic when benzodiazepines are used for other indications, such as anxiety, because smaller doses are needed to produce the therapeutic effect and tolerance is less likely to develop under those treatment conditions.

Another consequence of long-term use of benzodiazepines is the development of dependence, and the signs and symptoms that emerge when benzodiazepine treatment is discontinued are similar to those that are evident following termination of barbiturate treatment. Like barbiturate withdrawal, signs and symptoms of benzodiazepine withdrawal can be separated into categories based on their severity. Minor withdrawal symptoms include increased anxiety, involuntary muscle twitches, tremor, progressive weakness, dizziness, visual illusions, nausea, insomnia, weight loss and orthostatic hypotension; major withdrawal symptoms include tonic-clonic seizures and psychosis resembling delirium tremens that occurs when alcohol use is discontinued [182]. More recently, the importance of other withdrawal symptoms, such as sleep disturbances, has been recognized [168, 199]. Although the signs and symptoms of withdrawal are similar for benzodiazepines and barbiturates, the time course for the development of dependence and the emergence of withdrawal varies slightly between these classes of drugs. Benzodiazepine dependence only becomes evident after long periods of treatment, often requiring 3 months or longer [255]. Moreover, because of the long duration of action of benzodiazepines and the formation of active metabolites, withdrawal might not emerge until 3–7 days after discontinuation of treatment. The availability of benzodiazepines with long durations of action increases the feasibility of using a drug with a slow offset to maintain more constant blood levels of a benzodiazepine while slowly reducing the dose. In this manner, benzodiazepine use can be decreased while avoiding the emergence of robust withdrawal.

Like other drugs that act at gamma-aminobutyric acid-A receptors, benzodiazepines are abused, and benzodiazepine abuse appears to be increasing. From 1992 to 2002, admissions for treatment of primary abuse of benzodiazepines increased 79%; during the same period, overall admissions for substance abuse treatment increased 22% (The Drug and Alcohol Services Information System Report, Substance Abuse and Mental Health Services Administration; available at http://www.oas.samhsa.gov/2k5/tranquilizerTX/tranquilizerTX.htm, 2005). Despite these recent increases, the incidence of primary benzodiazepine abuse remains low among the general population; however, benzodiazepine abuse is high in some groups, particularly among people who abuse other drugs. For example, the incidence of benzodiazepine use is high among opioid abusers [77, 88]. Dependence can develop during chronic benzodiazepine abuse, and the emergence of withdrawal can impact treatment outcome. Individuals sometimes prolong their drug use or abuse in order to avoid withdrawal, and relapse is common as they try to alleviate withdrawal symptoms [10]. For example, when treatment is discontinued in those using benzodiazepines for insomnia, the relapse rate is 43% [168]. Similarly, 50% of polydrug abusers experiencing withdrawal from large doses of benzodiazepines resume drug use within 2–3 days, with individuals describing extreme measures taken to avoid withdrawal [217]. Thus, emergence of benzodiazepine withdrawal could have severe consequences in drug abusers, possibly leading to increased abuse of benzodiazepines and other drugs.

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Animal Models of Drug Dependence: Motivational Perspective

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Contents

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Definitions Relevant to Animal Models

Drug addiction, also known as substance Dependence [6], is a chronically relapsing disorder characterized by (i) compulsion to seek and take the drug, (ii) loss of control in limiting intake, and as defined by the present author and others, (iii) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence with a lowercase "d") [63, 107].

Drug addiction has been conceptualized as a disorder that involves elements of both impulsivity and compulsivity, in which impulsivity can be defined behaviorally as "a predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others" [81]. Compulsivity can be defined as elements of behavior that result in perseveration in responding in the face of adverse consequences or perseveration in the face of incorrect responses in choice situations. The compulsivity element is analogous to the symptoms of Substance Dependence outlined by the American Psychiatric Association (i.e., continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance) [6].

Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle comprising three stages—preoccupation/

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_15,

anticipation (craving), binge/intoxication, and withdrawal/negative affect. Impulsivity often dominates at the early stages, and compulsivity dominates at terminal stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior [57] (Fig. 1). Negative reinforcement can be defined as the process by which removal of an aversive stimulus (e.g., negative emotional state of drug withdrawal) increases the probability of a response (e.g., dependence-induced drug intake). These three stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state known as addiction [63]. The present review will focus on the role of animal models of dependence associated with the negative emotional state of the withdrawal/negative affect stage of the addiction cycle (Fig. 1).

The diagnostic criteria for addiction described by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [6] have evolved over the past 30 years, with a shift from the emphasis and necessary criteria of tolerance and withdrawal to other criteria directed more at compulsive use. In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, tolerance and withdrawal form two of seven potential criteria. The criteria for substance Dependence closely resemble those outlined by the *International Statistical Classification of Diseases and Related Health Problems* [147]. The number of criteria met by individuals meeting the criteria for addiction vary with the severity of addiction, the stage of the addiction process, and the drug in question, but the criteria are well represented by symptoms that coalesce around the withdrawal/negative affect and preoccupation/anticipation stages [22, 24] (Fig. 1).

Unfortunately, the word "dependence" can have multiple meanings. Any drug, including non-abused drugs, can produce dependence if it is defined as the manifestation of a withdrawal syndrome upon cessation of drug use. However, meeting the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria for substance Dependence is much more than a manifestation of a withdrawal syndrome; it is equivalent to addiction. For the purposes

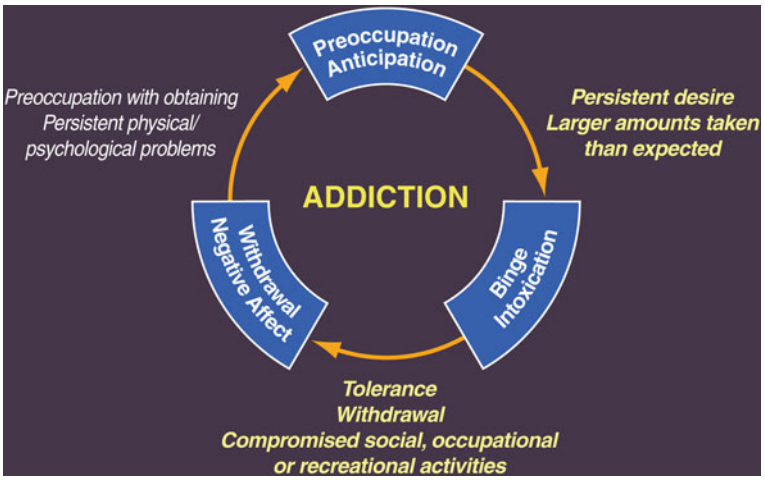

Fig. 1 Diagram describing the three stages of the addiction cycle—preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect—from a psychiatric perspective with the different criteria for substance dependence incorporated from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. Bolded symptoms from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, reflect changes during the withdrawal/negative affect (tolerance, withdrawal, and compromised social, occupational, or recreational activities) stage and the increased motivation to take the drug as a result (persistent desire, larger amounts taken than expected). Reprinted with permission from [59] (American Psychiatric Publishing Inc.)

of this chapter, "dependence" with a lowercase "d" will refer to the manifestation of a withdrawal syndrome, whereas "Dependence" with a capital "D" will refer to substance dependence defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, or addiction. The terms "substance Dependence" (defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition), "addiction", and "alcoholism" will be held equivalent for this chapter.

Important for the present chapter is the distinction between physical or somatic signs of withdrawal and the motivational signs of withdrawal. Both reflect dependence with a lowercase "d," but only the motivational signs of withdrawal will be argued to be relevant to the syndrome of addiction (see discussion of somatic vs. motivational withdrawal below). Thus, although historically the diagnostic criteria have focused on physical (somatic) signs of withdrawal, more motivational signs have been neglected, and the argument of the present treatise is that motivational signs of withdrawal remain a critical aspect of the addiction process.

Different drugs produce different patterns of addiction with emphasis on different components of the addiction cycle. Probably the classic drugs of addiction are opioids. A pattern of intravenous or smoked drug taking evolves, including intense intoxication, the development of tolerance, escalation in intake, and profound dysphoria, physical discomfort, and somatic withdrawal signs during abstinence. Intense preoccupation with obtaining opioids (craving) develops that often precedes the somatic signs of withdrawal and is linked not only to stimuli associated with obtaining the drug but also to stimuli associated with withdrawal and internal and external states of stress. A pattern develops in which the drug must be obtained to avoid the severe dysphoria and discomfort of abstinence. Other drugs of abuse follow a similar pattern but may involve more the binge/intoxication stage (e.g., psychostimulants and alcohol) or less binge/intoxication and more withdrawal/negative affect and preoccupation/anticipation stages (e.g., nicotine and cannabinoids).

Animal Models of Withdrawal

Somatic Signs

Two drugs, opioids and alcohol, provide classic examples of the somatic signs of withdrawal and have served as models for measures of withdrawal per se. Indeed, as discussed above, these somatic measures are basically a "red herring" for the more motivational measures of withdrawal from the perspective of negative reinforcement, drug seeking, and craving associated with acute and protracted abstinence. However, the somatic signs of withdrawal are an index of dependence with a lowercase "d" and provide a quantifiable measure by which to assess the level of dependence and to relate to more motivational measures.

For opioids, somatic withdrawal signs in humans are dramatic, dose- and duration-of-abstinence-dependent, and include a number of overt measurable signs such as yawning, lacrimation, rhinorrhea, perspiration, gooseflesh, tremor, dilated pupils, anorexia, nausea, emesis, diarrhea, weight loss, and elevations in temperature and blood pressure [49]. In animals (rodents), opioid withdrawal signs are well characterized when precipitated with administration of a competitive opioid antagonist such as naloxone [36, 76]. A weighted scale was developed and widely adopted that included graded signs of weight loss, diarrhea, escape attempts, wet dog shakes, abdominal constrictions, facial fasciculations/teeth chattering, salivation, ptosis, abnormal posture, penile grooming/erection/ejaculation, and irritability [36] (Table 1). When the somatic signs of opioid withdrawal are directly compared with more motivational measures, the motivational measures are more sensitive and show more efficacy in defining the withdrawal state [112]. Spontaneous withdrawal shows many of the same signs, but they are significantly less intense [92].

For alcohol, the somatic signs of withdrawal in humans are equally dramatic but also life threatening and are characterized by tremor,

increases in heart rate, increases in blood pressure, increases in body temperature, anorexia, and convulsions. In its severest form, alcohol withdrawal can result in pronounced hyperthermia that can evolve into delirium tremens, a state of marked sympathetic hyperactivity, hyperthermia (which can be fatal), and hallucinations [40]. In animals (rodents), alcohol withdrawal signs are characterized by hyperactivity, tail tremors, tail stiffness, head tremors, general tremors, ventromedio-distal flexion, wet shakes, teeth chattering, akinesia, spastic rigidity, and induced and spontaneous convulsions [71] (Table 1). With alcohol, the withdrawal is only spontaneous because no known competitive antagonist can precipitate withdrawal. Similar to opioids, withdrawal from alcohol is dose- and duration-of-abstinence-dependent, with peak withdrawal ranging from 10 to 16 h with high-dose blood alcohol levels at the time of withdrawal (300–400 mg/dl) [71].

Table 1 Somatic withdrawal signs

Opioid withdrawal	
Rats	*Humans*
Weight loss	Weight loss
Diarrhea	Diarrhea
Escape attempts	Yawning
Wet dog shakes	Lacrimation
Abdominal constrictions	Rhinorrhea
Facial fasciculations	Perspiration
Teeth chattering	Gooseflesh
Salivation	Tremor
Ptosis	Dilated pupils
Abnormal posture	Anorexia
Penile grooming	Nausea
Erection/ejaculation	Emesis
Irritability	Hyperthermia
	Increased blood pressure

Alcohol withdrawal	
Rats	*Humans*
Hyperactivity	Tremor
Tail tremors	Increased heart rate
Tail stiffness	Increased blood pressure
Akinesia	Increased body temperature
Spastic rigidity	Anorexia
Convulsions	Convulsions
	Hyperthermia
	Delirium tremens

Motivational Signs

Animal models of the withdrawal/negative affect stage include increases in anxiety-like responses, measures of conditioned place aversion (rather than preference), and increases in reward thresholds using brain stimulation reward to precipitated withdrawal or spontaneous withdrawal from chronic administration of a drug [30, 34, 73, 94, 111, 112] (Table 2).

Anxiety-Like Symptoms

A common response to acute withdrawal and protracted abstinence from all major drugs of abuse is the manifestation of anxiety-like responses. Animal models have revealed anxiety-like responses to all major drugs of abuse during acute withdrawal, with the dependent variable often a passive response to a novel and/or aversive stimulus, such as the open field or elevated plus maze, or an active response to an aversive stimulus, such as defensive burying of an electrified metal probe. Withdrawal from repeated administration of cocaine produces an

Table 2 Animal models of the different stages of the addiction cycle

Stage of addiction cycle	Animal models
Binge/intoxication	• Drug/alcohol self-administration • Conditioned place preference • Brain stimulation reward thresholds • Increased motivation for self-administration in dependent animals
Withdrawal/negative affect	• Anxiety-like responses • Conditioned place aversion • Withdrawal-induced drug self-administration
Preoccupation/anticipation	• Drug-induced reinstatement • Cue-inducedreinstatement • Stress-induced reinstatement

anxiogenic-like response in the elevated plus maze and defensive burying test, both of which are reversed by administration of corticotropin-releasing factor antagonists [13, 109] (Fig. 2). Precipitated withdrawal in opioid dependence and nicotine dependence also produces anxiety-like effects [37, 44, 113]. Spontaneous ethanol withdrawal produces anxiety-like behavior [11, 19, 55, 91, 96, 127, 129].

Dysphoria-Like Symptoms

Place aversion has been used to measure the aversive stimulus effects of withdrawal, mostly in the context of opioids [43, 123] (Fig. 3). In contrast to conditioned place preference, rats exposed to a particular environment while undergoing precipitated withdrawal from opioids spend less time in the withdrawal-paired environment when subsequently presented with a choice between that environment and an unpaired environment. Such an association continues to be manifested weeks after animals are "detoxified" (e.g., after the morphine pellets are removed [10, 122]) and can be measured from 24 h to 16 weeks later [43, 122, 123]. Additionally, a place aversion in opioid-dependent rats can be observed with doses of naloxone below which somatic signs of withdrawal are observed [112]. Although naloxone itself will produce a place aversion in non-dependent rats, the threshold dose required to produce a place aversion decreases significantly in dependent rats [43].

The place aversion to opioids does not require maintenance of opioid dependence for its manifestation, and a variation of this approach is to explore the place aversion produced following naloxone injection after a single acute injection of morphine. Acute opioid dependence has been defined as the precipitation of withdrawal-like signs by opioid antagonists following a single opioid dose or short-term administration of an opioid agonist [75]. Rats show a reliable conditioned place aversion precipitated by a low dose of naloxone after a single morphine injection

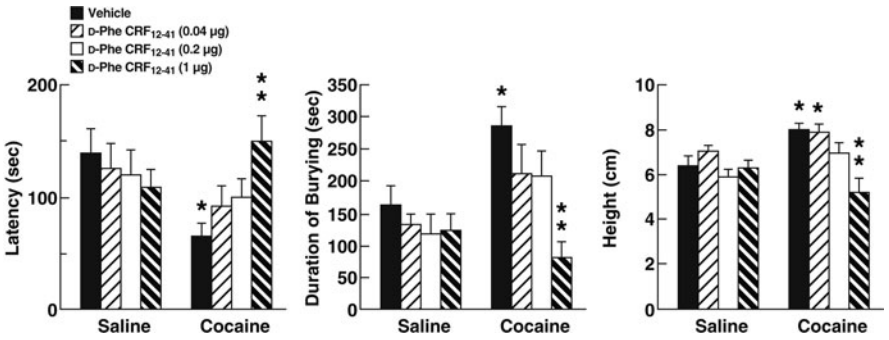

Fig. 2 Effect of intracerebroventricular administration of the corticotropin-releasing factor (CRF) antagonist D-Phe $CRF_{12–41}$ on anxiogenic-like effects in the defensive burying paradigm following chronic cocaine administration. Rats received chronic cocaine (20 mg/kg, intraperitoneally, for 14 days) or saline (1 ml/kg, intraperitoneally). Animals then were tested in the defensive burying paradigm 48 h after the last injection. D-Phe $CRF_{12–41}$ (0, 0.04, 0.2, and 1.0 mg/5 ml) was administered immediately after the animal touched the electrified probe and received the shock and 5 min before the testing session. Data are expressed as mean ± SEM (n = 10–14/group). The left panel shows the latency to start burying (in seconds) for all experimental groups ($^{*}p < 0.05$, compared with saline/vehicle group; $^{**}p < 0.01$, compared with cocaine/vehicle group; Duncan post hoc test). The middle panel represents the total duration of burying behavior expressed in seconds for all experimental groups ($^{*}p < 0.05$, compared with chronically saline-treated groups; $^{**}p < 0.01$, compared with cocaine/vehicle group; Duncan post hoc analysis). The right panel represents the height of bedding material, expressed in centimeters, at the junction between the probe and the wall of the testing cage ($^{*}p < 0.05$, compared with saline/vehicle group; $^{**}p < 0.01$, compared with other chronically cocaine-treated groups; Duncan post hoc analysis). Reprinted with permission from [13] (Springer Science+Business Media)

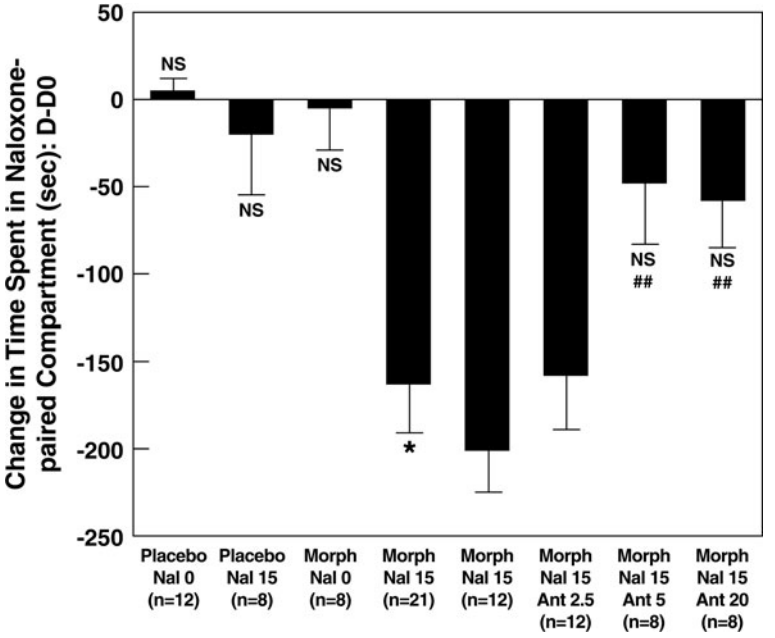

Fig. 3 The corticotropin-releasing factor −1 antagonist antalarmin (Ant) reduced naloxone (NAL)-precipitated place aversion conditioning in morphine (Morph)-dependent rats. Morphine dependence was induced by subcutaneous implantation of two slow-release, morphine-containing pellets, each containing 75 mg of morphine base. Placebo-pelleted rats received placebo morphine pellets also implanted subcutaneously. Separate groups of morphine-dependent rats that received naloxone (15 μg/kg, subcutaneously) immediately prior to conditioning (Morph-Nal) were also injected 30 min before naloxone on days 6, 8, and 10 with antalarmin (2.5, 5, 10, or 20 mg/kg, intraperitoneally; $n = 8$–12/group). Although antalarmin at doses of 2.5 and 5 mg/kg was ineffective, doses of 10 and 20 mg/kg blocked the place aversion produced by naloxone in morphine-dependent rats and returned values to levels observed with naloxone in placebo-pelleted rats and in morphine-without naloxone (Morph-Nal 0) rats. $^{*}p < 0.05$, within each dose group treatment, Wilcoxon signed-ranks test. NS refers to no significant place preference or place aversion with the Wilcoxon signed-ranks test. $^{\#\#}p < 0.01$, compared with Morph-Nal 15 group; between-group comparisons, Mann-Whitney test (ΔD). Reprinted with permission from [121]

that reflects a motivational component of acute withdrawal [9]. Similar acute withdrawal-like effects have been observed using anxiety-like responses following bolus injections of ethanol [148].

Reward Thresholds

Electrical brain stimulation reward or intracranial self-stimulation has a long history as a measure of activity of the brain reward system and of the acute reinforcing effects of drugs of abuse. All drugs of abuse, when administered acutely, decrease brain reward thresholds [68]. Brain stimulation reward involves widespread neurocircuitry in the brain, but the most sensitive sites defined by the lowest thresholds involve the trajectory of the medial forebrain bundle that connects the ventral tegmental area with the basal forebrain [88]. Although much emphasis was focused initially on the role of the ascending monoamine systems in the medial forebrain bundle, other non-dopaminergic, descending systems in the medial forebrain bundle clearly have a key role [47].

Acute intravenous cocaine self-administration in animals reduces reward thresholds, consistent with the well-documented effects of drugs of abuse in lowering brain reward thresholds [51]. However, with more prolonged access to the drug, the decreases in reward thresholds (i.e., rewarding effects) are replaced with elevations in reward threshold (i.e., anti-rewarding effects) after the initial decrease in reward thresholds,

presumably reflecting an acute withdrawal or opponent process-like effect. Such elevations in reward threshold begin rapidly, can be observed within a single session of self-administration, and are greater with greater exposure to cocaine [53], bearing a striking resemblance to human subjective reports [20, 130]. Chronic administration or self-administration of all drugs of abuse produces elevations in reward thresholds during spontaneous or precipitated acute withdrawal (Fig. 4). These elevations in threshold can be short (minutes to hours) or can last for days, depending on dose, drug, time of exposure, and precipitant.

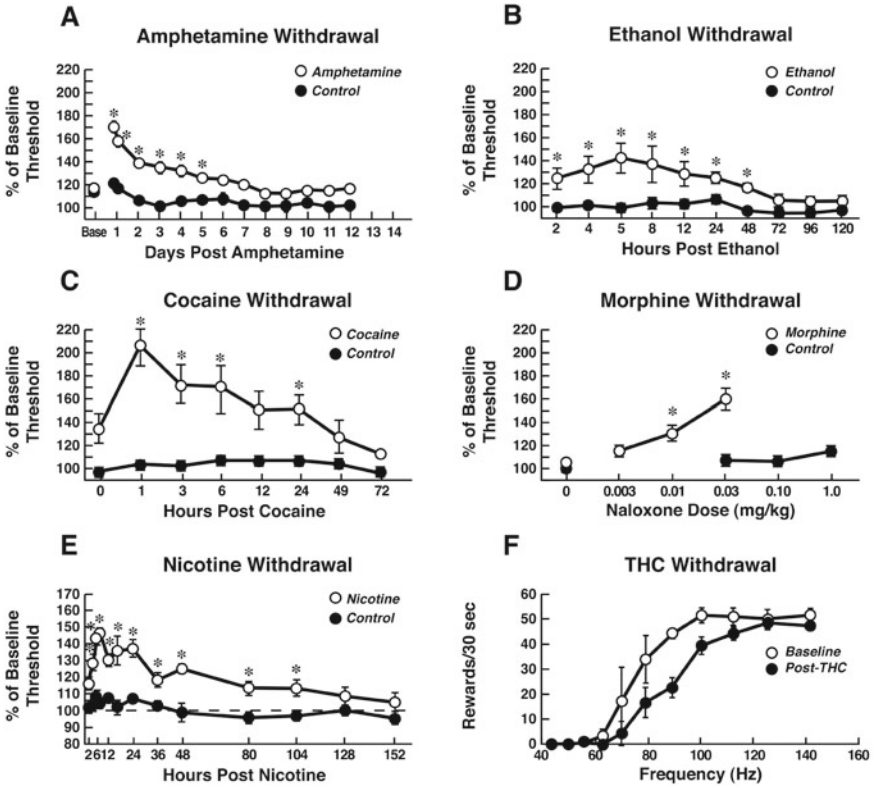

Fig. 4 (**A**) Mean intracranial self-stimulation reward thresholds (± SEM) in rats during amphetamine withdrawal (10 mg/kg/day for 6 days). Data are expressed as a percentage of the mean of the last five baseline values prior to drug treatment. $^{*}p < 0.05$, compared with saline control group. Reprinted with permission from [94] (Springer Science+Business Media). (**B**) Mean intracranial self-stimulation thresholds (± SEM) in rats during ethanol withdrawal (blood alcohol levels achieved: 197.29 mg%). Elevations in thresholds were time-dependent. $^{*}p < 0.05$, compared with control group. Reprinted with permission from [111]. (**C**) Mean intracranial self-stimulation thresholds (± SEM) in rats during cocaine withdrawal 24 h following cessation of cocaine self-administration. $^{*}p < 0.05$, compared with control group. Reprinted with permission from [73]. (**D**) Mean intracranial self-stimulation thresholds (± SEM) in rats during naloxone-precipitated morphine withdrawal. The minimum dose of naloxone that elevated intracranial self-stimulation thresholds in the morphine group was 0.01 mg/kg. $^{*}p < 0.05$, compared with control group. Reprinted with permission from [112]. (**E**) Mean intracranial self-stimulation thresholds (± SEM) in rats during spontaneous nicotine withdrawal following surgical removal of osmotic minipumps delivering nicotine hydrogen tartrate (9 mg/kg/day) or saline. $^{*}p < 0.05$, compared with control group. Data adapted from [30]. (**F**) Mean intracranial self-stimulation thresholds (± SEM) in rats during withdrawal from an acute 1.0-mg/kg dose of Δ^9-tetrahydrocannabinol (THC). Withdrawal significantly shifted the reward function to the right (indicating diminished reward). Reprinted with permission from [34] (Elsevier). Note that because different equipment systems and threshold procedures were used in the collection of the above data, direct comparisons among the magnitude of effects induced by these drugs cannot be made

Animal Models of Increased Drug Taking During Dependence

Escalation in Drug Self-Administration with Prolonged Access

A progressive increase in the frequency and intensity of drug use is one of the major behavioral phenomena characterizing the development of addiction and has face validity with the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition: "The substance is often taken in larger amounts and over a longer period than was intended" [6]. A framework with which to model the transition from drug use to drug addiction can be found in recent animal models of prolonged access to intravenous cocaine self-administration. Historically, animal models of cocaine self-administration involved the establishment of stable behavior from day to day to allow the reliable interpretation of data provided by within-subject designs aimed at exploring the neuropharmacological and neurobiological bases of the reinforcing effects of acute cocaine. Until 1998, after acquisition of self-administration, rats typically were allowed access to cocaine for 3 h or less per day to establish highly stable levels of intake and stable patterns of responding between daily sessions. This was a useful paradigm for exploring the neurobiological substrates for the acute reinforcing effects of drugs of abuse.

However, in an effort to explore the effects of differential access to intravenous cocaine self-administration on cocaine-seeking in rats, rats were allowed access to intravenous cocaine self-administration for 1 or 6 h per day [2]. One-hour access (short access) to intravenous cocaine per session produced low and stable intake as observed previously. In contrast, 6-h access (long access) to cocaine produced drug intake that gradually escalated over days (Fig. 5). Increased intake was observed in the extended-access group during the first hour of the session, with sustained intake over the entire session and an upward shift in the dose-effect function, suggesting an increase in hedonic set point. When animals were allowed access to different doses of cocaine, both the long- and short-access animals titrated their cocaine intake, but the long-access rats consistently self-administered almost twice as much cocaine at any dose tested, further suggesting an upward shift in the set point for cocaine reward in the escalated animals [3, 27, 72]. Such increased self-administration in dependent animals has now been observed with cocaine, methamphetamine, nicotine, heroin, and alcohol [2, 4, 37, 54, 87] (Fig. 5). This model is a key element for evaluating the motivational significance of changes in the brain reward and stress systems in addiction that lead to compulsivity in addiction. Similar changes in the reinforcing and incentive effects of cocaine have been observed following extended access and include increased cocaine-induced reinstatement after extinction and decreased latency to goal time in a runway model for cocaine reward [26]. Altogether, these results suggest that drug taking with extended access changes the motivation to seek the drug. Whether this enhanced drug taking reflects a sensitization of reward or a reward deficit state remains under discussion [132], but the brain reward and neuropharmacological studies outlined below argue for a reward deficit state driving the increased drug taking during extended access.

Withdrawal-Induced Drinking

Historically, animal models for the negative reinforcement associated with ethanol dependence have proven difficult, especially with rodents. Induction of physical dependence could enhance preference for ethanol [28, 29, 50, 101, 108, 110, 131, 146], but other reports did not support enhanced preference for ethanol in dependent animals [17, 82, 145]. Recently, reliable and useful models of ethanol consumption in dependent rats and mice have been developed in several laboratories. For example, in a major advance, ethanol first was established as a reinforcer, and then the animals were made dependent. The

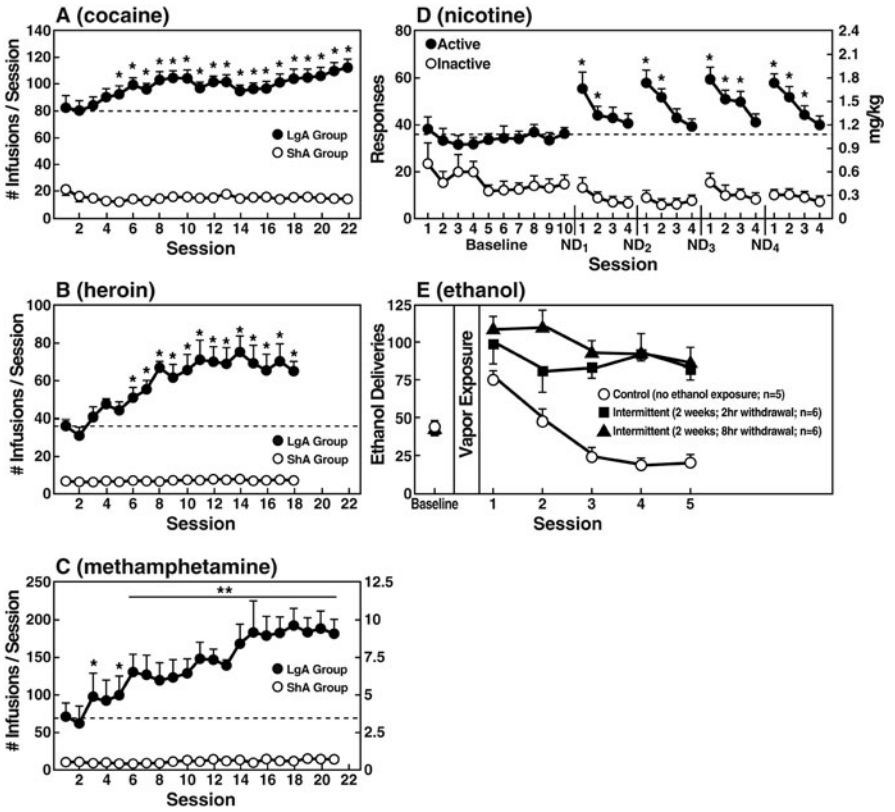

Fig. 5 (**A**) Effect of drug availability on cocaine intake (mean ± SEM). In long-access (LgA) rats ($n = 12$) but not in short-access (ShA) rats ($n = 12$), mean total cocaine intake started to increase significantly from session 5 ($p < 0.05$; sessions 5 to 22 compared with session 1) and continued to increase thereafter ($p < 0.05$; session 5 compared with sessions 8–10, 12, 13, 17–22). Reprinted with permission from [2] (American Association for the Advancement of Science). (**B**) Effect of drug availability on total intravenous heroin self-infusions (mean ± SEM). During the escalation phase, rats had access to heroin (40 mg per infusion) for 1 h (ShA rats, $n = 5$–6) or 11 h per session (LgA rats, $n = 5$–6). Regular 1-h (ShA rats) or 11-h (LgA rats) sessions of heroin self-administration were performed 6 days per week. The *dotted line* indicates the mean (± SEM) number of heroin self-infusions of LgA rats during the first 11-h session. $^{*}p < 0.05$ compared with first session (paired *t*-test). Reprinted with permission from [4]. (**C**) Effect of extended access to intravenous methamphetamine self-administration as a function of daily sessions in rats trained to self-administer 0.05-mg/kg/infusion of intravenous methamphetamine during a 6-h session. Short-access group (ShA), 1-h session ($n = 6$). Long-access group (LgA), 6-h session ($n = 4$). All data were analyzed using two-way analysis of variance (dose × escalation session within ShA or LgA group). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, vs. Day 1. Reprinted with permission from [54] (Springer Science+Business Media). (**D**) Total 23-h active and inactive responses after repeated cycles of 72 h of nicotine deprivation (ND) followed by 4 days of self-administration ($^{*}p < 0.05$ vs. baseline). Reprinted with permission from [37]. (**E**) Ethanol deliveries (mean ± SEM) in rats trained to respond for 10% ethanol and then either not exposed to ethanol vapor (control, $n = 5$) or exposed to intermittent ethanol vapor (14 h on/10 h off) for 2 weeks and then tested either 2 h ($n = 6$) or 8 h ($n = 6$) after removal from ethanol vapor. $^{*}p < 0.05$, significant increase in operant self-administration of ethanol in rats receiving intermittent vapor exposure compared with control. No difference was observed between rats exposed to intermittent vapor and tested either 2 or 8 h after ethanol withdrawal. Reprinted with permission from [87] (Wiley)

animals were maintained through liquid diet or continuous alcohol vapor exposure at blood alcohol levels that produced mild-to-moderate physical withdrawal symptoms when the ethanol was removed, but significant motivational signs measured by changes in brain stimulation reward during acute withdrawal from ethanol were observed [111]. Therefore, any somatic

withdrawal symptoms that the rats experienced would be predictably quite mild and would not be expected to physically interfere with their ability to respond. Animals showed reliable increases in self-administration of ethanol during withdrawal in which the amount of intake approximately doubled and the animals had blood alcohol levels from 0.10 to 0.15 gm% after 12 h of self-administration [101].

Further development of this model showed that animals exposed intermittently (14 h on/10 h off) to the same amount of ethanol as continuously exposed animals showed even more dramatic increases in self-administration during acute withdrawal [87] (Fig. 5). Systematic exploration of the parameters that determine the maximum increase in ethanol self-administration and blood alcohol levels showed that animals exposed to intermittent ethanol via alcohol vapor chambers developed dependence more rapidly [87]. The intermittent paradigm has produced dependent animals that achieved blood alcohol levels of 0.15 gm% in a 30-min session [97] and display increased responding on a progressive-ratio schedule, indicative of increased motivation to consume alcohol [136].

Relapse, or the return to alcohol abuse following periods of abstinence, is one of the principle characteristics of substance dependence on alcohol. The development of dependence has been suggested to play an important role in the maintenance of compulsive use and relapse following periods of abstinence.

In human alcoholics, numerous symptoms that can be characterized by negative emotional states persist long after acute physical withdrawal from ethanol. Fatigue and tension have been reported to persist up to 5 weeks post-withdrawal [5]. Anxiety has been shown to persist up to 9 months [105], and anxiety and depression have been shown to persist in up to 20–25% of alcoholics for up to 2 years post-withdrawal. These symptoms, post-acute withdrawal, tend to be affective in nature and subacute and often precede relapse [7, 48]. A factor analysis of Marlatt's relapse taxonomy found that negative emotion, including elements of anger, frustration, sadness, anxiety, and guilt, was a key factor in relapse [149], and the leading precipitant of relapse in a large-scale replication of Marlatt's taxonomy was negative affect [70]. In secondary analyses of participants in a 12-week clinical trial with alcohol dependence and not meeting criteria for any other *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, mood disorder, the association with relapse and a subclinical negative affective state was particularly strong [78]. This state has been termed "protracted abstinence" and has been defined in humans as showing a Hamilton Depression rating $\geq$8 with the following three items consistently reported by subjects: depressed mood, anxiety, and guilt [78].

Animal work has shown that prior dependence lowers the "dependence threshold" such that previously dependent animals made dependent again display more severe physical and motivational withdrawal symptoms than groups receiving alcohol for the first time [14, 15, 18, 19]. This supports the hypothesis that alcohol experience and the development of dependence in particular can lead to relatively permanent alterations in responsiveness to alcohol. However, relapse often occurs even after physical withdrawal signs have ceased, suggesting that the neurochemical changes that occur during the development of dependence can persist beyond the final overt signs of withdrawal ("motivational withdrawal syndrome").

A history of dependence in male Wistar rats can produce a prolonged elevation in ethanol self-administration in daily 30-min sessions after acute withdrawal and detoxification [99, 100, 102, 117]. This increase in self-administration of ethanol is accompanied by increases in blood alcohol levels and persists for up to 8 weeks post-detoxification. The increase in self-administration is also accompanied by increased behavioral responsivity to stressors and increased responsivity to antagonists of the brain corticotropin-releasing factor systems [35, 117, 129]. The persistent increase in ethanol self-administration has been hypothesized to involve an allostatic-like adjustment such that the set point for ethanol reward is elevated [64, 102]. These persistent alterations

in ethanol self-administration and residual sensitivity to stressors can be arbitrarily defined as a state of "protracted abstinence." Protracted abstinence defined as such in the rat spans a period after acute physical withdrawal has disappeared when elevations in ethanol intake over baseline and increased behavioral responsivity to stress persist (2–8 weeks post-withdrawal from chronic ethanol).

Significant self-administration of high amounts of ethanol similar to those observed in alcohol-preferring animals and during protracted abstinence has been observed using other methods. Here, the animals showed tolerance but no somatic withdrawal; motivational withdrawal has not yet been evaluated. Rats that receive passive intragastric infusion of ethanol for 3–6 days at levels observed in ethanol-preferring strains (3.3–12.2 g/kg/d) and are allowed access to intragastric self-infusion maintained high levels of ethanol self-administration (4–7 g/kg/d) [31]. Intermittent access to 20% ethanol (three 24-h sessions per week for 6 weeks) using a two-bottle choice procedure induced high ethanol consumption in rats to levels up to 5–6 g/kg/d [116]. However, blood alcohol levels in 30-min two-bottle choice sessions in the intermittent 20% animals were significantly lower (averaging approximately 60 mg% in Wistar rats) than those observed in dependent animals (see above).

Motivational Changes Associated with Increased Drug Intake During Dependence

The hypothesis that compulsive drug use is accompanied by a chronic perturbation in brain reward homeostasis has been tested in an animal model of escalation in drug intake with prolonged access combined with measures of brain stimulation reward thresholds. Animals implanted with intravenous catheters and allowed differential access to intravenous self-administration of cocaine or heroin showed increases in drug self-administration from day to day in the long-access group but not in the short-access group. The differential exposure to drug self-administration had dramatic effects on reward thresholds that progressively increased in long-access rats but not in short-access or control rats across successive self-administration sessions [1, 52] (Fig. 6). Elevation in baseline reward thresholds temporally preceded and was highly correlated with escalation in cocaine intake. Post-session elevations in reward thresholds failed to return to baseline levels before the onset of each subsequent self-administration session, thereby deviating more and more from control levels. The progressive elevation in reward thresholds was associated with the dramatic escalation in cocaine consumption that was observed previously. After escalation had occurred, an acute cocaine challenge facilitated brain reward responsiveness to the same degree as before but resulted in higher absolute brain reward thresholds in long-access compared with short-access rats [1]. Similar results have been observed with extended access to heroin [52] in which rats allowed 23-h access to heroin showed a time-dependent increase in reward thresholds that paralleled the increases in heroin intake (Fig. 6).

Another reflection of the change in motivation associated with dependence is a measure of reinforcement efficacy measured by changes in progressive-ratio responding. In the progressive-ratio procedure, rats are allowed to reach baseline responding for cocaine under a fixed-ratio 1 schedule of reinforcement. For a progressive-ratio schedule, the response requirement (i.e., the number of lever responses required to receive a drug injection, or "ratio") increases using an exponential function, such as $5^{(0.2 \cdot \text{infusion number})} - 5$, yielding response requirements of 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 146, 178, 219, 268, etc. [103]. Sessions on this schedule are terminated when more than three-times the animal's longest baseline inter-response time has elapsed since the last self-administered cocaine injection [16]. Animals normally respond for 11–15 injections of cocaine, and the breakpoint is defined as

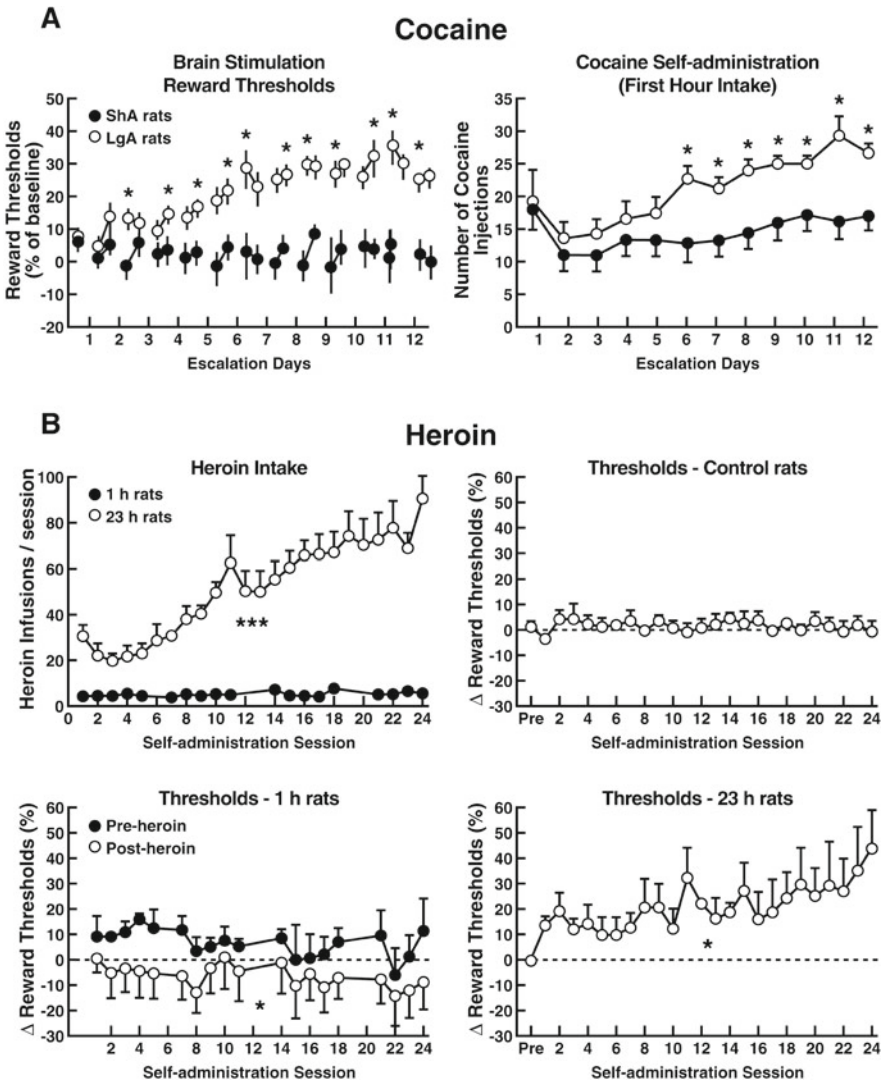

Fig. 6 (**A**) Relationship between elevation in intracranial self-stimulation reward thresholds and cocaine intake escalation in short-access (1-h, ShA) and long-access (6-h, LgA) rats. (*Left*) Percent change from baseline intracranial self-stimulation thresholds. (*Right*) Number of cocaine injections earned during the first hour of each session. $^{*}p < 0.05$, compared with drug-naive and/or ShA rats, tests of simple main effects. Reprinted with permission from [1]. (**B**) Unlimited daily access to heroin escalated heroin intake and decreased the excitability of brain reward systems. (*Top left*) Heroin intake (20 μg per infusion) in rats during limited (1-h) or unlimited (23-h) self-administration sessions. $^{***}p < 0.001$, main effect of access (1 or 23 h; two-way, repeated-measures analysis of variance). (*Top right*) Percent change from baseline intracranial self-stimulation thresholds in control rats that remained heroin-naive for the duration of the experiment and had intracranial self-stimulation thresholds assessed at the same time-points as the 23-h rats. (*Bottom left*) Percent change from baseline intracranial self-stimulation thresholds in 1-h rats. Daily post-thresholds assessed immediately after each heroin self-administration session were lowered compared with pre-thresholds assessed immediately before each self-administration session in 1-h rats. $^{*}p < 0.05$, main effect of heroin on reward thresholds (two-way, repeated-measures analysis of variance). (*Bottom right*) Percent change from baseline intracranial self-stimulation thresholds in 23-h rats. Reward thresholds assessed immediately after each daily 23-h self-administration session became progressively more elevated as exposure to self-administered heroin increased across sessions. $^{*}p < 0.05$, main effect of heroin on reward thresholds (two-way, repeated-measures analysis of variance). Reprinted with permission from [52]

the highest completed ratio in a session. The dependent measure in the progressive-ratio experiments is the total number of injections obtained per session and the breakpoint. Extended access to drugs resulting in escalation also is associated with an increase in breakpoint for cocaine in a progressive-ratio schedule, suggesting an enhanced motivation to seek cocaine or an enhanced efficacy of cocaine reward [93, 140]. Similar results have been observed with methamphetamine and withdrawal-induced drinking in rats made dependent with ethanol vapor [136] (Fig. 7).

Neurobiological Bases of Increased Drug Taking During Dependence

In a within-system adaptation, repeated drug administration elicits an opposing reaction within the same system in which the drug elicits its primary reinforcing actions. For example, if the synaptic availability of the neurotransmitter dopamine is responsible for the acute reinforcing actions of cocaine, then the within-system opponent process neuroadaptation would be a decrease in synaptic availability of dopamine.

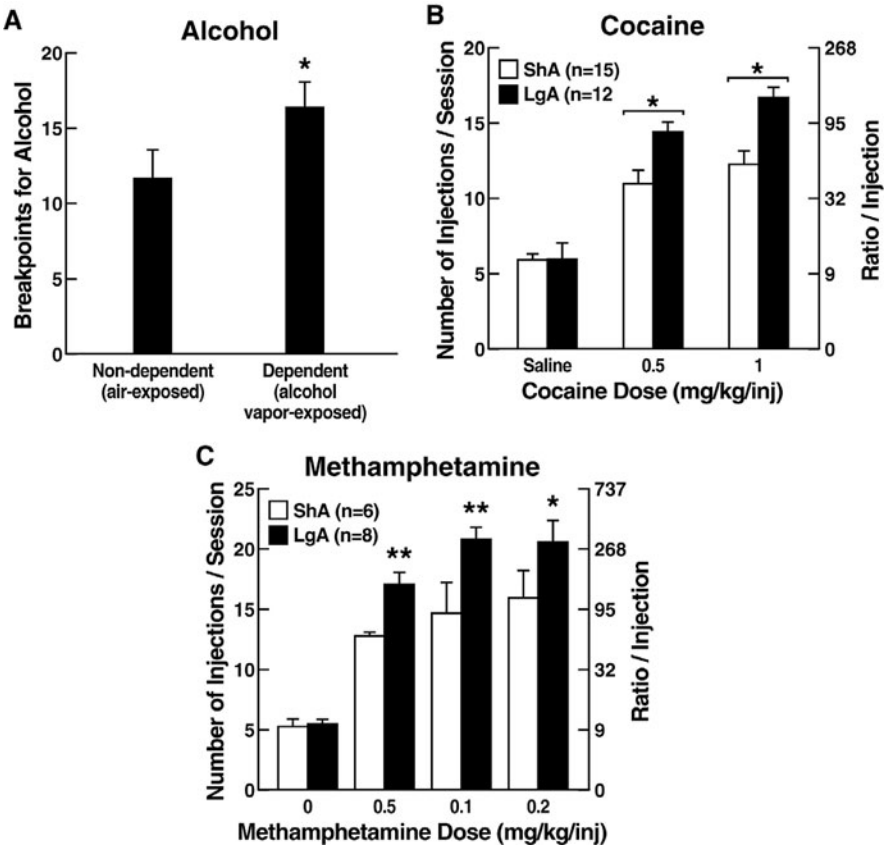

Fig. 7 (**A**) Breakpoints for responding for alcohol in dependent and non-dependent rats. $^{**}p < 0.01$, significant effect of alcohol exposure. Reprinted with permission from [136] (Wiley). (**B**) Dose-response function of cocaine responding under a progressive-ratio schedule of reinforcement in short-access (1-h, ShA) and long-access (6-h, LgA) rats. Test sessions ended when rats did not achieve reinforcement within 1 h. Data are expressed as the number of injections/session on the left axis and the ratio per injection (inj) on the right axis. $^{*}p < 0.05$, compared with ShA at each dose tested. Reprinted with permission from [140] (Elsevier). (**C**) Dose-response function of methamphetamine responding under a progressive-ratio schedule of reinforcement in short-access (1-h, ShA) and long-access (6-h, LgA) rats. Test sessions ended when rats did not achieve reinforcement within 1 h. Data are expressed as the number of injections/session on the left axis and the ratio per injection on the right axis. $^{*}p < 0.05$, $^{**}p < 0.01$, compared with ShA at each dose tested. Reprinted with permission from [141]

In a between-system adaptation, repeated drug administration recruits a different neurochemical system, one not involved in the acute reinforcing effects of the drug but that when activated or engaged acts in opposition to the primary reinforcing effects of the drug. For example, chronic cocaine may activate the neuropeptide dynorphin, and dynorphin produces dysphoria-like effects that would be opposite to those of dopamine.

Within-System Changes: Dopamine

Within-system neuroadaptations to chronic drug exposure include decreases in function of the same neurotransmitter systems in the same neurocircuits implicated in the acute reinforcing effects of drugs of abuse during drug withdrawal in animal studies. Decreases in activity of the mesolimbic dopamine system and decreases in serotonergic neurotransmission in the nucleus accumbens are well documented [79, 106, 143, 144]. Imaging studies in drug-addicted humans have consistently shown long-lasting decreases in the numbers of dopamine D_2 receptors in drug abusers compared with controls [134]. Additionally, cocaine abusers have reduced dopamine release in response to a pharmacological challenge with a stimulant drug [77, 135]. Decreases in the number of dopamine D_2 receptors, coupled with the decrease in dopaminergic activity, in cocaine, nicotine, and alcohol abusers results in decreased sensitivity of reward circuits to stimulation by natural reinforcers [74, 133]. These findings suggest an overall reduction in the sensitivity of the dopamine component of reward circuitry to natural reinforcers and other drugs in drug-addicted individuals.

Psychostimulant withdrawal in humans is associated with fatigue, decreased mood, and psychomotor retardation and in animals is associated with decreased motivation to work for natural rewards [12] and decreased locomotor activity [95], behavioral effects that may involve decreased dopaminergic function. Animals during amphetamine withdrawal show decreased responding on a progressive-ratio schedule for a sweet solution, and this decreased responding was reversed by the dopamine partial agonist terguride [12, 90], suggesting that low dopamine tone contributes to the motivational deficits associated with psychostimulant withdrawal.

Under this conceptual framework, other within-system neuroadaptations would induce increased sensitivity of receptor transduction mechanisms in the nucleus accumbens. Activation of adenylate cyclase, protein kinase A, cyclic adenosine monophosphate response-element binding protein, and ΔFosB has been observed during drug withdrawal [84, 86, 114, 115]. The ΔFosB response is hypothesized to represent a neuroadaptive change that extends long into protracted abstinence [85].

Between-System Changes: Role of Corticotropin-Releasing Factor

A prominent role for activation of brain stress systems in acute withdrawal and protracted abstinence has been established [58]. Corticotropin-releasing factor, norepinephrine, and dynorphin all have been shown to be activated by withdrawal from drugs of abuse. Perhaps the most compelling data derive from studies of the extrahypothalamic corticotropin-releasing factor system. Corticotropin-releasing factor controls hormonal and behavioral responses to stressors, but the extrahypothalamic corticotropin-releasing factor system is hypothesized to mediate behavioral responses to stressors [45]. Small molecule corticotropin-releasing factor−1 antagonists [55, 91] and intracerebral administration of a peptidergic corticotropin-releasing factor−1/corticotropin-releasing factor−2 antagonist into the amygdala [96] blocked the anxiety-like behavior induced by acute ethanol withdrawal. Corticotropin-releasing factor antagonists injected intracerebroventricularly or systemically also block the potentiated anxiety-like

responses to stressors observed during protracted abstinence from chronic ethanol [19, 129]. The effects of corticotropin-releasing factor antagonists have been localized to the central nucleus of the amygdala [96]. Precipitated withdrawal from nicotine produces anxiety-like responses that are also reversed by corticotropin-releasing factor antagonists [37, 127].

Using the conditioned place aversion paradigm, the opioid partial agonist buprenorphine dose-dependently decreased the place aversion produced by precipitated opioid withdrawal. Systemic administration of a corticotropin-releasing factor−1 receptor antagonist and direct intracerebral administration of a peptide corticotropin-releasing factor−1/corticotropin-releasing factor−2 antagonist also decreased opioid withdrawal-induced place aversions [46, 121]. Functional noradrenergic antagonists also blocked opioid withdrawal-induced place aversion [25].

The ability of corticotropin-releasing factor antagonists to block the anxiogenic-like and aversive-like motivational effects of drug withdrawal would predict motivational effects of corticotropin-releasing factor antagonists in animal models of extended access to drugs (Table 3). Corticotropin-releasing factor antagonists selectively blocked the increased self-administration of drugs associated with extended access to intravenous self-administration of cocaine [119], nicotine [37], and heroin [41].

A particularly dramatic example of the motivational effects of corticotropin-releasing factor in dependence can be observed in animal models of ethanol self-administration in dependent animals. During ethanol withdrawal, extrahypothalamic corticotropin-releasing factor systems become hyperactive, with an increase in extracellular corticotropin-releasing factor within the central nucleus of the amygdala and bed nucleus of the stria terminalis of dependent rats [32, 80, 89]. The dysregulation of brain corticotropin-releasing factor systems is hypothesized to underlie not only the enhanced anxiety-like behaviors but also the enhanced ethanol self-administration associated with ethanol withdrawal.

Supporting this hypothesis, exposure to repeated cycles of chronic ethanol vapor produced substantial increases in ethanol intake in rats both during acute withdrawal and during protracted abstinence (2 weeks post-acute withdrawal) [87, 99]. The subtype non-selective corticotropin-releasing factor receptor antagonists α-helical corticotropin-releasing factor$_{9–41}$ and D-Phe corticotropin-releasing factor$_{12–41}$ (intracerebroventricular administration) reduced ethanol self-administration in dependent and post-dependent animals [117, 128]. When administered directly into the central nucleus of the amygdala, a corticotropin-releasing factor−1/corticotropin-releasing factor−2 antagonist blocked ethanol self-administration in ethanol-dependent rats during withdrawal

Table 3 Role of corticotropin-releasing factor in dependence

		Corticotropin-releasing factor antagonist effects			
Drug	Withdrawal-induced changes in extracellular corticotropin-releasing factor in CeA	Withdrawal-induced anxiety-like or aversive responses	Baseline self-administration or place preference	Dependence-induced increases in self-administration	Stress-induced reinstatement
Cocaine	↑	↓	—	↓	↓
Opioids	↑	↓	—	↓	↓
Ethanol	↑	↓	—	↓	↓
Nicotine	↑	↓	—	↓	↓
Δ^9-THC	↑	↓			

—, no effect; blank entries indicate not tested. CeA, central nucleus of the amygdala. Δ^9-THC, Δ^9-tetrahydrocannabinol

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[32]. Systemic injections of small-molecule corticotropin-releasing factor−1 antagonists also blocked the increased ethanol intake associated with acute withdrawal [33, 55, 91]. These data suggest an important role for corticotropin-releasing factor, primarily within the central nucleus of the amygdala, in mediating the increased self-administration associated with dependence (Table 3).

Between-System Changes: Role of Other Neuropharmacological Systems

Although less well developed, functional norepinephrine antagonists block excessive drug intake associated with dependence on ethanol [138], cocaine [140], and opioids [42]. A focal point for many of these effects is the extended amygdala but at the level of the bed nucleus of the stria terminalis.

A kappa-opioid antagonist also blocks the excessive drinking associated with ethanol withdrawal and dependence [137]. Recently, some have argued that the effects of corticotropin-releasing factor in producing negative emotional states are mediated by activation of κ opioid systems [69]. However, κ receptor activation can activate corticotropin-releasing factor systems in the spinal cord [118], and there is pharmacological evidence that dynorphin systems can also activate the corticotropin-releasing factor system.

Significant evidence suggests that activation of neuropeptide Y in the central nucleus of the amygdala can block the motivational aspects of dependence associated with chronic ethanol administration. Neuropeptide Y administered intracerebroventricularly blocked the increased drug intake associated with ethanol dependence [125, 126]. Injection of neuropeptide Y directly into the central nucleus of the amygdala [38] and viral vector-enhanced expression of neuropeptide Y in the central nucleus of the amygdala also blocked the increased drug intake associated with ethanol dependence [124].

Thus, acute withdrawal from drugs of abuse increases corticotropin-releasing factor in the central nucleus of the amygdala that has motivational significance for the anxiety-like effects of acute withdrawal and the increased drug intake associated with dependence (Fig. 8). Acute withdrawal also may increase the release of norepinephrine in the bed nucleus of the stria terminalis and dynorphin in the nucleus accumbens, and both may contribute to the negative emotional state associated with dependence. Decreased activity of neuropeptide Y in the central nucleus of the amygdala also may contribute to the anxiety-like state associated with ethanol dependence. Activation of brain stress systems (corticotropin-releasing factor, norepinephrine, dynorphin) combined with inactivation of brain anti-stress systems (neuropeptide Y) elicits powerful emotional dysregulation in the extended amygdala. Such dysregulation of emotional processing may be a significant contribution to the between-system opponent processes that help maintain dependence and also set the stage for more prolonged state changes in emotionality such as protracted abstinence.

Homeostatic vs. Allostatic View of Dependence

The development of the aversive emotional state that drives the negative reinforcement of addiction has been defined as the “dark side” of addiction [65, 66] and is hypothesized to be the b-process of the hedonic dynamic known as opponent process when the a-process is euphoria. Two processes are hypothesized to form the neurobiological basis for the b-process: loss of function in the reward systems (within-system neuroadaptation) and recruitment of a negative emotional state via the brain stress or anti-reward systems (between-system neuroadaptation) [61, 63]. Anti-reward is a construct based on the hypothesis that brain systems are in place to limit reward [66]. As dependence and withdrawal develop, brain stress systems such as corticotropin-releasing factor, norepinephrine,

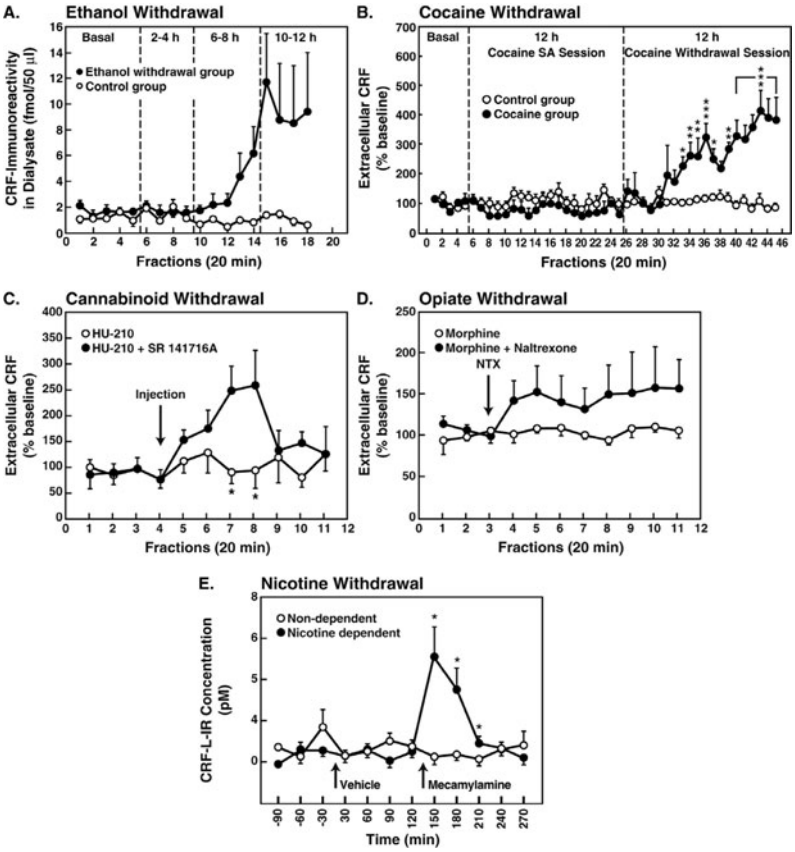

Fig. 8 (**A**) Effects of ethanol withdrawal on corticotropin-releasing factor (CRF)-like immunoreactivity in the rat amygdala determined by microdialysis. Dialysate was collected over four 2-h periods regularly alternated with non-sampling 2-h periods. The four sampling periods corresponded to the basal collection (before removal of ethanol), and 2–4 h, 6–8 h, and 10–12 h after withdrawal. Fractions were collected every 20 min. Data are represented as mean ± SEM ($n = 5$ per group). Analysis of variance confirmed significant differences between the two groups over time ($p < 0.05$). Reprinted with permission from [80]. (**B**) Mean (± SEM) dialysate corticotropin-releasing factor (CRF) concentrations collected from the central nucleus of the amygdala of rats during baseline, 12 h cocaine self-administration (SA), and a subsequent 12-h withdrawal period (cocaine group, $n = 5$). CRF levels in rats with the same history of cocaine self-administration training and drug exposure, but not given access to cocaine on the test day (Control group, $n = 6$). Data are expressed as percentages of basal CRF concentrations. Dialysates were collected over 2-h periods alternating with 1-h non-sampling periods as shown by the timeline at the top. During cocaine self-administration, dialysate CRF concentrations in the cocaine group were decreased by about 25% compared with control animals. In contrast, termination of access to cocaine resulted in a significant increase in CRF release that began approximately 5 h post-cocaine and reached about 400% of pre-session baseline levels at the end of the withdrawal session. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, Simple effects after overall mixed-factorial analysis of variance. Reprinted with permission from [98] (John Wiley & Sons, Inc). (**C**) Effects of cannabinoid CB_1 antagonist SR 141716A (3 mg/kg) on CRF release from the central nucleus of the amygdala in rats pretreated for 14 days with cannabinoid CB_1 agonist HU-210 (100 mg/kg). Cannabinoid withdrawal induced by SR 141716A was associated with increased CRF release ($^{*}p < 0.005$, $n = 5$–8). Vehicle injections did not alter CRF release ($n = 5$–7). Data were standardized by transforming dialysate CRF concentrations into percentages of baseline values based on averages of the first four fractions. Reprinted with permission from [104] (American Association for the Advancement of Science). (**D**) Effects of morphine withdrawal on corticotropin-releasing factor (CRF) release in the central nucleus of the amygdala. Withdrawal was precipitated by administration of naltrexone (NTX) (0.1 mg/kg) in rats prepared with chronic morphine pellet implants. Reprinted with permission from [142] (Wiley). (**E**) Effect of mecamylamine (1.5 mg/kg, intraperitoneally)-precipitated nicotine withdrawal on CRF release in the central nucleus of the amygdala measured by in vivo microdialysis in chronic nicotine pump-treated (nicotine-dependent, $n = 7$) and chronic saline pump-treated (non-dependent, $n = 6$) rats. $^{*}p < 0.05$ compared with non-dependent. Reprinted with permission from [37]

and dynorphin are recruited (Fig. 8), producing the negative emotional state [8, 56, 83]. At the same time, within the motivational circuits of the ventral striatum-dorsal striatum, reward function decreases. The combination of decreases in reward neurotransmitter function and recruitment of anti-reward systems provides a powerful source of negative reinforcement that contributes to compulsive drug-seeking behavior and addiction.

An overall conceptual theme argued here is that drug addiction represents a break with homeostatic brain regulatory mechanisms that regulate the emotional state of the animal. However, the view that drug addiction represents a simple break with homeostasis is not sufficient to explain a number of key elements of addiction. Drug addiction, similar to other chronic physiological disorders such as high blood pressure, worsens over time, is subject to significant environmental influences, and leaves a residual neuroadaptive trace that allows rapid "re-addiction" even months and years after detoxification and abstinence. These characteristics of drug addiction imply more than simply a homeostatic dysregulation of hedonic function and executive function, but rather a dynamic break with homeostasis of these systems that has been termed "allostasis."

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, is defined as "stability through change," and differs significantly from homeostasis [120]. Allostasis involves a feed-forward mechanism rather than the negative feedback mechanisms of homeostasis, with continuous reevaluation of need and continuous readjustment of all parameters toward new set points. Allostatic mechanisms have been hypothesized to be involved in maintaining a functioning brain reward system that has relevance for the pathology of addiction [64]. Repeated challenges, such is the case with drugs of abuse, lead to attempts of the brain via molecular, cellular, and neurocircuitry changes to maintain reward stability but at a cost. For the drug addiction framework elaborated here, the residual deviation from normal brain reward threshold regulation is termed an "allostatic state." This state represents a combination of chronic elevation of reward set point engaged by the motivational changes involving decreased function of reward circuits and recruitment of anti-reward systems, and both may contribute to the compulsivity of drug seeking and drug taking. How these systems are modulated by other known brain emotional systems localized to the extended amygdala and how individuals differ at the molecular-genetic level of analysis to convey loading on these circuits remain challenges for future research.

Animal Models of Dependence: Validity and Relevance to Treatment

Relevance of Face Validity

Animal models of motivational dependence with a lowercase "d" have substantial face validity. The hypothetical constructs associated with the models of motivational dependence—anxiety, dysphoria, and decreased reward—all are hypothesized to reflect such symptoms in humans. However, the major limitation of face validity here is that arguing that a rat is truly experiencing "dysphoria" is virtually impossible because no verbal reports can be obtained from a rat. In contrast, from a behaviorist perspective, one could argue that a verbal report in a human is only one measure of dysphoria and that the human symptoms could also be measured in a place aversion situation. Clearly, the translation of animal models to the human condition has not reached such a level of sophistication. With regard to other symptoms of addiction associated with dependence, such as escalation with extended access or dependence-induced drinking, face validity is again limited. Animals in the conditions constructed by the researcher are indeed self-administering intoxicating amounts of drugs. However, the social situations for animals versus humans are vastly different, and a requirement for true face validity would be restrictive and non-productive. Certainly, some new information would be obtained if one had

a model of free-ranging rats drinking ethanol in the context of burrow dominance hierarchy. Such studies can and have been done with success in non-human primates in which the social impact has more construct validity for the human condition. Indeed, construct validity—not face validity—in animal models is critical for the heuristic study of biological processes in the human condition and more specifically the understanding of the neurobiology of addiction.

Construct Validity

The models of dependence with a lowercase "d" and other symptoms associated with Dependence with a capital "D" outlined in this chapter have construct validity (i.e., they have explanatory power for the human condition or functional equivalence for the human condition). For example, ample evidence indicates impaired reward function in animals showing escalation in drug intake with extended access to intravenous drugs of abuse and in animals with withdrawal-induced excessive drinking. Similarly, evidence exists for impaired stress responsivity during drug withdrawal that is paralleled in the human condition [39, 62, 97]. Ample evidence suggests that the decrease in dopaminergic function in the mesolimbic dopamine system in rats during acute withdrawal is robust in humans [133].

Emphases on face validity [23] may be misplaced and can be argued to undermine progress in the field. For example, the method of induction of opioid dependence (e.g., pellets vs. self-administration) appears to matter little compared with the dose of opioid employed (Table 4). Clearly, high opioid doses over time produce dose-dependent dependence with a lowercase "d" and excessive drug seeking measured by intake or reinforcement efficacy. Different patterns of administration of the drug (intermittent exposure to ethanol vs. continuous ethanol) may also ultimately have motivational effects [87]. However, the unspoken view that to have a valid model of alcoholism "one must show that a rat can drink whiskey from a bottle in a paper bag on a street corner while smoking a cigarette" is misleading and counterproductive. A case in point is a comparison of a classic Southern European alcoholic (who never showed public intoxication but imbibed several bottles of wine per day and clearly met the criteria for Dependence with a capital "D" when deprived of alcohol) to the binge alcoholic of Northern Europe. Would one argue that the biological bases of liver toxicity, frontal cortex dysfunction, or activation of the brain stress systems during motivational withdrawal sufficient to induce excessive drinking are different for such different phenotypes of alcoholism?—presumably not in the domin of cancer, diabetes, pain, and obesity. Numerous examples exist of induction of a disease state independent of the exact human pattern of disease induction that have construct validity for understanding the underlying biology, but not necessarily face validity, of cancer, diabetes, pain, and obesity. Thus, emphasis must be placed on construct validity and reliability of animal models and not the red herring of face validity.

Relevance to Medications Development

The thesis of this chapter is that animal models of motivational dependence provide a heuristic

Table 4 Heroin self-administration as a function of opioid induction procedure

Method of induction	Escalation time	Total heroin intake*	References
Morphine pellets (2 × 75 mg, subcutaneously)	0–3 days	~1,200 μg/kg (8 h)	[139]
Heroin self-administration (12-h access; 60 μg/kg/infusion)	0–20 days	~2,400 μg/kg (12 h)	[42]
Heroin self-administration (23-h access; 60 μg/kg/infusion)	0–35 days	~3,000 μ/kg (23 h)	[21]

*Note that the total dose per day, extrapolated to 24 h, would be similar with all three methods of induction.

framework for understanding a key, and previously neglected, source of reinforcement associated with addiction. An interactive, iterative process can be established whereby existing medications that interact with the withdrawal/negative affect stage of the addiction cycle would be used to validate and improve animal and human laboratory models and then predict viable candidates for novel medications [60, 67]. Medications currently on the market for the treatment of addiction have provided not only a window on the opportunities for facilitating treatment but also are forming a means for evaluating future medications development. A combination of excellent and validated animal models of addiction and an enormous surge in understanding through basic research of the neurocircuits and neuropharmacological mechanisms involved in the neuroadaptative changes that account for the transition to dependence and the vulnerability to relapse have provided numerous viable targets for future medications development. Development of human laboratory studies for these stages of the addiction cycle is critical and will allow dynamic iterative feedback to and from the animal models key to the identification of novel candidates for treatment [67]. Novel neurobiological targets will be derived from this basic research on addiction with a focus on the withdrawal/negative affect stage and protracted abstinence component of the preoccupation/anticipation stages of the addiction cycle. Indeed, some would argue that targets that restore homeostasis of reward function rather than block reward function will be significantly more valuable to the field [66, 67].

Acknowledgements Supported by the Pearson Center for Alcoholism and Addiction Research and National Institutes of Health grants AA06420 and AA08459 from the National Institute on Alcohol Abuse and Alcoholism, DA04043 and DA04398 from the National Institute on Drug Abuse, and DK26741 from the National Institute of Diabetes and Digestive and Kidney Diseases. The author would like to thank Michael Arends for his assistance with manuscript preparation.

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Novel Methodologies: Proteomic Approaches in Substance Abuse Research

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Contents

Introduction

The comprehensive sequencing of human and other important genomes has enhanced our understanding of the cellular organization and function in higher organisms. This has been largely accomplished by the innovations in large-scale analysis of mRNA expression (microarrays, serial analysis of gene expression, and differential display). Genomics-based approaches have led to unprecedented advances in our understanding of the biological basis of substance abuse; however, the next step in systems biology is the examination of coordinated expression of the entire complement of proteins including modifications and protein-protein interactions—proteomics. The broad scale analysis of proteins in health and disease is essential given that proteins are central components of cellular physiology carrying out the greater part of biological events in the cell, even though certain mRNAs can act as effector molecules. Furthermore, it is important to note that mRNA and protein analysis are not interchangeable, with each governed by distinct spatial, temporal, and physiological processes that generally prevent correlation of mRNA and protein expression in neuronal systems [1, 19].

Proteomics involves the evaluation of the entire complement of proteins in a biological system with respect to structure, expression level, protein-protein interactions, and post-translational modifications—often referred to as structural, functional, and expression proteomics, respectively. The majority of early efforts in proteomics have been directed toward comparison of differential protein expression and identification in disease and control tissues. However, changes in protein abundance do not define protein function exclusively as many vital functions are brought about by post-translational modifications, interactions among proteins, and differential distribution in subcellular components. Multiple proteomic strategies are needed to capture the involvement of regulatory mechanisms that affect protein abundance and function such as protein-protein interactions and subcellular distribution.

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_16,

The advent of proteomics can be attributed in part to the rapid development of mass spectrometry, bioinformatics and the current accessibility of vast protein database from various organisms. These rapid advancements have improved our understanding of the cellular structure and function within the brain and the roles of various proteins and protein interactions in health and disease. However, the central nervous system poses unique challenges to proteomic inquires including the temporal and spatial expression characteristics of neurons and glia, the cellular heterogeneity of brain regions, the connectivity and communication between neurons and the dynamic structural and functional alterations in neurons and glia that occur as a function of the interaction between the organism and the environment, development, learning and memory, and disease. These challenges can be overcome to some extent by combining specific isolation and fractionation procedures with high-throughput protein separation and analysis strategies to yield a more global view of the proteome in different physiological states than has been available previously. For example, prior to the advent of high-throughput proteomics technologies, our knowledge of protein alterations and the durations of those alterations induced by substance abuse was limited to less than 100 proteins—primarily expression levels of protein assessed either individually or a few proteins at a time. With the development of proteomic technologies and strategies, it is now possible to evaluate significant portions of the neuroproteome (thousands of proteins) from crude homogenates to discrete cellular domains. Proteomic analysis strategies allow the simultaneous assessment of thousands of proteins of known and unknown function, thereby enabling a more comprehensive view of the protein orchestration in addictive disorders. Broad-scale evaluations of protein expression are well suited to the study of drug abuse, particularly in light of the complexity of the brain compared with other tissues, the multigenic nature of drug addiction, the vast representation of expressed proteins in the brain, and our relatively limited knowledge of the molecular pathology of this illness.

The development of innovative strategies has been ongoing in neuro-proteomics, particularly for studying the post-translational modifications, mapping of proteins from multi-protein complexes, and mapping of organelle proteomes [13]. An understanding of the proteins in neurons along with their expression levels and their post-translational modifications, as well as the protein-protein interaction maps, would revolutionize addiction biology and addiction medicine in that we would then be able to expand our knowledge of the biochemical alterations specifically associated with substance abuse. Such information would be used to identify new targets for medication development.

Technology and Methods for Expression Proteomics

Protein Fractionation

The biological samples subjected to proteomic analysis in neuroscience include tissue, distinct cell populations and cerebrospinal fluid. Each type of sample is extremely complex as the protein constituents vary in charge, molecular mass, hydrophobicity, and post-translational modification, as well as spatial and temporal expression. The coding genes for the central nervous system fluctuate between 25,000 and 30,000 [81]. This added complexity of neuro-proteome will be overwhelming if we hypothesize that each protein on average has 10 splice variants, cleavage products, and post-translational modifications, yielding approximately 250,000–300,000 protein isoforms to assess. Currently, there are no proteomic methods that have the capacity to separate and identify the entire proteome. One approach is to reduce the complexity of the proteome by subcellular fractionation procedures, allowing a more thorough assessment of cellular domains (e.g. synapse, membrane, nucleus, and cytoplasm) while enriching less abundant proteins that may not be detectable at the level of whole cell protein analysis [88].

Protein stability and purity as well as prevention of protein degradation and modification are of critical importance throughout various stages of proteomic analysis. Rapid removal of brain tissue, dissection, and freezing are imperative for the maintenance of the proteome state in the sample. Protease and phosphatase inhibitors are used to help prevent degradation and dephosphorylation of proteins during protein preparation [61]; however, care should be taken that adducts and charge trains are not introduced by these inhibitors. Purification of proteins from other cellular substances is also necessary; for example, lipids, several proteins (e.g., albumin and immunoglobulin are particularly abundant in the brain), and nucleic acids should be eliminated from the protein sample. The most common methods of purification rely on selective precipitation including acetone and trichloroacetic acid, although a number of commercially available kits are available [70].

Cerebrospinal Fluid

Cerebrospinal fluid is secreted by the choroid plexus in the lateral ventricles and is found in the cerebral ventricles and in the subarachnoid space flowing down the spinal canal, as well as upwards over the brain convexities. Cerebrospinal fluid is an important determinant of extracellular fluid surrounding neurons and glia in the central nervous system, removes harmful brain metabolites, provides mechanical cushion, and serves as a conduit for peptide hormones secreted by hypothalamus. Cerebrospinal fluid is in steady state with the extracellular fluid; thus it is considered to contain biochemical constituents that reflect neural activity.

While proteomic studies of neuronal tissue have multiple challenges including the use of post-mortem tissue and invasive biopsies from ante-mortem tissues, cerebrospinal fluid proteomics is amenable for serial analysis by minimally invasive lumbar puncture. A change in the expression of cerebrospinal fluid constituents may provide important insights into various central nervous system diseases by improving our understanding of the molecular basis of disease as well as providing disease biomarkers. Given the low protein concentration (~150–450 μg/ml) and high salt concentration (>150 mmol/L) of cerebrospinal fluid and the abundance of albumin (~60% of the total cerebrospinal fluid protein) and immunoglobulin [23], it is necessary to deplete these abundant proteins (e.g. affinity removal and solid phase extraction) and reduce the salt concentration (e.g. protein affinity columns, ultrafiltration, and dialysis) to improve protein recovery and allow better detection of less abundant proteins. The limitation, depletion of some of the proteins of interest, can be overcome by a separate analysis of the depleted abundant proteins to ensure analysis of proteins interacting with the abundant proteins.

Cellular Domains

Several recent proteomics studies have employed fractionation methods that allow collection of multiple cellular components from one tissue source [16, 31, 85]. This allows a greater amount of each fraction to be used at the start, thereby enabling analysis of less abundant proteins. As the fractions are generated from the same samples, the experimental variability is reduced, with the additional advantage of an additive increase in the whole proteome analyzed. The crucial drawback has been the overlap of the proteins between fractions.

Cytoplasm

Since the current proteomic strategies rely heavily of two-dimensional gel electrophoresis, which has been optimized for the analysis of soluble protein fractions, it is not surprising that the vast majority of initial phases of proteomic analysis have focused on profiling of the cytoplasm. The vast majority of key regulators of the signaling pathways are housed in the cytoplasm, besides regulating the expression of receptors and channeling important cytodynamic

information between the nucleus and the membrane proteins. Some of the recent studies profiling the cytoplasm have revealed interesting new paradigms in our understanding of neurobiology.

Nucleus

The nucleus has a high degree of organization, consisting of structurally and functionally distinct compartments: nucleolus, nuclear speckles, nuclear pore complex, and nuclear envelope. The nucleus is a highly organized organelle consisting of domains fundamental for preserving the homeostasis of the cellular milieu. The profiling of the nuclear proteome in neuroscience has been the slowest of all subcellular fractions. However, there have been some good studies documenting the need to do so. In addition to the soluble fraction of the nucleus, there has been an interest in other compartments of the nucleus—nuclear envelope, nuclear pore complex and nucleolus—although no studies using such methods have been published to date in addiction biology research.

Mitochondria

The mitochondria is a complex structure involved in fundamental processes, such as the tricarboxylic acid cycle, β-oxidation of fatty acids, urea cycle, electron transport, oxidative phosphorylation, apoptosis and heme synthesis. Neuroproteomic analyses of the mitochondria have focused on the abundance in different brain regions [45, 103]. Datasets from mitochondrial proteomes from different species and tissues have documented 400–700 mitochondrial associated proteins which will enable scientists to better understand the mitochondrial machinery in health and disease [54, 89].

Membrane

Membrane and the membrane-associated proteins constitute nearly a third of the cellular proteins and represent targets of approximately two thirds of pharmaceutical agents [82, 99]. These proteins are involved in various cellular processes including signal transduction, cell adhesion, exocytosis, metabolite, and ion transport. As membrane proteins are amphipathic, the hydrophobicity nature makes them difficult to study and necessitates different strategies for analysis as compared with cytosolic proteins, for example. Therefore, while great strides have been made toward the analysis of soluble cellular proteins, the analysis of membrane proteins reported in proteomic analyses has been under-represented [97]. The traditional proteomic approach of two-dimensional gel electrophoresis has many limitations for analyzing membrane proteins [11], including the insolubility of hydrophobic proteins in non-detergent sample buffer, alkaline isoelectric points of most hydrophobic proteins, which are difficult to resolve on the basic extent of acrylamide gels. To a large extent, these issues can be overcome using a variety of combinations of liquid chromatographic separation techniques.

Synaptosomes and Postsynaptic Density

Synapses can be fractionated into synaptosomes as well as distinct pre and post-synaptic components. Synaptosomes constitute of the entire presynaptic terminal (including mitochondria and synaptic vesicles) and portions of the postsynaptic terminal (including postsynaptic membrane and postsynaptic density). The study of synaptic proteomes is an important starting point in neuroscience to understand complex brain functions. Critical for understanding neuroplasticity as well as neuropathology associated with drugs of abuse.

Synaptosomes are subcellular membranous structures formed during mild disruption of brain tissue. The shearing forces cause the nerve endings to break off and subsequent resealing of the membranes form the synaptosomes. The synaptosomes have a complex structure equipped with components of signal transduction, metabolic pathways, and organelles as well

as structural components required for vesicular transport. Synaptosomes can be isolated from brain homogenate by differential and density-gradient centrifugation [76].

The postsynaptic density is a disk-like structure with a thickness of ~30–40 nm and width of ~100–200 nm. The most important structures associated with it are the cytoskeletal proteins, regulatory enzymes, and neurotransmitter receptors and associated proteins. These constitute a very highly structured framework with a definite association of the receptors and ion channels with the signaling molecules and the cytoskeletal elements to play an imperative role in signal transduction as well as synaptic plasticity. There are several available fractionation methods for isolation of the postsynaptic density [64, 91].

Separation

Gel-Based Methods

Expression proteomics refers to the determination of protein levels without regard to post-translational modifications. Gel-based as well as chromatographic separation approaches have been integral in generating proteomic profiles in numerous tissues including brain; however, research into the neuroproteome to date has been predominantly gel based.

Two-Dimensional Gel Electrophoresis

The basic principles of two-dimensional gel electrophoresis remain the same since its introduction, namely the separation of proteins by isoelectric focusing (1st dimension) followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (2nd dimension), which involves the separation by molecular weight of proteins [41, 60]. In standard two-dimensional gel electrophoresis experiments, approximately 1,000–2,000 protein spots are visualized on a gel representing the most abundant proteins while other less abundant proteins are largely obscured by the more abundant proteins. Subcellular fractionation can be used to enrich the representation of less abundant proteins. Caveats of the two-dimensional gel electrophoresis procedure include: (1) the possibility of co-migration of proteins (i.e. many proteins in a spot, (2) migration of proteins as multiple spots (i.e. due to charge trains, post-translational modifications, isoforms, etc.), (3) intensive image analysis requiring manual removal of artifacts, (4) inability or difficulty of large and hydrophobic proteins to isolated in first dimension gels, and (5) poor representation of highly acidic and basic proteins (i.e. membrane bound proteins). In general, two-dimensional gel electrophoresis variability is approximately 20–30% due to sample preparation, reagent sources, staining methods, image analysis software, and technical expertise and experience [53].

Isoelectric Focusing

Following protein solubilization, the next step in two-dimensional gel electrophoresis is isoelectric focusing, which separates the proteins in the first dimension according to their isoelectric point. The isoelectric point of a protein is primarily a function of the amino acid side chains, which are protonated or deprotonated depending on the pH of the solution in which the protein is present. For isoelectric focusing, protein samples are loaded onto strip gels consisting of a gradient of pH values and electrophoresis leads protein migration depending on the net charge of each protein in the sample. At a specific isoelectric point, the protein will reach the point in the pH gradient where the net charge of the protein is zero and stop migrating.

Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis

Next, the isoelectric focusing gel or strip is equilibrated with sodium dodecyl sulfate and placed on top of the sodium dodecyl sulfate acrylamide gel. The equilibration step is necessary to allow the sodium dodecyl sulfate molecules to complex with the proteins and produce anionic

complexes with net negative charge roughly equivalent to the molecular weight of the protein. Proteins are electrophoresed migrating out of the isoelectric focusing gel and into the sodium dodecyl sulfate gel, where they separate according to molecular weight (second dimension). Both conventional sodium dodecyl sulfate-polyacrylamide gel electrophoresis instruments, such as those used for Western blotting and special purpose apparatuses can be used for this step.

Gel Staining

Following electrophoresis, it is imperative to visualize gel spots for subsequent isolation and mass spectrometry analysis. Coomassie Brilliant Blue, silver nitrate, and negative staining are common post-electrophoresis methods available for the two-dimensional gel-based proteomics analysis. The sensitivity of these stains range from 100 ng (e.g. Coomassie Brilliant Blue) to 1 ng (e.g. silver) for individual protein spot detection [59, 75]. In acidic medium, Coomassie Brilliant Blue binds to the amino acids by electrostatic and hydrophobic interactions; however, some of the proteins release the dye during the de-staining procedure, which may cause problems with reproducibility and quantitative reliability. Coomassie Brilliant Blue is compatible with mass spectrometry as complete de-staining of the gel can be achieved using bicarbonate. As a rule of thumb, proteins detected visually by Coomassie stain are sufficiently abundant enough for characterization by mass spectrometry. Disadvantages of Coomassie Brilliant Blue staining include low sensitivity and a narrow dynamic range, which is, however, better than silver stain. Silver staining is widely used for quantitative analysis due to its high sensitivity. Despite its excellent sensitivity, silver staining lacks reproducibility, has a limited linear dynamic range, involves subjective judgment of the staining end-point, and interferes with the mass spectrometry compatibility, resulting in a much lower sequence coverage compared with Coomassie staining [55]. Even though silver staining is still used currently, there has been an increasing trend to use the new-generation fluorescent stains.

Fluorescence-based detection methods are more sensitive than the absorbance based methods given the difference in detected and incident wavelengths, which lead to lower background values [96]. SyproRuby™ dye (Molecular Probes, Eugene, OR), the first of the fluorescent stains, is part of a stable organic complex composed of ruthenium that interacts non-covalently with basic amino acids in proteins [6]. The stain can be visualized using a wide range of excitation sources commonly used in the image analysis systems. It has a sensitivity that approximates silver staining with a linear dynamic range of three orders of magnitude. DeepPurple™ (GE Healthcare, Piscataway, NJ) possesses a broad dynamic detection range over four orders of magnitude with limited speckling and background staining [49, 79], appears to result in increased peptide recovery from in-gel digests compared with SyproRuby™ stain, and improves matrix-assisted laser desorption ionization-time of flight mass spectrometry-based identification of less abundant protein spots by increasing sequence coverage [87].

Two-Dimensional Difference in Gel Electrophoresis

Whereas two-dimensional gel electrophoresis has been the workhorse of proteomics for several decades, the method has been plagued by issues of reproducibility and quantitation given that multiple gels have to be compared. Two-dimensional difference in gel electrophoresis [92] allows the labeling of two to three samples with different dyes on the same two-dimensional gel, thereby reducing spot pattern variability and the number of gels in an experiment—with the result of making spot matching much more simple and accurate. The most popularized experimental design has been the use of a pooled internal standard (sample composed of equal aliquots of each sample in the experiment) labeled with the Cy2 dye and labeling control and experimental samples with Cy3 or

Cy5 dyes swapped equally across the samples, respectively. Following 1st and 2nd dimension electrophoresis, gels are sequentially scanned for Cy2, Cy3, and Cy5 labeled proteins by the following lasers/emission filters; 488-/520-, 532-/580- and 633-nm/670-nm, respectively. The scanned images of the fluorescence labeled proteins are sequentially analyzed by differential in-gel analysis (performs Cy5/Cy3: Cy2 normalization) followed by biological variation analysis (performs inter-gel statistical analysis to provide relative abundance in various groups). These log abundance ratios are then compared between the control and diseased/treatment samples from all the gels using statistical analysis (t-test and analysis of variance).

A modification of two-dimensional difference in gel electrophoresis in which cyanine dyes that label all of the cystine residues of proteins are labeled has been introduced with a detection limit for saturation labeling of 0.1 ng or protein per spot as opposed to 1 ng protein per spot thereby reducing the amount of protein sample required for analysis [78]. This procedure provides a very attractive alternative for performing quantitative two-dimensional difference in gel electrophoresis when dealing with low sample amounts, typical in neuroscience, even though only two saturation dyes are currently available (Cy3 and Cy5).

Chromatographic Separation of Proteins

The coupling of efficient chromatographic and electrophoretic separation methods with high-performance mass spectrometry hold great promise for qualitative and quantitative characterization of highly complex protein mixtures. The advances in chemical tagging and isotope labeling techniques have enabled the quantitative analysis of proteomes. Multidimensional liquid chromatographic separation (also known as multidimensional protein identification technology [94]) is typically based on using ≥ 2 physical properties of peptides (size, charge, hydrophobicity, and affinity) to reduce the complexity of the proteome. Methods commonly used employed to separate peptides based on physical and chemical properties include ultracentrifugation (density), capillary electrophoresis (size and charge), isoelectric focusing (isoelectric point), size-exclusion chromatography (stoke's radius), ion-exchange chromatography (charge), hydrophobic interaction chromatography (hydrophobicity), reverse-phase chromatography (hydrophobicity), and affinity chromatography (biomolecular interactions).

A major advantage of multidimensional approaches over two-dimensional gel electrophoresis methods is the ability to isolate less abundant proteins as well as the proteins with extreme isoelectric point, molecular weight, and hydrophobicity [20, 63, 94]. In most multidimensional separation approaches, proteins are digested into peptides prior to separation, yielding complex peptide mixtures but with increased solubility due to the elimination of non-soluble hydrophobic peptides—a critical caveat for the study of membrane proteins that are insoluble in aqueous buffers.

Several strategies have been developed for relative quantitation of protein expression between samples, including: (1) isotopic labeling of separate protein mixtures, (2) combined digestion of the labeled proteins followed by multidimensional liquid chromatographic separation, (3) automated tandem mass spectrometry of the separated peptides, and (4) automated database search to identify the peptide sequences and quantify the relative protein abundance based on the tandem mass spectrometry.

Isotope-Coded Affinity Tags (ICAT and iTRAQ)

ICAT used to be one of the most popular methods for quantitative proteome analysis before the inception of iTRAQ multiplex quantitation strategy [22]. The ICAT reagent is comprised of a cysteine-reactive group, a linker containing the heavy or light isotopes (d8/d0) and a biotin affinity tag. The labeling method involves *in vitro* derivatization of cysteine residues in a protein with d0 or d8 followed by enzymatic

digestion of the combined sample. All cysteine biotin tagged residues are selectively separated by avidin column followed by further separation using reverse phase chromatography. The isotopically tagged peptides give quantitative mass spectrometry analysis based on the relative peak intensities/areas of d0 and d8 labeled peptides [22]. Another advantage is the ability to analyze peptides with molecular weight more than 3,000 daltons easily due to the mass difference between the coded isoforms is sufficiently large.

A major limitation of ICAT is the exclusive analysis of cysteine-containing peptides (10–20% of the peptides). The resolution is greatest in the case of smaller peptides where the d8/d0 ratio is higher and with peptides that have multiple cysteine residues [73]. Another limitation is that the biotin affinity tag remains linked to the peptides throughout the analysis causing shifts in chromatographic separation, shifts in the mass/charge ratio and changes to tandem mass spectrometry spectra relative to the unlabelled peptides complicating the manual or computer–assisted interpretation [15, 22]. Most analyses of ICAT have utilized the combination of strong cation exchange chromatography with reverse-phase microbore liquid chromatography coupled with on-line mass spectrometry and tandem mass spectrometry [21, 44, 94]. Data-dependent software is used to select specific mass/charge peptides for collision-induced dissociation, alternating mass spectrometry and tandem mass spectrometry scans for collecting qualitative and quantitative data. Alternative strategies such as per-methyl esterification of carboxylic acid groups [17], specific labeling of lysine residues [65], and peptide *N*-termini [56] have also been used recently. Quantification software have been developed that can assemble a composite ratio for a protein based on the calculated expression ratio from all the peptides from a single protein such as XPRESS (http://tools.proteomecenter.org/XPRESS.php) and ProICAT™ (Applied Biosystems, Foster City, CA). The data obtained from the above software programs can be analyzed collectively using INTERACT for multiple experiments [24].

iTRAQ methodology is an extension of ICAT, which uses four isobaric reagents (114, 115, 116 and 117), allowing the multiplexing of four different samples in a single liquid chromatography-tandem mass spectrometry experiment. More recently, iTRAQ 8Plex, which has four more isobaric reagents (113, 118, 119 and 121) in addition to the traditional four iTRAQ reagents, expands the possibilities of using more experimental variables for comparison. A major advantage of this technique over the ICAT is the ability to label multiple peptides per protein, which increases the confidence of identification as well as quantitation. A recent study comparing two-dimensional gel electrophoresis and iTRAQ reported a confidence interval of 0.24 for isobaric tagging versus 0.31 for two-dimensional gel electrophoresis as well a greater range of expression ratios [10]. A more recent study compared two-dimensional difference in gel electrophoresis, ICAT and iTRAQ, and reported that iTRAQ was more sensitive than the ICAT, which was equi-sensitive to two-dimensional difference in gel electrophoresis. The complementary nature of these techniques was confirmed by the limited overlap of the proteins characterized [100].

Top–Down Proteomics

The aforementioned techniques (bottom–up proteomics) are based on consistent enzymatic conversion of proteins to peptides. It is customary to accurately make mass measurements by a tandem mass spectrometry of lower molecular weight peptides rather than higher molecular weight intact proteins; however, bottom–up approach increases the sample complexity and the entire sequence coverage for proteins is rarely achieved—limiting site-specific post-translational modification analysis of proteins. Such limitations have renewed interest in top–down proteome characterization strategies. Such techniques characterize individual proteins by mass spectrometry *without* prior enzymatic cleavage. Capillary isoelectric focusing coupled with Fourier transform-ion cyclotron resonance

mass spectrometry is one such strategy for analyzing complex protein mixtures using a top–down approach [35, 93]. One potential major limitation is the level of information is not always sufficient for confident protein identification due to the possibilities of point mutations, post-translational modifications and the presence of open reading frames having high sequence homology. This problem can be overcome somewhat by incorporation of isotopically labeled amino acids into the cellular proteins of unicellular model organisms. The partial amino acid content information obtained combined with capillary isoelectric focusing-Fourier transform-ion cyclotron resonance, enables identification of proteins from genome databases without tandem mass spectrometry information [35, 51]. Other limitations include the large amount of sample required and the low throughput that is not amenable to automation.

Mass Spectrometry

Mass spectrometers consist of three major units: the ion source, the mass analyzer, and the ion detection system. Mass spectrometry is based on the separation of ionized proteins or peptides based on the mass/charge ratio. Tandem mass spectrometry, on the other hand, couples two mass spectrometers in time and space and has revolutionized the field of expression and functional proteomics [80]. Tandem mass spectrometry involves selection of peptides of a certain mass and the subsequent fragmentation and mass analysis (in two stages). In the first stage, the precursor ion produced by the ion source is selected for fragmentation. The fragmentation results in production of product ions to be analyzed in the second stage of mass analysis. The inconvertible link between the precursor ion and the product ions is responsible for the unique molecular specificity of tandem mass spectrometry.

Ion Source

A number of ionization technologies exist including: fast ion bombardment [4], matrix-assisted laser desorption ionization [37], and electrospray ionization [14]. Matrix-assisted laser desorption ionization and electrospray ionization are the techniques of choice for most proteomic applications of neuroscience research. Matrix-assisted laser desorption ionization works through mixing the protein sample with a light-absorbing matrix that forms a crystal. This is usually done on some form of plate with multiple positions for different samples. When the plate is pulsed with a laser of a particular wavelength, the energy from the laser is absorbed by the crystal matrix and the proteins within the crystal are ionized and desorbed (ejected) from the plate into the mass analyzer.

In electrospray ionization (and nanospray ionization), ions are produced in a liquid phase. The protein sample, in a solvent solution, is ejected as a mist of droplets from a charged capillary tip. As the solvent in the droplets evaporates the total charges of the proteins in the droplet remain but with a reduced surface area of the droplet. This continues to a point at which individual ions leave the droplet. Individual ions then pass on into the mass analyzer.

Mass Analyzers

Whichever method of ionization is used, once the ions are created they must be separated before being detected in such a way as to provide information on the mass/charge ratio. Mass analyzers do not actually detect the ions or measure ion mass; they are only used to separate ions according to their mass/charge ratio. A number of mass analyzer types exist: time of flight, quadrupole, ion trap, and Fourier transform-ion cyclotron resonance.

Time-of-flight mass analyzers can be thought of as a tube. The ionized proteins enter the tube by passing through a high voltage accelerator. The speed at which the ion travels is proportional to its mass. A number of ions are produced simultaneously and pass through the time-of-flight tube and to a detector; the ions with a higher mass/charge ratio will travel faster and

reach the detector first. Since the distance traveled and time are all known, the mass/charge ratio can be calculated, and from that the mass.

Quadrupole mass analyzers also involve ions traveling down what can be thought of as a tube. In this case though, the tube consists of four parallel rods. The rods are two pairs of two that can be tuned to different currents and radio frequencies. The two pairs of rods have opposite currents and shifted radio frequencies allowing a form of tuning in which only ions of a particular mass/charge ratio pass though the tube. A range of mass/charge ratios can be scanned, generating a mass/charge profile of the sample. Quadrupole mass analyzers are often used with an electrospray ionization ion source.

Ion trap mass analyzers use the same principles as the quadrupole in that specific combinations of current and radio frequencies are used to select particular mass/charge ratios. The ion trap can be thought of as a small ball with one electrode around the equator and two more electrodes at the poles. Ions are introduced into the center of the ball and are kept in orbits within the trap. By changing current and radio frequency combinations, particular mass/charge ratio ions are ejected from the ion trap through a port to the detector. By scanning though these voltages and radio frequencies, a complete mass/charge profile can be made.

A number of hybrids of these separation strategies exist, all of which are generally designed to increase the accuracy of mass/charge ratio measurements and sensitivity to less abundant ions. Time-of-flight analyzers can be placed in series (time of flight/time of flight) with a reflectron or collision cell between them; quadrupoles and time of flight can be placed in series (Q-time of flight), and extremely powerful magnets and Fourier transform algorithms (Fourier transform-ion cyclotron resonance) can be used to determine the mass/charge ratios of all ions within an ion trap. Detectors change the kinetic energy of the ions into an electrical current that can be measured and passed along to a computer. While these detectors give information on abundance of ions, quantitation of protein abundance differences between samples by mass spectrometry is limited unless samples are linked to isotopes (see ICAT).

All of these mass spectrometry techniques can be applied to complex protein samples, i.e. a mixture of hundreds or thousands of proteins. It is important to separate the use of mass spectrometry instruments to separate proteins from the mass spectrometry used for protein identification, as will be described later. As described below, quantitative analysis by mass spectrometry is limited to techniques like ICAT. For researchers looking to profile the expression of proteins in a large number of samples, mass spectrometry can be problematic and requires a great deal of time on expensive instruments.

Protein Identification

No matter the separation and quantitation methods used, at the end of the experiment the proteins must be identified. Most approaches use mass spectrometry. Peptide mass fingerprinting and tandem mass spectrometry are the main methods for determining protein identities. Peptide mass fingerprinting was developed by a number of research groups [32, 50, 62] and begins with digestion of a protein with an enzyme, typically trypsin. Trypsin cleaves proteins at very specific locations, resulting in a series of peptides. If this mixture of peptides is analyzed by mass spectrometry, a series of peptide masses is created. These masses are searched against databases using one of a number of programs (e.g. ProFound and MASCOT). These programs take DNA sequence databases translated into protein sequence and calculate the resulting peptide masses if these protein sequences were digested with trypsin. The peptide masses generated from the mass spectrometry of the digested protein of interest are then compared against these databases and the protein can be identified. Peptide mass fingerprinting of spots from two-dimensional gel electrophoresis is one very common application. Gel plugs are either excised by hand or by robot. These plugs contain the proteins of interest, and the proteins are digested in the plugs with trypsin. With

visual stains, the plug must often be destained, and some stains work better than others. Silver stains which use gluteraldehyde are not compatible with mass spectrometry.

Even if mass spectrometry instead of two-dimensional gel electrophoresis is chosen as the method of protein separation, mass spectrometry is also used for protein identification, through a process called tandem mass spectrometry. A number of different strategies exist for tandem mass spectrometry; in general the process entails the selection of one ion/peptide generated during initial mass spectrometry and then fragmenting this ion/peptide into smaller pieces and measuring the mass of the resulting ions. These secondary ions can be decoded into peptide sequence information, which is searched against protein sequence databases to identify the protein. Almost all of the ionization and mass analyzer types can be used for tandem mass spectrometry, provided that the instrument is appropriately configured. One tandem mass spectrometry method that is particularly suited for proteome determination, but less so for quantitation, is multidimensional protein identification technology [94]. In this method, all the proteins in a sample are digested and loaded onto liquid chromatographic columns (see previous explanation). After fractionation of the peptides, the peptides are fed into a tandem mass spectrometry instrument for protein identification. This method has identified thousands of proteins, can detect membrane proteins, and is similar in concept to shotgun sequencing of DNA.

Some of the more traditional methods for identifying proteins are still used for proteomic experiments. Edman protein sequencing can be performed on proteins or peptides extracted from gels or blotted from gels, although the method is limited by low throughput and requires a comparatively large amount of protein. Another technique is the Far Western blot where a two-dimensional gel electrophoresis gel is blotted and probed with an antibody against a specific protein. This approach does not offer much progress over conventional immunoblotting.

Protein Arrays

Due to some of the limitations of electrophoresis and mass spectrometry methods, selected research groups are attempting to create proteomic chips/arrays [66, 98]. Antibodies or other affinity reagents (e.g. aptamers, peptides) are spotted onto some sort of matrix. Hundreds to thousands of spots are on a single array. A labeled sample is then washed across the array and proteins bind to their specific antibody. The process can also be reversed whereby the protein samples of interest are spotted onto the matrix and then probed with different affinity reagents. While these array or chip approaches have potential for greatly increasing the throughput of proteomic experiments, the use of affinity reagents as the separation method is a severely limiting factor and cannot be ignored. A high-quality antibody is needed for each protein of interest and each modification of that protein. In order to generate quantitative data from antibody arrays, and because association kinetics between different antibodies and antigens can vary tremendously, relative concentrations of each antibody and antigen have to optimized for each protein. Though there seem to be a number of pitfalls to proteomic chips/arrays as an open screen technique they do hold promise for routine examination of a small group of proteins. Well-known pathways or gene families could be easily examined by such an approach.

Implementation for Drug Abuse Studies

Proteomic Analysis of Cocaine

Whereas several studies have assessed gene and subsequent protein expression as a function of cocaine administration in humans and animal models, few studies to date have employed high-throughput proteomic technologies to examine the effects of psychomotor stimulant administration on protein expression patterns in discrete

brain regions. Two examples of such approaches in this area include comparative analyses of proteomic alterations in the nucleus accumbens of cocaine overdose victims and controls and a complementary study in this region from rhesus monkeys self-administering cocaine for 18 months and controls.

The abuse liability of cocaine has been linked to the direct effects of the drug on dopamine uptake blockade, yielding elevated extracellular dopamine concentrations that occur in discrete areas of the brain, specifically the nucleus accumbens, ventral tegmental area, and prefrontal cortex—regions of the mesolimbic dopamine pathway, which originates in the ventral tegmental area and projects to several forebrain regions, most notably the nucleus accumbens. Numerous studies in rodent self-administration models have demonstrated definitively an important role for the nucleus accumbens in the reinforcing effects of cocaine [27, 29, 30, 67, 104]. Recent imaging studies in humans have revealed cocaine-induced functional activation of the nucleus accumbens following acute drug administration in cocaine-dependent subjects [7] and bilateral activation of the nucleus accumbens following imagery-induced drug craving [40]. In addition to the acute neurochemical and neurophysiological changes that occur as a function of cocaine, continued administration exerts biochemical adaptations in reinforcement-relevant brain regions [43, 57, 95] that are apparent at the structural, genomic, and proteomic levels and likely provide the biochemical foundation for sensitization, craving, withdrawal, and relapse [58]. For example, studies in rodent models indicate that chronic cocaine administration leads to persistent or even permanent biochemical alterations in the cyclic AMP pathway (e.g. [9, 69, 77, 90]), activator protein 1 family members (e.g. [33, 34, 68]), glutamate, dopamine, gamma-aminobutyric acid and opiate receptors, growth factors, cytoskeletal elements, and circadian genes [2, 3, 18, 28, 36, 46, 84, 101, 102].

Whereas animal studies have advanced our understanding of the neurobiological basis of drug addiction, the evaluation of similar questions in human tissue are few, yet are essential. Although there are many difficulties with post-mortem brain studies, it is one of the most promising ways to view biochemical changes that are relevant to human drug abusers and to educate the public about the consequences of cocaine abuse. By assessing changes in defined biochemical pathways in human post-mortem tissue, we can begin to ascertain the fundamental molecular and biochemical processes that are associated with long-term cocaine use. Furthermore, studies utilizing human post-mortem tissue will reveal whether the regulatory adaptations that occur in rodents and monkeys are applicable to human brain, and will reveal which changes are state or trait markers in human drug abusers.

To examine the neuropathological consequences of chronic cocaine abuse in the human brain, two-dimensional gel electrophoresis was used to compare protein alterations in the nucleus accumbens between cocaine overdose victims and controls [86]. The nucleus accumbens was dissected from coronal blocks of frozen brain tissue that had been obtained previously from subjects that were matched on a number of demographic and pathological indices. Tissue was fractionated into membrane, nuclear, and cytoplasmic fractions as previously described [31, 83], with only cytosolic fractions used for this study. Following image normalization between gels, spots with significantly differential image intensities were identified, excised, and trypsin digested. Differentially expressed proteins were identified by matrix-assisted laser desorption ionization-time of flight-time of flight mass spectrometry. Mass lists were submitted to MASCOT using GPS Explorer to search against the National Centre for Biotechnology Information non-redundant *primate* database for protein identification. The criterion for identification included a MASCOT confidence interval greater than 95%. Protein identification was confirmed by checking the protein mass and isoelectric point accuracy. One thousand four hundred seven spots were found to be present in a minimum of 5 subjects per group, and the intensity of 18 spots was found to be

differentially abundant between the groups, leading to the eventual positive identification of 15 proteins by peptide mass fingerprinting. In addition, 32 spots that were constitutively expressed were positively identified by peptide mass fingerprinting. The identified proteins can be categorized as cell structure, synaptic plasticity/signal transduction, mitochondria, and metabolism and are representative of functional classes that have been shown to be affected either directly or indirectly by cocaine administration. For example, previous studies in human cocaine overdose victims have reported significant dysregulation of ionotropic glutamate receptors in mesolimbic brain areas (ventral tegmental area and nucleus accumbens)—an effect that likely has far-reaching implications in terms of the mechanisms that support increased expression as well as the physiological implications of this upregulation. For example, liprin α3 (up-regulated over 2.5-fold in cocaine overdose victims) belongs to a family of proteins whose post-synaptic expression is involved in the transport of *N*-methyl-*D*-aspartate receptor vesicles along microtubules. Along with increased beta-tubulin (2.72-fold in cocaine overdose victims), these results begin to provide a framework that could mediate the increased levels of ionotropic glutamate receptor subunits at the membrane surface in cocaine overdose victims [31].

In addition to protein alterations that likely are involved in the maintenance of ionotropic glutamate receptor expression, the abundance of several metabolic proteins was altered in cocaine overdose victims, which may be related to the consequence of increased ionotropic glutamate receptor expression—such as increased calcium flux and resulting oxidative stress. For example, peroxiredoxin 2, a neuronal protein involved in redox regulation, was decreased in cocaine overdose victims. Previous studies have shown that cocaine administration increases lipid peroxidation [42], alters antioxidant enzyme activity, and elevates reactive oxygen species in dopaminergic projection areas [12, 48]. The mitochondrial protein ATP synthase beta chain, a protein that produces ATP from ADP, which is generated from electron transport complexes involved in mitochondrial respiration, was also decreased in cocaine overdose victims. These data provide but two examples by which chronic cocaine profoundly affects processes that are integral to normal neuronal function (i.e. decreased ability to reduce reactive oxygen species and improper functioning of energy metabolism). Such changes are likely reflected in changes in glucose metabolism and utilization following cocaine administration in rats [71], monkeys [47, 72], and humans [7, 74]. Understanding the coordinated involvement of multiple proteins in the human brain as a function of cocaine abuse provides unique insight into the molecular basis of the disease, offers new targets for pharmacotherapeutic intervention for drug abuse-related disorders, and has the potential to reshape the debate on which biochemical indices are most relevant to the human condition.

Whereas studies in the human brain are important for understanding the neuropathological consequences of chronic cocaine intake, factors such as agonal state, post-mortem interval, variability in drug intake, disease comorbidity, etc. may affect the stability of proteins as well as their post-translational modification. The use of non-human primate models of cocaine self-administration provides a critical bridge between human studies and basic research whereby the aforementioned variables that may confound human post-mortem studies are better controlled, allowing more precise correlation between drug intake and altered protein expression and function. Using a non-human primate model of cocaine self-administration with chronic access (18 months), the effects on protein abundance and phosphorylation were determined in the nucleus accumbens of rhesus monkeys using two-dimensional difference in gel electrophoresis and two-dimensional gel electrophoresis followed by gel staining with Pro-Q® Diamond phospho-protein gel stain, respectively. As detailed for the aforementioned studies in human post-mortem tissue, gel images were normalized for each set of experiments and spots with significantly differential image intensities

($P < 0.05$) were identified, excised, and trypsin digested and analyzed by matrix-assisted laser desorption ionization time of flight/time of flight mass spectrometry. Eighteen positively identified were found to be differentially expressed in the accumbens between the groups—a significant number of which were either directly or indirectly related to the hyperglutamatergia identified in both cocaine overdose victims and rhesus monkeys self-administering cocaine [31, 85]. Interestingly, the study identified several proteins that complement/supplement the results of the study in cocaine overdose victims, including proteins involved in cell structure, synaptic plasticity/signal transduction, metabolism, and mitochondrial function. Specifically, glial fibrillary acidic protein, syntaxin binding protein 3, protein kinase C isoform, adenylate kinase isoenzyme 5, and mitochondria-related proteins were increased in monkeys self-administering cocaine while beta-soluble *N*-ethylmaleimide-sensitive factor attachment protein and neural and non-neural enolase were decreased. In addition to determination of overall protein abundance, the study also explored the "functional" proteome of the accumbens, in this case by evaluating the expression of phosphorylated proteins. Of the identified spots on the gel, 15 phosphoproteins were positively identified, including increased levels of gamma-aminobutyric acid-A receptor-associated protein 1, 14-3-3 gamma protein, glutathione s-transferase, and brain type aldolase and decreased levels of beta-actin, Rab GDP dissociation inhibitor, guanine deaminase, peroxiredoxin 2 isoform b, and several mitochondrial proteins. Results from this study complement previous studies of cocaine-induced biochemical alterations in cocaine overdose victims using an animal model that closely recapitulates the human condition. The findings suggest a coordinated dysregulation of proteins related to cell structure, signaling, metabolism, and mitochondrial function that likely indicate long-term compromised cellular function. The reversal or attenuation of these biochemical alterations are important targets for addressing the neuropathology associated with drug abuse.

Proteomic Analysis of Alcohol

Similar to cocaine, the majority of proteomic analyses for alcohol abuse have been conducted in human post-mortem tissue, and the research has been guided largely by previous studies detailing significant changes in brain morphology, such as cortical and subcortical atrophy. Alcohol-induced changes in cortical and subcortical structure volumes have been correlated with both white and gray matter damage, and overall brain shrinkage in alcoholism is largely attributable to cortical white matter loss [8, 25]. Thus, in one of the first published proteomic studies of the effects of alcohol in the human brain, Matsumato and colleagues compared the proteomic profile of white matter in the dorsolateral prefrontal cortex between controls, uncomplicated alcoholics (>80 g of ethanol/day, no post-mortem evidence of cirrhosis or Wernicke-Korsakoff syndrome), alcoholics complicated with hepatic cirrhosis (>80 g of ethanol consumed per day, post-mortem confirmation of hepatic cirrhosis and no post-mortem evidence of Wernicke-Korsakoff syndrome), reformed alcoholic (>120 g of beer/day for 10 years, abstained last 14 years, no post-mortem evidence of cirrhosis or Wernicke-Korsakoff syndrome). The elegant experimental design addresses multiple comparisons simultaneously, including the effects of alcoholism in the human brain (controls vs. uncomplicated alcoholics), peripheral versus centrally mediated effects on protein alterations (uncomplicated alcoholics vs. alcoholics complicated with hepatic cirrhosis), and the transient or permanent nature of alcoholism on brain protein changes (uncomplicated alcoholics vs. reformed alcoholics). Following dissection of the dorsolateral prefrontal cortex, crude protein homogenate was isolated from each subject and separated using two-dimensional gel electrophoresis followed by protein identification using matrix-assisted laser desorption ionization time-of-flight mass spectrometry. The study found 60 protein spots that were differentially expressed between controls and alcoholics, of which

18 were positively identified, representing 11 proteins including proteins involved in cell structure and metabolism, with the most interesting finding being that thiamine deficiency may be related to alcohol-induced brain damage to this region. Interestingly, NADH2 dehydrogenase and fructose-biphosphate aldolase C were the only two proteins that were differentially expressed between the uncomplicated and complicated alcoholics.

Complementary proteomic analyses have also been conducted in the genu [38] and splenium [39] of the corpus callosum—a structure the volume of which is decreased in alcoholics [26]. The corpus callosum is of particular interest given that it is the major white matter structure connecting the total cerebral hemispheres, allowing exchange of sensory, motor, and cognitive information. Using similar cohorts and proteomic approaches, two regions of the corpus callosum were assessed—the genu and splenium. In the splenium, 43 proteins were found to be differentially expressed between alcoholics and controls, with 26 proteins present in the complicated alcoholic group that were involved in oxidative stress, lipid peroxidation, and apoptosis networks. The prevalence of protein alterations in the complicated alcoholic group suggests a potential relationship with liver dysfunction and cirrhosis. Similarly, 50 identified proteins were differentially expressed in alcoholics in the genu of the corpus callosum, with seven proteins unique to the uncomplicated alcoholic group and 28 unique to the complicated alcoholic group. Differentially expressed proteins were categorized as cytoskeletal, metabolic, oxidative stress related, calcium regulation, and signaling proteins. Comparative analysis between the three studies indicated significant region-specific protein expression in different regions of white matter (corpus callosum genu, corpus callosum splenium, and dorsolateral prefrontal cortex), suggesting that there are regional differences in their susceptibility to the effects of chronic alcohol.

In addition to determining potential protein correlates of regional white matter alterations induced by alcohol, separate studies have explored alcohol-induced alterations in the hippocampus of human post-mortem tissue [52] and in the nucleus accumbens and amygdala of a rodent model of chronic alcohol intake [5]. These regions are known to be sensitive to the effects of alcohol with changes in the functional integrity that affect short-term and spatial memory and reward circuitry. Both studies utilized standard two-dimensional gel electrophoresis approaches and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry analysis. In the human post-mortem study, crude protein homogenates from the hippocampus were compared between uncomplicated alcoholics and controls. Seventeen proteins were identified that were differentially expressed between the groups—proteins involved in metabolism, signaling, and oxidative stress. Comparison with other data from this group emphasizes the regional specificity of alcohol-induced changes and provides a framework for determining the biochemical mechanisms of alcohol-induced neuropathology.

In addition to the use of human post-mortem tissue to understand the effects of alcohol, the field has benefited by the use of well characterized rodent models that exhibit varying degrees of alcohol consumption. As the aforementioned studies in humans have provided exceptional insight into the pathology associated with chronic alcohol intake, the continuum of alcohol abuse and alcoholism includes biochemical changes in regions associated with the rewarding effects of alcohol—for example, the nucleus accumbens and amygdala. Using the inbred alcohol-preferring rat line, Bell and colleagues compared the effects of alcohol access (continuous, multiple scheduled access, and ethanol naïve) on the expression of proteins obtained from crude protein homogenates. Data revealed proteins in the accumbens and amygdala that changed in the same direction in the continuous and multiple scheduled access groups, suggesting that these proteins were altered as a function of alcohol consumption. In addition, numerous proteins were found to be differentially expressed based on brain region and on exposure to alcohol. The amygdala appeared to

be more sensitive to the cellular stress-related effects of chronic alcohol, whereas protein identifications in the accumbens reflected alterations in synaptic and cytoskeletal activity, which led the authors to suggest increased neuronal function. Examination of the differentially expressed proteins identified in this study in other behavioral models and at various times along the alcohol exposure continuum is warranted.

Conclusions

The advent of proteomics technologies provides a unique opportunity to discover and explore biochemical substrates and consequences associated with abused substances. Results from rodent, non-human primate, and human post-mortem studies indicate significant impairments in neuronal function and plasticity in several brain regions. To date the majority of studies have utilized rodents to model human cocaine intake; however, growing evidence indicates the need to refine rodent and non-human primate models to better recapitulate human drug intake and associated neuropathologies. As in other psychiatric and neurological illnesses, researchers should identify the molecular pathologies associated with cocaine addiction in humans and attempt to recapitulate such biological alterations in animal models.

Understanding the coordinated involvement of multiple proteins with chronic cocaine and alcohol addiction provides insight into the molecular basis of drug dependence in general and may offer novel targets for pharmacotherapeutic intervention. Although significant advances have been made in the identification of neurochemical and neurobiological substrates involved in the behavioral effects of abused drugs, the relationship between these effects and resultant alterations in protein expression remains in its infancy, and the application of this information to the development of treatment strategies has not been fruitful for several reasons. One explanation is that studies in the areas of neurobehavioral pharmacology and molecular biology have proceeded in relative isolation of each other. To date, there have been few published studies combining models of self-administration with proteomic approaches. Other possible explanations include: (1) the inappropriate use of experimental models, (2) reliance on non-neuronal systems or neuronal tissue not directly involved in the reinforcing effects of the drug, and (3) the lack of definable neural substrates at the cellular or biochemical level. The combination of appropriate behavioral models of drug reinforcement, specific neurobiological systems, and state-of-the-art molecular techniques will provide the most pertinent data for understanding the molecular basis of drug reinforcement and for potentially establishing novel targets for treatment.

A more detailed understanding of the molecular and biochemical cascades in specific neuronal populations and the interactions between well-defined neuronal populations within discrete brain regions could lead to a greater knowledge of the basic neurobiological processes involved in drug reinforcement. Future efforts investigating the biological basis of drug reinforcement should be directed at specific cellular targets in brain regions considered to be involved in drug reinforcement, and should focus on cortical influence on behavior—structures that are best studied in human post-mortem tissue and in non-human primate models. The integration of basic neuroscience and behavior offers the most productive avenue for delineating the complexity of the neurobiological underpinnings of drug reinforcement and the subsequent development of effective pharmacotherapies to treat addiction.

Acknowledgements Supported in part by funding of the following NIH grants: DA012498, DA003628, DA06634 (SEH).

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Part IV
Clinical Aspects of Alcohol and Drug Addiction

Alcohol: Clinical Aspects

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Contents

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Introduction

Alcohol is both the oldest and the most widely used psychoactive substance in the world. The use of alcohol is a part of most cultures worldwide, and it is recognized that there are both positive and negative aspects of alcohol consumption. Positive aspects might include the stimulation of appetite, aiding in sleep, and reduction in the incidence of heart disease. The negative aspects include poor judgment, liver disease, hypertension, memory problems, and even death. Of course, as with all drugs, there is a risk of addiction to alcohol, which exacerbates the negative aspects of alcohol use and leads to its own sequelae of complications and disorders. The National Institute on Alcohol Abuse and Alcoholism notes that "men who drink 5 or more standard drinks in a day (or more than 14 per week) and women who drink 4 or more in a day (or more than 7 per week) are at increased risk for alcohol-related problems" [75].

There are six levels of alcohol use: abstention, experimentation, social or recreational use, habituation, abuse, and, finally, addiction. Abstention is non-use. Experimentation is the use of alcohol for curiosity and without any subsequent drug-seeking behavior. Social or recreational use of alcohol involves sporadic infrequent drinking without any real pattern. Habituation involves drinking with an established pattern, but without any major negative consequences. Abuse of alcohol is the continuation of drinking despite negative consequences.

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_17,

Finally, addiction to alcohol involves a compulsion to drink, an inability to stop drinking, and the progression of major life dysfunction with continued use [48].

In the United States, the per-capita consumption of alcohol from beer, wine, and spirits combined in 2006 was 2.27 gallons. This value had risen from 2.23 gallons in 2005, a 1.8% increase. Essentially, since 1999 there has been a general increase in per-capita consumption of alcohol [76].

Alcohol dependence is a significant cause of morbidity and mortality in the United States and worldwide. The World Health Organization reports that about 140 million people throughout the world suffer from alcohol dependence [43]. Worldwide, alcohol causes 1.8 million deaths per annum. Eight million people in the United States are dependent on alcohol [37, 60]. Mortality rates follow drinking levels. A European study of 25 countries found that a rise of 1 liter per capita in alcohol intake was associated with a 1% rise in all causes of morbidity [45]. In Europe, men between the ages of 15 and 29 years have a 1 in 3 to 1 in 4 chance of dying as a result of alcohol [60]. The global economic burden of alcohol was estimated to be in the range of $210–665 billion in 2002 [3].

In the United States, more than 50% of adults have a close family member who is dependent on alcohol [20]. More than 25% of youths under the age of 18 years are aware of a relative who is dependent on alcohol [43]. Alcohol dependence runs in families [5, 16, 67].

The burden of the alcohol dependence disease is not equal across all regions. The disease impact of alcohol dependence is greatest in regions where the per-capita consumption is highest, such as Latin America, as compared with the Middle East. Additionally, other factors, such as increasing economic growth, have raised the risk of alcohol dependence in Europe [84].

Alcohol consumption increases the risk of harm or death in the context of the operation of heavy machinery, fires, falls, and water activities. In the United States, approximately 40% of all traffic fatalities are alcohol related [14]. Trauma and aggressive behavior are associated highly with alcohol consumption less than 6 h prior to the event.

Alcohol-Related Disorders

Alcohol is associated with many physical and mental disorders. Perhaps the most well-documented physical disorder is alcohol-related liver disease. Alcohol-induced fatty liver disease and obesity are both associated with progression to cirrhosis [13, 21]. In the United States, more than 900,000 individuals have cirrhosis; about 33% of these cases are attributed to excessive alcohol consumption. Typically, the development of cirrhosis requires the consumption of at least 80 g of ethanol daily for 10–20 years [61]. Additionally, the presence of hepatitis C virus in the context of alcohol dependence is associated with increased rates of cirrhosis [88, 91]. Women have an increased incidence of liver cirrhosis due to a greater level of alcohol consumption than men; however, there also might be increased susceptibility due to female gender [18, 80]. Globally, esophageal cancers, head and neck cancers, and liver cancers are of great concern, and are associated with alcohol abuse or dependence [10].

Individuals with mental illness are susceptible to alcohol abuse and dependence. This, in part, may be due to attempts to self-medicate anxiety, mania, or depression. Drinking alcohol in excess tends to worsen underlying psychiatric illness. Excessive use of alcohol is associated with a poorer chance of recovery from anxiety and depressive disorders [44]. Bipolar disorders and other impulse control disorders are associated with high rates of alcohol dependence. Dually diagnosed individuals have a poorer prognosis than those with just one of these disorders [23, 97]. Drinking more than 29 drinks per week can double the risk of a psychiatric disorder. Dementing illnesses, such as Alzheimer's or multi-infarct dementia, can be worsened or be caused by alcohol, and the relationship between the two can be difficult to determine [90]. Alcohol abuse and dependence are common

in individuals with schizophrenia and worsen symptoms of the disease [30, 34, 59]. Individuals with mental illness tend to underreport their use of alcohol [96].

Age of Onset of Drinking Behavior

The age of onset of drinking has a significant role in outcomes. An individual who starts drinking before the age of 15 years is approximately 4 times more likely to develop alcohol dependence, and this rate increases the earlier the onset of drinking [25]. Data collected from the 2005 National Survey on Drug Use and Health found that the mean age of the initiation of alcohol use among 12–20 year olds was 14 years [76]. Furthermore, according to the Monitoring the Future survey in 2004, 33.9% of eighth graders reported recreational use of alcohol within the past year [76]. The risk of developing alcohol dependence and a more relapsing illness is greater in adolescents compared with adults [46]. Notably, between 20 and 30% of early alcohol drinkers progress to heavy drinking in adulthood [32, 38]. Children who drink often have behavioral problems, especially conduct disorders [28, 51]. Frequently, adolescents, much like adults, are self-medicating for anxiety and depression [56, 87].

Alcohol dependence is a heterogeneous disorder and consists of subtypes, each with "varying degrees of biological and psychosocial antecedents" [6, 16, 52, 92]. The relationship between biological vulnerability, the environment, and their interactions in the development of alcohol dependence is the subject of active research [55]. Current evidence suggests that alcoholism is 50–60% determined genetically in both men and women [27]. The term "psychiatric pharmacogenetics" has now entered the alcohol literature. Its purpose is to use genetic testing to predict, on an individual level, which treatment will be efficacious [41].

Contrary to conventional wisdom, there are a number of studies showing that alcohol dependence is not always a chronic and progressive disease. This assertion is based on longitudinal studies and national surveys. It appears that those who develop alcohol dependence in middle age have the most stability in terms of the disease. In this population, alcoholism can be a chronic remitting disease [38, 39, 100, 102, 103]. In contrast, individuals who develop alcoholism over the age of 50 years will often decrease their drinking as they age. Interestingly, alcohol dependence in those over 65 years of age continues to increase in the United States.

Recently, the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions analyzed recovery rates of alcohol-dependent adults over a 1-year period. This population tended to be middle-aged, white males who were well educated (60% college educated); thus the generalizability is limited. More than half of the 4,422 adults had experienced the onset of alcohol dependence between the ages of 18 and 24, and only 25% had ever received any treatment for alcohol problems. At 1 year, 35.9% were fully recovered (17.7% low-risk drinkers plus 18.2% abstainers), 25% were still dependent, 27.3% were in partial remission, and 11.8% were "asymptomatic drinkers". Only 25% of the group had ever received any type of treatment [20].

Ethnicity, Gender, Place of Residence, and Religion Affect Alcohol Consumption

Ethnicity is a complex and multifaceted construct, and often the terms used by demographers do not reflect the different subgroups. For example, Korean Americans and Chinese Americans are both considered as "Asian", but drinking patterns are quite distinct between these two groups. A study conducted in 2004 found a lower rate of alcohol dependence in Chinese-American college students (5%) as compared with Korean-American college students (13%)

[29]. First-generation Mexicans and native-born Mexicans behave differently in their drinking patterns [12, 35]. Whites have the highest consumption levels, followed by Latinos and, then, Blacks. There is considerable ethnic disparity in the progression of drinking behavior. White men peak first (18–25 years), followed by Hispanic and Black men, with peak ages between 26 and 30 years. Although levels of drinking tend to be low among native-born Latinos, acculturation stress increases alcohol abuse and dependence with migration and first-generation populations [9, 12]. Ethnicity and socioeconomic status are also tied to the level of drinking [36].

Currently, women have nearly the same rates of alcohol dependence as men. This is in contrast with 1940, when men were more than twice as likely to be alcohol dependent. Interestingly, women often have a more severe disease course—perhaps due to reduced access to care, a greater time period before seeking treatment, or both.

Despite common misperceptions, the extent of drinking among Native Americans varies tremendously by tribe. The proportion of Native Americans who reported being current drinkers ranged from a low of 30% to a high of 84%. This wide range of reported drinking behavior is indicative of considerable variance between Native American tribes' alcohol use. Furthermore, it has been reported that Northern reservations have a higher incidence of hospital admittance for an alcohol-related medical problem than Southern reservations (111/1,000 versus 11/1,000, respectively) [99]. On some Native American reservations, high quantities of alcohol are consumed per episode, but the frequency of binge drinking is low [78].

Location also matters. Urban and suburban dwellers have higher rates of dependence compared with their rural counterparts. Drinking styles also differ.

Religion appears to be an important determinant for drinking [68]. Jews, Episcopalians, and Baptists living in rural areas show low rates of alcohol dependence compared with the general population.

Clinical Picture

Alcoholism can present in a multitude of ways, and at times its clinical effects can be subtle. Whilst there is no typical clinical pattern for an individual's progression from excessive drinking to alcohol dependence, there are certain themes that prevail. These are based on the pathophysiology of alcohol.

An early manifestation of excessive drinking is intoxication. This can begin with one's peers or by the influence of an older individual or family member. Some individuals note stress, depressed mood, or negative affect as a driving force, although at times it is elation. For others, there is an urge to drink, or "craving". Although the concept of craving appears simple, the craving literature has found it difficult to define with consensus. When alcohol consumption leads to repeated bouts of intoxication and becomes a fixed pattern of behavior, the likelihood of alcohol-related problems increases.

As the body adapts to excessive alcohol consumption, tolerance develops. With tolerance, an increasingly greater amount of alcohol consumption is needed to obtain the same physiologic effects. This can manifest as worsening grades or sick days among college students and workers and, for both, an increase in stress within interpersonal relationships, often characterized by greater irritability and moodiness. Furthermore, driving while under the influence of alcohol becomes more likely, and can lead to legal complications as well as morbidity and mortality to drivers, passengers, and other bystanders.

Heavy drinking can lead to blackouts, a failure to recall the events around the intoxication, due to the brain's inability to process and lay down the memory in the hippocampus.

Hangovers, which are associated with headaches and nausea, can manifest the next morning after a bout of heavy drinking. Often, as duties and responsibilities lapse, attention to hygiene can wane, and the chronic drinker's demeanor and behavior change. Memory lapses or forgetfulness may become more evident. Also, the chronic excessive drinker may report

guilt, remorse, and self-loathing after consuming alcohol and might conceal his or her drinking in order to avoid dealing with others. Such individuals tend to minimize the severity of their drinking behavior and its impact on others.

When drinking is being concealed, social isolation tends to occur, and to block or dampen guilt and anxiety, "relief drinking" can happen. Relief drinking may serve not only to temper these feelings but also to reduce transiently the resulting insomnia. Relief drinking might also ameliorate temporarily withdrawal symptoms upon drinking cessation (often starting within a few hours), which are the consequence of the sympathetic nervous system hyperactivity. These symptoms can include tremulousness and anxiety, and can proceed to a spectrum of serious withdrawal patterns, including delirium tremens. Despite any painful consequences such as loss of relationships, employment, legal entanglements, and physical and psychological complications, drinking can become the individual's sole goal. The physical features of the disease are described below.

Signs and Symptoms

Cardiovascular System

While it has been consistently shown that light-to-moderate drinking reduces the risk of coronary artery disease, there still remain severe risks to the cardiovascular system for people who are heavy alcohol drinkers [57, 64, 83, 85]. Cardiovascular conditions that may result from heavy drinking include hypertension, cardiac arrhythmias, and dilated cardiomyopathy.

The relationship between hypertension and heavy alcohol use has been known for more than three decades. While a mechanism has yet to be elucidated, several clinical studies have confirmed this relationship [54, 58, 65]. Clinicians in all fields of medicine should be aware that hypertension can be the result of heavy and chronic alcohol consumption.

The incidence of cardiac arrhythmias following excessive alcohol consumption is commonly known as "holiday heart phenomenon" following the observation that supraventricular arrhythmias in alcoholics most often occur on Mondays or between Christmas and New Year's Day [31]. While the direct cause of arrhythmias following heavy drinking is not explicitly known, it has been suggested that it could be due to myocardial damage, vagal reflexes, electrolyte or metabolic effects, or changes in conduction and refractory periods. Regardless of the root cause, the incidence of cardiac arrhythmias doubles for heavy drinkers compared with light drinkers [17].

Dilated cardiomyopathy is characterized by an enlarged heart with weakened contraction. Sustained heavy alcohol use is thought to be a major contributing factor to dilated cardiomyopathy [53]. Whilst the prevalence of alcohol-induced dilated cardiomyopathy is not fully known, it is estimated to be less than those who have alcohol-related liver cirrhosis [24]. The clinical picture may initially involve non-specific electrocardiographic findings and possible rhythm disturbances but may progress to congestive heart failure, chronic rhythm disturbances, and even death [7, 82].

Gastrointestinal System

Excessive alcohol consumption can cause gastroesophageal reflux disease, gastritis, or ulcers in the lining of the stomach. These can manifest as a burning in the throat or stomach or complaints of dark stools (i.e., melena). In individuals who present with a long history of gastroesophageal reflux disease, there is an increased incidence of Barrett's esophagus. Barrett's esophagus, a metaplastic conversion of the mucosa of the lower esophagus, is a well-known precursor lesion for esophageal cancer.

Chronic excessive alcohol consumption can cause varices, both gastric and esophageal. When varices rupture, often during severe retching, the individual may present with bright red blood. Bleeding varices are life-threatening

medical emergencies. Mallory-Weiss tears from esophageal varices often require monitoring in intensive care settings due to their risk for rebleeding with a high rate of blood loss.

Hepatic System

Chronic excessive alcohol consumption is associated with an increased risk for the development of liver disease. In the United States, 2 million people have alcoholic liver disease, ranging in severity from fatty liver to alcoholic hepatitis and end-stage cirrhosis [72].

Fatty liver is the accumulation of fatty acids in the liver. The pathogenesis of fatty liver is due to the overproduction of protonated nicotinamide adenine dinucleotide from alcohol dehydrogenase, which, in turn, leads to the inhibition of fatty acid oxidation, the citric acid cycle, and gluconeogenesis [62]. It is the inhibition of fatty acid oxidation, as well as an increased synthesis of triglycerides, followed by the inhibition of the secretion of lipoprotein from the liver, which all contribute to fatty liver [93].

Alcoholic hepatitis causes inflammation of the liver along with areas of fibrosis and necrosis. In the United States, approximately 10–35% of heavy drinkers develop alcoholic hepatitis. It can take months to years to develop this condition, and the only method to arrest its progress is through abstinence. Nevertheless, even with the cessation of alcohol consumption, the resulting scarring of the liver and any other collateral damage remain [69]. The mortality rate in individuals with alcoholic hepatitis is 15–20%, and even despite abstinence, many cases progress to cirrhosis [79].

Cirrhosis is characterized by progressive scarring of the liver due to the toxic effects of excessive alcohol use and alcohol's metabolites. Cirrhosis, the most advanced form of alcoholic liver disease, is the leading cause of death among alcoholics. Approximately 10,000 to 24,000 Americans die each year from cirrhosis due to excessive alcohol use [22]. Individuals with a diagnosis of both alcoholic hepatitis and cirrhosis have a death rate of more than 60% over a 4-year period. Most individuals die within the first 12 months of receiving the diagnosis [72]. Whilst the progression of cirrhosis might be halted by abstinence, cirrhosis is very difficult to treat, and the damage to the liver cannot be reversed.

Endocrine System

Pancreatitis, both acute and chronic, is another complication of excessive alcohol use. Pancreatic insufficiency or malabsorption presents with gray, foul-smelling stools that float. Pancreatitis typically manifests with pain in the center of the abdomen that radiates to the back. Pancreatitis ranges from an uncomfortable but stable condition to a medical emergency, depending on the severity of the event. Individuals with chronic pancreatitis may have calcifications that can be seen on a plain radiographic film.

Diabetes, both Type I and Type II, can be a consequence of excessive alcohol use. The development of Type I diabetes is rare and due to almost complete destruction of the pancreas. Type II diabetes is more common and due to weight gain from carbohydrate ingestion. Hypogonadism and osteoporosis are other complications. Thyroid disease also can be a sequela of excessive alcohol use, abuse, or dependence.

Rheumatic and Immune System

Chronic excessive alcohol consumption has been linked with an increase in illness and death from infectious diseases. Due to alcohol's immunosuppressive effects, there is an increased susceptibility to bacterial pneumonia, pulmonary tuberculosis, and hepatitis C. There is even some speculation that chronic excessive alcohol users are at increased risk for HIV infection due to lowered immune response, and those with HIV

may have a quicker progression from HIV to full-blown AIDS [72].

Gout is a common complication of chronic excessive alcohol consumption. Podagra (pain in the big toe) is a typical complaint. Alcohol use appears to mitigate certain autoimmune conditions such as systemic lupus erythematosis and rheumatoid arthritis.

Hematologic/Hematopoietic System

Anemias, both macrocytic and microcytic, are possible. Macrocytic anemia can be due to folate or vitamin B_{12} deficiency. An increased mean corpuscular volume can reflect macrocytic anemia. Of note, an increased mean corpuscular volume can also be a result of liver disease when the lipid bilayers that hold the red cell do not form correctly. When liver disease is severe, platelets can be destroyed or can sequester in an enlarged spleen. Microcytic anemias are related to active bleeding or blood loss and should prompt evaluation for a gastrointestinal disorder or lesion. Sideroblastic anemia can also occur.

Central Nervous System

The brain is sensitive to alcohol's toxic effects. Areas that are particularly sensitive include the hippocampus and the cerebellum, which can result in memory deficits and dementias as well as abnormal gaits and intention tremors. Rarely, central pontine myelinolysis can occur. These central nervous system deficits will be discussed in detail below.

Peripheral Neurologic System

Changes in position and vibration sense occur after prolonged excessive alcohol use and are due to vitamin B_{12} or folate deficiencies, or both. Myopathy can be a rare manifestation of alcohol dependence.

Integumentary System (Skin)

Psoriasis vulgaris, acne rosacea, and erythropoietic protoporphyria are all common skin conditions associated with excessive alcohol use. With liver disease, spider nevi, telangiectasias, palmar erythema (reddened palms), spider angiomas, and hepatic porphyrias, particularly porphyria cutanea tarda (bullous erosions, blistering, crusting lesions, and scarred healing with hyperpigmentation or depigmentation on the face, the side of the neck, and the back of the hands), might be found.

Nutritional Status

Low levels of potassium, magnesium, and phosphorus are common among individuals with severe alcohol dependence. Hypophosphatemia and hypomagnesemia also can be complications of severe nutritional deficiency. A refeeding syndrome that can lead to diaphragmatic paralysis and respiratory failure can occur. On many blood chemistries, magnesium and phosphorus are not part of the panel. Therefore, it is prudent to check these electrolytes in an alcohol-dependent individual who appears nutritionally compromised. Low levels of potassium can cause additional medical complications (particularly cardiovascular) if not replaced; however, this can be difficult to achieve in the setting of low magnesium. Therefore, magnesium and potassium need to be replenished simultaneously. As noted previously, thiamine replacement is also often required.

Oncology

An increasing number of cancers are being associated with excessive alcohol use or dependence.

Traditionally, alcohol-related cancers include oropharyngeal, esophageal, gastric, pancreatic, and rectal cancers. In women, alcohol abuse has been reported to contribute to the etiology of breast cancer.

Fetal Development

The consumption of alcohol during pregnancy has been linked with poor birth outcomes, the potential for long-term developmental disabilities, and the manifestation of fetal alcohol spectrum disorder, which includes fetal alcohol syndrome [2]. In 2004, it was estimated that a half-million women in the United States reported drinking alcohol during pregnancy. Nearly 1 in 5 of these women admitted to binge drinking. The resulting prevalence of American women drinking alcohol during pregnancy is 13% [33].

It has been estimated that the annual cost of care for those diagnosed with fetal alcohol spectrum disorders is $3.6 billion and that the lifetime cost for a single individual is $2.9 million [63]. These numbers are staggering considering that maternal alcohol use during pregnancy is one of the leading causes of preventable birth defects and developmental disabilities in the United States [40]. The health care community continues to emphasize prevention and stresses abstinence from alcohol for women who are pregnant or considering becoming pregnant. Research into the clinical management of persons diagnosed with fetal alcohol spectrum disorders is still emerging, but human studies using behavioral intervention are encouraging.

The clinical manifestations of fetal alcohol exposure fall under the classification of fetal alcohol spectrum disorders. Fetal alcohol spectrum disorders can be further subdivided into four categorical syndromes: (1) fetal alcohol syndrome; (2) partial fetal alcohol syndrome; (3) alcohol-related neurodevelopmental disorder; and (4) alcohol-related birth defects [8]. Approximately 1–4.8 of every 1,000 children born in the United States have fetal alcohol syndrome, and nearly 1 in 100 children are born with fetal alcohol spectrum disorders [89]. A clinical diagnosis of fetal alcohol syndrome requires alcohol exposure, a recognizable facial pattern that includes short palpebral fissures (<10th percentile), thin upper vermilion lip, and smooth philtrum, evidence of growth retardation or malformation, and evidence of neurocognitive defects. Fetal alcohol syndrome newborns may exhibit irritability, tremors, hypotonia, and even withdrawal symptoms. Partial fetal alcohol syndrome is diagnosed when there is confirmation of alcohol consumption during pregnancy and, while not all the features of fetal alcohol syndrome are present, neurocognitive and some craniofacial features are present. Children diagnosed with alcohol-related neurodevelopmental disorder do not typically have the growth retardation or facial features characteristic of fetal alcohol syndrome, but the resulting neurocognitive defects are more pronounced. A diagnosis of alcohol-related birth defect requires some of the facial features characteristic of fetal alcohol syndrome, but it is the behavioral features or structural abnormalities that are more prominent [70].

In addition to the physical impairments inflicted by alcohol, there is a spectrum of cognitive problems that children diagnosed with fetal alcohol spectrum disorders exhibit. These problems include difficulties with hyperactivity, sustained and focused attention, cognitive flexibility, learning and memory, and social understanding [50]. Aside from cognitive deficits, these children can also exhibit psychological and behavioral difficulties such as psychiatric problems, inappropriate sexual behavior, and alcohol and/or drug abuse [98]. In fact, 90% of those diagnosed with fetal alcohol spectrum disorders have some form of diagnosable psychiatric disorder ranging from attention deficit disorder to depression to schizophrenia. Fifty percent have been confined in either a mental health or criminal justice institution [63].

Although perinatal exposure to alcohol is known to be detrimental to fetal development, there is some debate as to whether it is ethanol or its metabolite acetaldehyde that causes the

developmental abnormalities found in fetal alcohol syndrome. Acetaldehyde is 10 times more teratogenic than alcohol [81]. However, this differential in teratogenicity is, perhaps, countered by the fact that blood ethanol concentration is 10 times higher than acetaldehyde in the typical person.

Acetaldehyde levels in excess of 35 μg can cause damage to a fetus, but acetaldehyde is rapidly metabolized by the placenta, and, after the third month of pregnancy, no acetaldehyde is detectable in the fetus [77]. The placenta is, however, permeable to ethanol, and the fetus does not have ethanol dehydrogenase, the enzyme required to break down ethanol. It is, therefore, reasonable to propose that an hour or two following alcohol ingestion, the ethanol concentration in the mother's blood may be falling while the ethanol concentration of the fetus may be rising [49]. Although it is not clear whether it is alcohol itself or its metabolite acetaldehyde that is responsible for the developmental abnormalities found in fetal alcohol spectrum disorders, the physical findings in fetal alcohol syndrome do point to an interesting fact: it is not the disruption of developing tissues, but rather the reduction in the number of cells and the subsequent cell migration abnormalities, particularly of the central nervous system, that causes the anomalies found in fetal alcohol syndrome.

Psychological and Psychiatric Complications of Alcohol

Individual differences in human physiology cause varying physical manifestations of the effects of both acute and long-term use of alcohol. Alcohol affects almost all organ systems through the natural progression of the disease. These are characterized as acute, chronic, and withdrawal effects.

Acute Effects

The acute effects of alcohol ingestion can be progressively tracked using the concentration of alcohol in a person's blood, or blood alcohol concentration. The unit of measurement for blood alcohol concentration is weight by volume, such as milligrams per deciliter, but can also be expressed as a percentage, such as 5% alcohol by volume [1]. The acute effects of alcohol consumption follow the typical dose-response relationship characteristic of all drugs in that the bigger the dose, the bigger the effect [72]. The typical progressive effects of alcohol intoxication in relation to blood alcohol concentration are illustrated in Table 1 [73, 74]; however, there is considerable personal variation.

The metabolism of alcohol occurs at a rate of about 1 ounce of pure alcohol (2 drinks) eliminated from the body every 3 h. Following alcohol consumption, it takes about 15–20 min for alcohol to reach the brain and cause impairment. The maximum blood alcohol concentration is reached 30–90 min following the ingestion of alcohol [71].

It is generally accepted that the consumption of a standard serving of alcohol (14 g, or 17.74 ml ethanol content) will increase the average person's blood alcohol concentration by 0.02–0.05%. The average person's blood alcohol concentration decreases approximately 0.015% per hour following complete cessation of alcohol intake. A blood alcohol concentration of 0.20% represents very serious intoxication. A blood alcohol concentration ranging between 0.35 and 0.40% could be potentially fatal alcohol poisoning. The accepted LD_{50} for alcohol—i.e., the dose that is lethal for 50% of the adult human population—is 0.40% [74].

Besides the well-known acute effects of alcohol consumption such as lowered inhibitions, impaired ability to drive, slowed reaction time, slurred speech, and blackouts, some rare complications can occur. These include alcohol-induced psychotic disorder, central pontine myelinolysis, and acute alcoholic myopathy.

Alcohol-induced psychotic disorder or alcohol hallucinosis occurs most often in the context of drinking but can also occur in the presence of withdrawal. It is characterized by the acute onset of visual and auditory hallucinations

Table 1 The progressive effects of alcohol

Blood alcohol concentration	Changes in behavior	Activity impairment
0.01–0.05	Relaxation	Impaired alertness
	Feeling of well-being	Impaired judgment
	Loss of shyness	Minor impairment of memory
	Loss of inhibitions	Minor impairment of reasoning
	Exaggerated behaviors	
0.06–0.10	Feeling of euphoria	Impaired coordination
	Feeling of pleasure	Impaired balance
	Numbness of feelings	Impaired speech
	Nausea and sleepiness	Impaired vision
		Slow reaction time
0.11–0.20	Anger	Impaired reasoning
	Mood swings	Impaired depth perception
	Feeling of sadness	Inappropriate social behavior
	Confusion	Impairment of motor coordination
	Feeling of restlessness	Slurred speech
	Nausea and vomiting	Severely impaired judgment
	Disorientation	Severe memory impairment
		Blackouts
0.21–0.30	Aggression	Loss of balance
	Depression	Loss of temperature regulation
	Stupor	Loss of consciousness
	Reduced sensations	May be difficult to awaken
	Nausea and vomiting	
0.31–0.40	Unconsciousness	Loss of bladder control
	Coma	Difficulty breathing
	Death possible	Slowed heart rate
0.41 and greater	Death	

Adapted from tables in National Institute on Alcohol Abuse and Alcoholism [73, 74] as well as Inaba and Cohen [48].

and often includes delusions of a persecutory nature. These hallucinations and delusions usually resolve within 48 h although in some cases they can last much longer.

Central pontine myelinolysis is a rare disorder that is most often found in individuals who abuse alcohol. This disorder typically evolves over days to weeks, and the individual presents with mental confusion along with dysarthria, mutism, dysphagia, conjugate gaze palsies, and facial and neck weakness. Chronic hyponatremia seems to be a precipitating factor in the development of central pontine myelinolysis. Characteristic of the complication is bilaterally symmetrical focal destruction of white matter in the ventral pons. Approximately 10% of individuals display extrapontine lesions in the thalamus, basal ganglia, cerebellum, and cerebral white matter. As the name of the disorder implies, these lesions are typified by a loss of myelin [26]. With proper support, individuals diagnosed with this condition typically regain some or all function after a few weeks [11].

Acute alcoholic myopathy is a severe and life-threatening disorder that typically presents following several days of binge drinking [42]. Individuals typically present with pain, tenderness, cramps, proximal weakness, and swelling of the muscles, which can lead to cardiac arrhythmias. Further complications of acute alcoholic myopathy include hyperkalemia, renal failure, and even death. Following abstinence, recovery takes from a few days to weeks.

Chronic Effects

Although the physical effects of chronic alcohol abuse or dependence are well characterized, the psychological and psychiatric consequences are

less familiar. Such chronic complications from chronic alcohol abuse or dependence include Wernicke's encephalopathy, Korsakoff's psychosis, alcoholic neuropathy, chronic alcoholic myopathy, and alcoholic dementia.

Wernicke's encephalopathy is caused by thiamin (vitamin B_1) deficiency and is usually diagnosed by a triad of symptoms: ataxia, oculomotor abnormalities, and global confusion [86, 104]. Wernicke's encephalopathy, however, is not just a condition of alcoholics but is found in people who are malnourished due to persistent vomiting, are experiencing starvation, or are undergoing renal dialysis. Gait ataxia is a prominent symptom, as are nystagmus and bilateral rectus palsies. The global confusion is characterized by sleepiness, disorientation, and inattention. Treatment (i.e., vitamin B_1 supplements) can correct most or all of the disturbances, but if left untreated, the mortality rate is 10–20%. Individuals surviving Wernicke's encephalopathy, however, tend to acquire Korsakoff's psychosis [4, 63].

Korsakoff's psychosis is a chronic amnesic disorder that can occur in individuals who have had Wernicke's encephalopathy. Like Wernicke's encephalopathy, Korsakoff's psychosis is the result of thiamin deficiency. It is manifested by retrograde and anterograde amnesia, the latter caused by an inability to lay down new memories. While immediate recall remains intact, short-term memory is impaired. Individuals are unaware of their memory deficits, and confabulation is common. The most probable cause of the memory deficits is lesions in the dorsal medial nuclei of the thalamus [94]. While 20% of individuals recover completely over several months with vitamin B_1 supplements, approximately 25% never recover and subsequently require long-term care [98].

Alcoholic neuropathy is the most commonly reported neurologic complication in people addicted to alcohol. These individuals present with paresthesias, pain, and weakness. These individuals also can have reduced pain and reduced temperature sensations. Typically, there is axonal degeneration and demyelination, possibly due to a neurotoxic effect of ethanol on the peripheral nerves [15, 66]. While recovery is possible, it requires total abstinence and may take months.

The development of chronic alcoholic myopathy manifests as a painless syndrome wherein the individual has muscle weakness. The severity of the myopathy is related directly to the amount of alcohol consumed [101]. It is thought that chronic alcoholic myopathy is the result of the toxicity of ethanol and its metabolites, such as acetaldehyde, as opposed to nutritional deficiencies [1, 50, 95]. Individuals typically improve a few months after the discontinuation of alcohol.

The diagnostic criteria for alcoholic dementia remain controversial. There are currently no acceptable criteria available to diagnose definite alcohol-related dementia. There do exist, however, criteria for diagnosing probable alcohol-related dementia. These criteria include: (1) a clinical diagnosis of dementia at least 60 days after alcohol exposure and (2) significant alcohol use as defined by 35 or more standard drinks/week for men and 28 or more standard drinks/week for women for 5 years or longer. Furthermore, the onset of dementia must fall within a 3-year period of significant alcohol use [47]. The neuropathic changes that usually accompany individuals diagnosed with alcoholic dementia include cortical atrophy, the loss of cortical neurons, and enlargement of the lateral ventricles [19]. The cognitive function of these individuals tends to improve after a few months of abstinence. Even the neuroimaging of these individuals reveals decreased ventricle dilation following a few months of abstinence [71].

Conclusions

Alcohol-related disorders are an important global health problem. Not only is there a significant economic burden, but the negative personal effects of excessive alcohol consumption may be both physically and psychologically devastating. Many factors including age of onset, ethnicity, gender, place of residence, and religion must all be considered in regard to the

clinical picture of alcohol use and abuse. The clinical picture of alcohol is different for everyone, but there are consistent themes based on the pathophysiology of alcohol. Intoxication, blackouts, and hangovers are all typical clinical manifestations of excessive alcohol use. While these manifestations may be readily apparent, other signs and symptoms may remain subtle, especially at the onset of excessive alcohol consumption. Many organ systems may be negatively affected by alcohol consumption. Alcohol-related liver disease, holiday heart phenomenon, gastroesophageal reflux disease, and anemia may all result from the prolonged use of alcohol, especially in excessive amounts. Furthermore, the excessive consumption of alcohol not only harms the individual who is drinking but may also have serious physical effects on the developing fetus. The psychological and psychiatric picture of alcohol consumption can be divided into acute and chronic effects. The acute effects of alcohol consumption, such as a loss of inhibitions and feelings of pleasure and euphoria, are well known, and these well-known effects entice individuals to consume alcoholic beverages. Finally, the continued excessive use of alcoholic beverages may result in severe chronic psychological and psychiatric effects such as Wernicke's encephalopathy or Korsakoff's psychosis.

Acknowledgements We thank Catharine Helms and Robert H. Cormier, Jr. for their assistance with manuscript preparation.

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Cocaine

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Contents

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Introduction

The effects of cocaine on the nervous system have been studied for over 100 years. Early observers noted that among the symptoms produced by frequent cocaine use, one of the most prominent was cocaine craving [40]. In time, this craving for cocaine develops into a disorder termed cocaine dependence. Cocaine dependence is a chronic disorder characterized by compulsive drug seeking, frequent relapses, and continued drug use despite negative consequences [24, 32, 44]. On a personal level, the disease is associated with devastating consequences including loss of employment, disruption of marriage and family stability, risk of imprisonment,

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_18,

and associated health risks such as viral hepatitis and HIV [19, 39]. On a societal level, costs associated with cocaine addiction include increases in violent crime, increased prevalence of bloodborne and sexually transmitted infections, and a soaring population of incarcerated addicts [33]. Data from 2006 indicate that there were 2.4 million current cocaine users aged 12 or older [118]. In this chapter, we review the definitions and diagnostic criteria for the various cocaine-related disorders as well as the current understanding of the molecular biological basis for these disorders and current approaches to treatment.

Historical Aspects

Cocaine is a naturally occurring substance derived from the leaves of the Erythrooxylum coca plant. Its use is thought to have originated over 5,000 years ago in religious ceremonies among the ancient civilizations of South America, but its use was increased greatly following the conquest of South America by the Spanish, who valued its effects in decreasing appetite and increasing stamina in the slaves who worked in the silver mines [43, 57, 122]. The first chemical purification of cocaine was achieved by Albert Niemann in 1860, and shortly thereafter it was incorporated into a variety of patent medicines and "tonics", including the original recipe for Coca-Cola, which was marketed as a temperance drink, "offering the virtues of coca, without the vices of alcohol" [43]. Its use was promoted by several prominent figures of the time, perhaps most notably by Sigmund Freud [43, 57]. Growing concern about the potential toxicity of cocaine led to the passage of the Harrison Narcotics Tax Act in 1914. However, cocaine continued to be sold over the counter in the United States in a variety of forms until 1916.

Sex and Gender Differences

A variety of studies over the past decade have shown that the responses of men and women to cocaine differ markedly in several important aspects [37, 82, 92]. These differences extend to all phases of the addictive process including induction, maintenance, relapse, and response to treatment. Compared with men, women have been reported to initiate cocaine use at later ages, but progress more rapidly from first use to dependence, a phenomenon termed "telescoping" [126]. Women have also been reported to experience decreased subjective effects of cocaine, including both positive ("feel high") and negative ("paranoid/suspicious", "heart racing/pounding") effects [116]. This phenomenon may be explained partly by the lower peak blood levels of cocaine observed in women after administration of the same dose of cocaine [73], although other studies have reported an increase in negative "nervousness" effects among women [67]. Cocaine-dependent women also have been reported to differ from their male counterparts in their subjective [2] and physiological [35] responses to stress, factors which may place them at increased risk for stress-induced relapse after an initial period of sobriety [37]. This is consistent with recent findings that severity of childhood trauma is predictive of cocaine relapse outcomes in women but not men [54]. Cocaine-dependent women also have been reported to have a higher pattern of psychiatric, medical, social/family, and employment problems than men [82]. Finally, cocaine-dependent men and women appear to differ in their response to different forms of treatment for cocaine dependence, with men, but not women, showing decreased rates of relapse following treatment with disulfiram [89]. Whilst progesterone was found to decrease the effects of smoked cocaine in women, this was not the case in men [30]. These findings highlight the need to consider individual factors including gender when discussing both the pathophysiology of and approaches to the treatment of cocaine dependence and abuse.

Pregnancy and Effects of Prenatal Exposure

The increasing prevalence in recent years of cocaine use among women of child-bearing age has significance not only for the women

themselves but for the potential consequences to children exposed *in utero*. The pathophysiology of cocaine's effects on the developing nervous system has been conceptualized as occurring along three inter-related pathways [68]. The first of these are the direct neurochemical effects of cocaine on the developing nervous system; the second are sequelae related to the vasoconstrictive effects of cocaine on both the fetal and placental vessels. Finally, and perhaps most insidious, are the epigenetic changes that may be induced by cocaine's effects on the developing brain, leading to long-term changes in both reward and stress-related circuits in the brain. A meta-analysis published in 2001 [38] of studies carried out on children who had been exposed to cocaine *in utero* suggested that after controlling for confounders, including prenatal exposure to tobacco, marijuana, or alcohol and the quality of the child's environment, there was no consistent negative association between prenatal cocaine exposure and physical growth, developmental test scores, or receptive or expressive language. However, studies using animal models of *in utero* cocaine exposure suggest that there may be latent differences in neurocircuitry that are not revealed until the offspring are exposed to various stressors in adulthood [12]. Moreover, neuroimaging studies of adolescents who were exposed prenatally to cocaine confirm the presence of subtle differences in brain activation [26]. These differences in brain function may interact with various environmental factors to increase the risk for a variety of adverse outcomes including the development of cocaine dependence. Additional effects of cocaine during pregnancy and development are discussed in Chapter "Alcohol and Drugs of Abuse in Pregnant Women: Effects on the Fetus and Newborn, Mode of Action, and Maternal Treatment".

Youth

In 2008, 1.8% of 8th graders, 3.0% of 10th graders, and 4.4% of 12th graders had used cocaine in the past year [84]. All of these numbers represent a decrease from the previous year's figures, suggesting that efforts aimed at primary prevention are having some effect. However, given the devastating consequences associated with cocaine abuse and dependence, they are certainly not cause for complacency. Results from the 2006 National Survey on Drug Use and Health [118] show that in 2006, there were 977,000 persons aged 12 or older who had used cocaine for the first time within the past 12 months; this averages to approximately 2,700 initiates per day. While these numbers may have declined somewhat in the past 2–3 years, this still represents a terrible loss to the affected individuals, their families, and their communities.

Criminality

Studies conducted in the 1990s suggested that the arrival of crack cocaine in urban centers in the United States and elsewhere was associated with a significant increase in the rates of a variety of types of crime [4, 45]. Concerns about the relationship between cocaine use and criminality have resurfaced at the end of the first decade of the twenty first century in connection with the drug wars currently taking place along Mexico's northern border.

Broadly speaking, the relationship between cocaine use and criminality can be considered in (at least) two complementary ways. The first is the relationship between cocaine use and criminality on the local level by users and small-scale dealers of cocaine. (Frequently these groups overlap.) The second is the relationship between the illegal sale of cocaine and criminality on the national or international scale. On the individual level, cocaine use and dependence clearly increase the likelihood of engaging in other criminal activity including prostitution, theft, and violent crime [19, 55]. Conversely, successful treatment of substance dependence is associated with decreased likelihood of reoffending among substance abusers in the criminal justice system [83]. On the national and international scale, the funds provided to international criminal organizations through the sale of illegal

drugs and the violence perpetrated by these organizations can undermine the stability of entire nations and regions. These findings highlight the need for new approaches to treatment for cocaine-abusing individuals in the criminal justice system, as well as improved national and international efforts to direct treatment to those in need.

Cocaine Dependence

Definition/Diagnostic Criteria

Cocaine dependence can be conceptualized in a number of different ways. As defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Text Revision [1], the diagnosis of cocaine dependence is based on the same criteria used to diagnose dependence on other drugs of abuse. These include the presence of three or more of the following within the past year:

1) tolerance, defined by either
    a. a need for increased amounts of the substance to achieve intoxication or the desired effect, or
    b. markedly diminished effect with continued use of the same amount of the substance,
2) withdrawal, manifested by either
    a. characteristic withdrawal syndrome for the substance, or
    b. the same (or a closely related) substance being taken to relieve or avoid withdrawal symptoms,
3) the substance is taken in larger amounts or over a longer period than was intended,
4) a persistent desire for, or unsuccessful efforts to cut down or control, substance use,
5) a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects,
6) important social, occupational, or recreational activities are given up or reduced because of substance use, and
7) substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., continued cocaine use despite recognition of cocaine-induced depression. . .) (adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Text Revision [1]).

Note that this definition does not require the presence of physiological dependence, although the presence of physiological dependence may contribute to making the diagnosis (i.e., criterion 1 or 2 above). Rather, as conceptualized in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, the diagnosis of cocaine dependence is made based primarily on the pattern of maladaptive behavior associated with its use.

Physiological dependence on cocaine is characterized by tolerance (criterion 1 above) and the occurrence of specific withdrawal symptoms when use is stopped. Symptoms of cocaine withdrawal include cocaine craving, depressed mood, sleep disturbance, appetite disturbance, and increased anxiety [6, 7, 20, 115]. These symptoms have been incorporated into the current diagnostic criteria for cocaine withdrawal (discussed below), and standardized instruments have been developed for rating the severity of these symptoms [63].

Neurobiology

Development of cocaine dependence is thought to be due to long-term consequences of repeated cocaine use in several areas of the brain, particularly those related to the processing of reward-related information and executive control of behavior [31, 62, 87, 88]. Molecular changes that occur following the chronic administration

of cocaine include changes in both the dopamine and glutamate signaling pathways. Chronic administration of cocaine increases the level of tyrosine hydroxylase, the rate-limiting enzymes in dopamine synthesis in the ventral tegmental area, and the glutamate receptor GluR1. These effects are mediated, at least in part, by the transcription factor cyclic AMP response element binding protein [87]. Up-regulation of cyclic AMP response element binding protein appears to increase the activity of negative feedback loops in the brain associated with tolerance and dependence. Another transcription factor that is induced by chronic cocaine exposure, ΔFosB, appears to contribute to sensitization (increased behavioral response to the same dose of a drug following repeated administration) [13].

Studies in animals show that the effects of cocaine use on the brain can be extremely long lasting and, in some cases, can continue to increase during a period of abstinence such that the abstinent user—far from being "back to normal" after a brief or even a prolonged period of abstinence—may be even more sensitive to drug-related cues than someone who is actively using [104]. In addition to the changes in brain chemistry described above, long-term exposure to cocaine can cause structural changes in the brain—particularly by increasing the number of dendritic branches and the density of spines in a part of the brain called the nucleus accumbens [96]. The nucleus accumbens is part of the limbic system that regulates our response to natural rewards such as food or sex. Dendrites, specifically dendritic spines, are the specialized parts of brain cells that receive input from other cells and other brain regions. Changes in the number and structure of dendritic branches in the nucleus accumbens may account for some of the extremely long-lasting changes in brain function seen in cocaine addiction [62, 86]. With this in mind, treatment strategies for cocaine dependence must focus on long-term treatment outcomes and the development of strategies for preventing or minimizing the impact of relapses over the lifetime of the cocaine-dependent individual.

Treatment Approaches

Pharmacological Treatments for Cocaine Dependence

Strategies for treating cocaine dependence include both pharmacological treatments (reviewed in [25, 64, 117]) and non-pharmacological treatments [28]. There are several promising medications for the treatment of cocaine dependence. These include GABAergic, dopaminergic, glutaminergic, and serotonergic medications, and even cocaine vaccines [64, 117]. Details of the effects of these medications are described in Chapter "Pharmacotherapy of Cocaine Addiction".

Self-Help Treatments for Cocaine Dependence

Non-pharmacological treatments for cocaine dependence include a variety of individual psychotherapies [21, 98], group therapies [123], and 12-step programs such as Narcotics Anonymous. Not surprisingly perhaps, the primary determinant of outcome for most such psychosocial treatments appears to be length of retention in treatment, with better outcomes generally reported by those treated 90 days or longer in both residential and outpatient settings [108]. These findings reinforce the need to focus on long-term outcomes and relapse prevention as the primary goal of treatments (both pharmacological and psychosocial) for cocaine dependence. Specific psychotherapeutic approaches to the treatment of cocaine dependence are discussed in more detail in the section below on craving and relapse.

Cocaine Abuse

Definition/Diagnostic Criteria

Cocaine abuse is defined by the same criteria used to define other substance abuse disorders

[1]. These include "a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) or the following occurring within a 12-month period:

1. recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
2. recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. recurrent substance-related legal problems (e.g., arrest for substance-related disorderly conduct)
4. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)" [1].

Compared with cocaine dependence, cocaine abuse is characterized by less frequent and less intense use, and the degree of social disruption is generally less severe, with an episodic—rather than a continuous—pattern of problematic use, neglect of responsibilities, and interpersonal conflict related to substance use [1]. However, it should be clear from the symptoms listed above that cocaine abuse and dependence occur along a continuum, with abuse often progressing to full dependence in months to years [93, 103].

Neurobiology

Cocaine abuse represents an earlier stage along the continuum from recreational use to dependence. It has been proposed that whilst changes in dopamine signaling are most important in the transition from recreational use to abuse (initiation of addiction), the transition from abuse to dependence (end-stage addiction) is due to changes in glutaminergic signaling from the anterior cingulate and orbitofrontal cortex to the nucleus accumbens [62]. These changes serve to decrease the value of natural rewards and to diminish cognitive control over drug seeking.

Treatment Approaches

Treatments for cocaine abuse are similar to those for cocaine dependence and include both pharmacological and psychosocial interventions. Promising pharmacological treatments for cocaine dependence and abuse are detailed in Chapter "Pharmacotherapy of Cocaine Addiction". Self-help (see above) and other non-pharmacological treatments (see below) are detailed within this chapter. Generally, compared with cocaine-dependent individuals, cocaine abusers present with less severe problems and tend to have better outcomes [108]. Nevertheless, the majority of cocaine users (75%) meet the criteria for both abuse and dependence. In most cases (57%), the criteria for abuse and dependence occur within the same year, and in a small percentage of cases (17%), the criteria for abuse are met only after the physiological criteria for dependence are already present [94]. Thus, the finding that a person meets the diagnostic criteria for abuse but not dependence should by no means be a cause for complacency.

Cocaine Intoxication

Definition/Diagnostic Criteria

Acute cocaine intoxication is typically characterized by a "high" feeling and stimulant effects including euphoria, increased pulse and blood pressure, and psychomotor activation. It also can

include any of the following: alertness, anger, anxiety, belligerence, cognitive impairment, gregariousness, grandiosity, hyperactivity, hypervigilance, impaired judgment, impaired social and occupational functioning, interpersonal sensitivity, mood lability, restlessness, stereotyped and repetitive behavior, increased talkativeness, and tension. With chronic intoxication, there also can be depressant effects such as social withdrawal, sadness, bradycardia, decreased blood pressure, and decreased psychomotor activity. Both acute and chronic intoxication are associated with impaired social and occupational function. Severe intoxication is associated with a number of medical complications including seizures, cardiac arrhythmias, hyperpyrexia, and vasoconstriction leading to increased risk for myocardial infarction, stroke, and even death.

Diagnostic criteria for cocaine intoxication include:

a. Recent use of cocaine.
b. A clinically significant maladaptive behavioral or psychological change (described above) that develops during or shortly after cocaine use.
c. Two (or more) of the following physical symptoms: (1) tachycardia or bradycardia, (2) pupillary dilation, (3) altered blood pressure (elevated or lowered), (4) chills or perspiration, (5) nausea or vomiting, (6) evidence of weight loss, (7) psychomotor agitation or retardation, (8) muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias, and (9) confusion, seizures, dyskinesias, dystonias, or coma.
d. The symptoms observed are not due to a general medical condition or better accounted for by another mental disorder [1].

Neurobiology

Cocaine, administered by any of the commonly used routes including snorting, smoking, and intravenous injection, enters the bloodstream and crosses the blood-brain barrier rapidly. While cocaine inhibits reuptake of all three monoamine neurotransmitters (dopamine, norepinephrine, and serotonin), both the acute effects of cocaine and the long-term changes responsible for the development of cocaine dependence are thought to be related primarily to its effects on dopamine signaling [88]. The neurotransmitter dopamine is synthesized in a small number of specialized dopamine-producing (dopaminergic) cells in the brain, and serves to regulate a number of important physiological processes. In particular, dopaminergic signaling in the limbic system, including the ventral tegmental area (which produces dopamine) and the nucleus accumbens (one of the main sites of dopamine's actions), functions to signal the presence of naturally occurring rewards. Cocaine-induced increases in dopamine activity within the nucleus accumbens have been associated with the "high" felt after its ingestion [53, 88]. In addition to its effects on the brain, cocaine can have direct effects on the circulatory system, leading to increased blood pressure and risk for myocardial infarction and stroke [5, 58, 65, 121].

Treatment Approaches

There are no specific treatments for cocaine intoxication, and in most cases acute cocaine intoxication can be managed with supportive care. Benzodiazepines are considered first-line treatment for agitation associated with acute cocaine intoxication. Typical antipsychotic medications (e.g., perphenazine and haloperidol) can be used for treatment of paranoia or psychosis associated with cocaine intoxication; however, these should be used with caution because of the possibility of acute hyperthermia syndromes associated with acute cocaine intoxication, which may be confused with neuroleptic malignant syndrome [50]. Cardiac or neurological symptoms associated with severe intoxication may require referral to an intensive care unit. Pregnant women will require additional monitoring since vasoconstriction associated with cocaine intoxication may lead to premature labor.

Given the chronic, relapsing nature of cocaine abuse and dependence, it is important to focus, as soon as possible, on planning for long-term treatment and relapse prevention. In most cases, referral to residential or other long-term treatment modalities can be made even prior to the resolution of the acute symptoms associated with cocaine intoxication.

Cocaine Withdrawal

Definition/Diagnostic Criteria

Withdrawal from cocaine occurs after cessation or reduction of heavy and prolonged cocaine use and is characterized by dysphoric mood and two or more of the following:

A. fatigue
B. vivid, unpleasant dreams
C. insomnia or hypersomnia
D. increased appetite
E. psychomotor retardation or agitation.

These symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning to be diagnosed as cocaine withdrawal [1]. In some cases, cocaine withdrawal is associated with a profound depression, and suicidal ideation and actions can occur.

Neurobiology

Cocaine withdrawal is thought to occur as the result of long-term adaptations in brain physiology and functioning caused by prolonged exposure to cocaine. Such adaptations are generally homeostatic in nature [66]. That is to say, they oppose the acute effects of cocaine and enable the brain to function as well as possible despite the greatly increased dopamine signaling induced by cocaine. The synaptic architecture and signaling properties of a number of brain regions, including the limbic system, frontal cortex, and amygdala, are reconfigured such that functioning in the presence of cocaine becomes the new "normal". The abrupt withdrawal or reduction of cocaine intake is perceived as a state of dopamine deficiency, and triggers the occurrence of the symptoms described above, as well as an intense desire to resume cocaine use in order to restore what is now perceived as a normal level of functioning. Molecular changes associated with the development of cocaine withdrawal include the accumulation of the transcription factor ΔFosB, increased cyclic AMP-cyclic AMP response element binding protein signaling in the medium spiny neurons of the nucleus accumbens, increases in tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis), and increased neurotrophin and cyclic AMP response element binding protein signaling in the ventral tegmental area, where the dopaminergic projections to the nucleus accumbens originate. These changes have the net effect of decreasing basal dopamine signaling but increasing the cocaine-stimulated release of dopamine, and thus reduce the body's ability to respond to rewards other than cocaine [77, 87, 88]. Importantly, while the acute phase of cocaine withdrawal typically resolves within several days, some of the neuroadaptations induced by prolonged exposure to cocaine may persist for months or even longer, resulting in a heightened sensitivity to both cocaine and cocaine-associated cues [74, 104]. Thus, the resolution of acute withdrawal symptoms does not imply that the person is no longer dependent on cocaine.

Treatment Approaches

There are no specific treatments for cocaine withdrawal, and in most cases acute cocaine withdrawal can be managed with supportive care (see also Chapter "Pharmacotherapy of Cocaine Addiction"). Mood changes including depression, irritability, anhedonia, emotional lability,

and disturbances in attention and concentration are common. In some instances, cocaine withdrawal can be associated with a profound depressive state, and suicidal ideation and actions are not infrequent. In these cases, hospitalization to prevent self-harm may be necessary. As noted above, resolution of acute withdrawal symptoms should not be construed as implying that the person is no longer dependent on cocaine. Therefore, as soon as possible, the focus of treatment should shift to planning for long-term treatment. Ideally, this should include referral to residential or other long-term treatment modalities with a focus on relapse prevention.

Cocaine Craving and Relapse

Definition/Diagnostic Criteria

Cocaine craving and relapse are not specific diagnoses but are associated with all cocaine-related disorders. As discussed above, prolonged use of cocaine results in an intense desire to consume more cocaine. This effect has been noted for over 100 years [40] and is one reason why cocaine dependence is so difficult to treat. Relapse refers to the resumption of drug use after a period of abstinence. However, defining relapse in cocaine users is complex since many users frequently engage in binge and other styles of periodic use, such that short intervals of abstinence are the rule even among current users [46]. Factors associated with increased risk for relapse include current levels of cocaine craving, exposure to stress or drug-related cues, and history of childhood abuse [54, 90, 110].

Neurobiology

As discussed above, prolonged exposure to cocaine or other drugs of abuse produces homeostatic changes in the brain, such that it is no longer able to function normally in the absence of the abused drug [66]. Changes in glutaminergic signaling from the anterior cingulate and orbitofrontal cortex to the nucleus accumbens may be important in the transition from abuse to dependence (end-stage addiction) [61, 62]. Animal studies suggest roles for the basolateral amygdala in cue-primed reinstatement, the ventral tegmental area in drug-primed reinstatement, and adrenergic innervation of the extended amygdala in stress-primed reinstatement [61]. All three forms of priming may converge on the anterior cingulate cortex and have a final common output through the core of the nucleus accumbens. Neuroimaging studies also support a role for the projections from the anterior cingulate and orbitofrontal cortex to the nucleus accumbens in drug addiction [15, 44, 62].

Parallel evidence from human laboratory and relapse outcome studies also substantiates preclinical evidence of neuroadaptations in brain stress and reward pathways that are associated with increased stress and drug cue-induced drug craving, anxiety, and dysfunctional physiological and neuroendocrine responses in treatment-engaged, cocaine-dependent individuals as compared with healthy social drinkers [36, 95, 109]. Stress and cue-induced cocaine craving and neuroendocrine responses have been shown to predict cocaine relapse outcomes [94, 109]. Brain imaging studies of stress and drug cue-induced cocaine craving show specific positive association within the dorsal striatum regions [111, 112], while inhibitory control deficits show decreased activity in the prefrontal and anterior cingulate regions in cocaine-dependent individuals [69].

Treatment Approaches

Treatments for cocaine craving and relapse are at the heart of all treatments for cocaine dependence and abuse. These include both pharmacological treatments, which are detailed in Chapter "Pharmacotherapy of Cocaine Addiction", and non-pharmacological treatments, which are described below.

Other Non-Pharmacological Approaches

Apart from the self-help treatments described above, other psychosocial approaches to the treatment of cocaine craving and relapse include contingency management, relapse prevention, general cognitive behavior therapy, and treatments combining cognitive behavior therapy and contingency management [28]. Contingency management interventions are based on principles of operant conditioning and offer monetary and/or non-monetary rewards that are contingent on negative toxicology screens, indicating abstinence from drug use [48]. This approach has been evaluated in several controlled trials [47, 59, 105–107] and has shown consistent, if modest, effects in reducing relapse (reviewed in [28]). Potential barriers to more widespread use of this approach include costs associated with monetary incentives and frequent drug testing as well as social prohibitions against paying drug users for "good behavior". However, some studies have found that contingency management approaches using prizes worth from $1 to $100 can achieve short-term abstinence with a lower per-client cost [91].

Relapse prevention is an alternative approach that focuses on identifying high-risk situations for relapse to drug use and avoiding or managing these situations by rehearsing alternative responses. Several studies have evaluated the effectiveness of relapse prevention techniques in cocaine-dependent subjects with mixed results. A 1991 study by Carroll et al. [10] that compared relapse prevention therapy with interpersonal psychotherapy found no significant main effect for treatment. However, among the subgroup of more severe users, subjects who received relapse prevention therapy were significantly more likely to achieve abstinence (54% vs. 9%) and to be classified as recovered (54% vs. 0%) than those who received interpersonal psychotherapy, while among the less severely addicted group, there was no difference between the two treatments. A 1994 study by the same research group comparing relapse prevention therapy with pharmacological treatment using the antidepressant imipramine or a combination of relapse prevention therapy plus desipramine found no significant effects on outcome for either relapse prevention therapy or medication. However, a 1-year follow-up study showed evidence of significant continuing improvement among the group who had gotten relapse prevention therapy [11]. Another study comparing relapse prevention therapy with 12-step programs in a group of 110 treatment-seeking subjects found no difference between the two treatments [125]. Thus, the available evidence is limited and does not strongly support relapse prevention therapy over other approaches to treating cocaine craving and relapse.

Cocaine Intoxication-Induced Delirium

Definition/Diagnostic Criteria

Cocaine intoxication-induced delirium refers to an acute disturbance in consciousness and cognition that occurs during cocaine intoxication—and is in excess of the cognitive disturbances usually associated with cocaine intoxication—and when the symptoms are sufficiently severe to warrant independent clinical attention. Diagnostic criteria for cocaine intoxication-induced delirium are identical to those for other substance-induced deliriums and include:

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. Evidence from the history, physical examination, or laboratory findings that: (1) these symptoms developed during the course of cocaine intoxication, and/or (2) cocaine use is etiologically related to the disturbance in consciousness [1].

Neurobiology

The precise molecular biological basis of cocaine intoxication-induced delirium is currently unknown. However, post-mortem studies of individuals with cocaine intoxication-induced delirium or chronic cocaine abusers have shown reduced levels of the mRNA encoding the dopamine transporter [14, 70] and the transcription factor NURR1 [3], which regulates the expression of the dopamine transporter. These changes would be expected to raise extracellular levels of dopamine in the brain and thus interfere with the normal modulatory roles of dopamine on a variety of signaling mechanisms throughout the brain.

Treatment Approaches

There is no specific treatment of cocaine intoxication-induced delirium, and in most cases the delirium can be managed with supportive care. However, such individuals will require more intensive monitoring than those with typical cocaine intoxication, due to the elevated risk for cocaine-induced rhabdomyolysis [99]. Hyperthermia in individuals with cocaine intoxication can be a sign of impending rhabdomyolysis. This condition must be recognized early to prevent secondary renal failure. Treatment of rhabdomyolysis focuses on ensuring adequate urine output and, possibly, alkalization of the urine. Dialysis may be necessary in extreme cases [52]. One study found that 24% of patients presenting to the emergency room for acute cocaine-related disorders had some degree of rhabdomyolysis, which in many cases was not apparent from the clinical history or physical examination, thereby making laboratory assessment—including measurement of serum creatinine phosphokinase and urinary myoglobin—an essential part of the evaluation and treatment of such individuals [124]. Cardiac monitoring also should be considered given the risk of cocaine-induced arrhythmias, vasoconstriction, and myocardial infarction [27].

Cocaine-Induced Psychotic Disorder

Definition/Diagnostic Criteria

Cocaine-induced psychotic disorder refers to the presence of psychotic symptoms in excess of those typically seen in individuals with cocaine intoxication or withdrawal. These can include delusions, hallucinations, or both. Delusions may be of any type but typically are paranoid and/or grandiose in nature. Diagnostic criteria for cocaine-induced psychotic disorder are the same as those used to diagnose other substance-induced psychotic disorders, and include:

a. Prominent hallucinations or delusions. Note: Do not include hallucinations if the person has insight that they are substance induced.
b. Evidence from the history, physical examination, or laboratory findings that: (1) these symptoms developed during the course of cocaine intoxication or withdrawal, and/or (2) cocaine use is etiologically related to the development of psychotic symptoms.
c. The disturbance is not better accounted for by a psychotic disorder that is not substance induced. Evidence that the symptoms are better accounted for by a primary psychotic disorder that is not substance induced might include the following:
    i. psychotic symptoms that precede the onset of cocaine use;

ii. psychotic symptoms that persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication,
iii. other evidence that suggests the existence of an independent non-substance-induced psychotic disorder (e.g., a history of recurrent non-substance-related episodes).

d. The disturbance does not occur exclusively during the course of a delirium [1].

There are two subtypes of cocaine-induced psychotic disorder: (1) "with delusions" if delusions are the predominant symptom and (2) "with hallucinations" if hallucinations are the predominant symptom.

Neurobiology

The precise molecular biological basis of cocaine-induced psychotic disorder is currently unknown. However, there is evidence for a genetic vulnerability to the development of psychotic symptoms in individuals who abuse cocaine. In particular, genetic variants associated with low plasma levels of dopamine beta-hydroxylase, an enzyme that converts dopamine to norepinephrine and thus affects the balance between these two neurotransmitters in the brain, have been associated with increased risk for cocaine-induced psychotic symptoms [22, 60]. Individuals with lower levels of dopamine beta-hydroxylase would be expected to have a higher ratio of dopamine to norepinephrine, and thus be more sensitive to drugs such as cocaine that lead to unbalanced dopamine signaling in the brain.

Treatment Approaches

There is no specific treatment of cocaine-induced psychosis, and in most cases the psychotic symptoms will resolve within a few days after cessation of cocaine use. Benzodiazepines can be used for individuals who are agitated. Care must taken in using neuroleptics to treat cocaine-induced psychosis because most antipsychotic medications will increase the QTc interval and may increase the risk for cocaine-associated cardiac arrhythmias [127].

Cocaine-Induced Anxiety Disorder

Definition/Diagnostic Criteria

Cocaine-induced anxiety disorder can occur during either cocaine intoxication or cocaine withdrawal. Like other substance-induced anxiety disorders, cocaine-induced anxiety disorder is distinguished from a primary anxiety disorder by the fact that a substance is judged to be etiologically related to the symptoms. Diagnostic criteria for cocaine-induced anxiety disorder are the same as those for other substance-induced anxiety disorders and include:

a. The presence of prominent anxiety, panic attacks, or obsessions or compulsions.
b. Evidence from the history, physical examination, or laboratory findings that: (1) these symptoms developed during the course of cocaine intoxication or withdrawal, and/or (2) cocaine use is etiologically related to the development of psychotic symptoms.
c. The disturbance is not better accounted for by an anxiety disorder that is not substance induced. Evidence that the symptoms are better accounted for by an anxiety disorder that is not substance induced might include:

- anxiety symptoms that precede the onset of cocaine use;
- anxiety symptoms that persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or
- other evidence that suggests the existence of an independent non-substance-induced anxiety disorder (e.g., a history of recurrent non-substance-related episodes).

Neurobiology

While the precise molecular biological basis of cocaine-induced anxiety disorder is unknown, it has been suggested that the development of cocaine-induced anxiety or panic symptoms can be explained in terms of limbic-neuronal hyperexcitability induced by cocaine through a kindling mechanism [71].

Treatment Approaches

There is no specific treatment of cocaine-induced anxiety disorder, and in some cases these symptoms will resolve within a few days after cessation of cocaine use. In cases where the symptoms do not resolve following cessation of cocaine use, treatment of cocaine-induced anxiety disorder is usually similar to treatment for a primary anxiety disorder such as generalized anxiety disorder, phobias, panic disorder, or obsessive-compulsive disorder. It has been suggested that clonazepam and/or carbamazepine may be more effective in the treatment of cocaine-induced panic symptoms than shorter-acting benzodiazepines such as alprazolam, possibly because of their greater anticonvulsant properties [71]. Of note, antidepressants, particularly tricyclic antidepressants, have been reported to be ineffective in the treatment of cocaine-induced panic symptoms. Indeed, one study found that 60% of individuals with cocaine-induced panic symptoms experienced a worsening of their symptoms when treated with tricyclic antidepressants [72].

Cocaine-Induced Mood Disorder

Definition/Diagnostic Criteria

Cocaine-induced mood disorder refers to a prominent and persistent disturbance in mood that is judged to be due to the direct physiological effects of cocaine. Diagnostic criteria for cocaine-induced mood disorders are the same as for other substance-induced mood disorders and include:

a. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following: (1) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities, or (2) elevated, expansive, or irritable mood.
b. Evidence from the history, physical examination, or laboratory findings that: (1) these symptoms developed during the course of cocaine intoxication or withdrawal, and/or (2) cocaine use is etiologically related to the development of psychotic symptoms.
c. The disturbance is not better accounted for by a mood disorder that is not substance induced.
d. The disturbance does not occur exclusively during the course of a delirium [1].

Neurobiology

The neurobiological mechanisms underlying the development of cocaine dependence and mood disorders share a number of similarities [8, 76]. These include a prolonged activation of the hypothalamic-pituitary-adrenal axis and overexpression of the neuropeptide corticotropin-releasing factor [42]. There is abundant evidence from both animal [29, 100] and human [110, 113] studies showing that stress and the associated increase in hypothalamic-pituitary-adrenal activity can trigger relapse to cocaine use. Conversely, prolonged elevation of hypothalamic-pituitary-adrenal activity as a result of chronic cocaine use may result in a negative affective state, which provides a powerful motivational force for the continuation of drug self-administration [66]. Treatments that target this heightened hypothalamic-pituitary-adrenal activity may thus represent important potential treatments for both mood [49, 85] and substance abuse [101] disorders.

Treatment Approaches

Mood disorders that are directly attributable to cocaine can be difficult to distinguish from the frequent case of comorbid cocaine abuse or dependence with a "primary" mood disorder, either major depression or bipolar disorder. By definition, substance-induced mood disorders arise only in association with intoxication or withdrawal states, whereas primary mood disorders may precede the onset of substance use or may occur during times of sustained abstinence. However, in many cases, both cocaine use and mood symptoms are long-standing, and it may be difficult to identify significant periods of time when either was absent. In addition, because the withdrawal state for cocaine can be relatively protracted, mood symptoms can persist in an intense form for several weeks after the cessation of cocaine use. Features that would suggest a primary mood disorder include: (1) persistence of mood symptoms for a substantial period of time (i.e., a month or more) after cessation of cocaine use, (2) the development of mood symptoms that are substantially in excess of what would be expected given the amount or the duration of cocaine use, or (3) a history of prior recurrent primary episodes of mood disorder [1].

Both cocaine-induced and primary mood disorders require clinical attention, especially when symptoms have been persistent and severe prior to treatment. The preponderance of evidence—from both randomized clinical trials that prospectively targeted both depression and cocaine dependence and randomized clinical trials in which a post hoc analyses demonstrated efficacy in the subgroup of cocaine abusers with comorbid depression—appears to support the use of antidepressant medication in those with comorbid major depression and cocaine dependence (reviewed in [97, 119]). In general, selective serotonin reuptake inhibitors appear to work poorly in dually diagnosed individuals (e.g., [18, 102]), whereas positive studies have used agents such as desipramine [9, 41] or bupropion [75] that are more activating.

Cocaine-Induced Sexual Dysfunction

Definition/Diagnostic Criteria

Cocaine-induced sexual dysfunction refers to a clinically significant sexual dysfunction resulting in marked distress or interpersonal difficulty that is judged to be explained fully by the direct physiological effects of cocaine. Subtypes may include cocaine-induced sexual dysfunction with: (1) impaired desire, (2) impaired arousal, (3) impaired orgasm, and (4) sexual pain [1].

Neurobiology

Acute administration of cocaine is associated with an increase in sexual drive, an effect that may be due to increased secretion of luteinizing hormone [23, 79]. However, chronic cocaine use induces a number of neuroendocrine abnormalities, including alterations in levels of prolactin secretion [17, 78] (hypothesized to occur as a result of increased dopamine depletion in the tubulo-infundibular tract [16, 23]). Elevated levels of prolactin would be expected to inhibit pituitary gonadotropin secretion [80], which may contribute to the development of cocaine-induced sexual dysfunction in some people.

Treatment Approaches

Since by definition cocaine-induced sexual dysfunction is explained fully by the direct physiological effects of cocaine, the primary focus of treatment should be on cessation of cocaine use. Expected improvements in sexual functioning may become a motivating factor to seek treatment for some cocaine-dependent subjects. When sexual function does not return to normal following a prolonged period of abstinence (i.e., 1 month or more), consideration should be

given to the possibility that the person has a primary sexual dysfunction. Contributing psychological factors such as possible comorbid major depression or anxiety disorders also should be taken into consideration. Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, or vardenafil) are commonly prescribed. However, some studies suggest that these drugs are taken more commonly to enhance sexual experience than to treat erectile dysfunction [51], and may contribute to unsafe sex practices [34] and the consequent risk for infection among active cocaine users as well as the risk for adverse cardiac events [56, 114]. Thus, it is important to take a careful sexual history and discuss openly the associated risks and benefits before prescribing these medications.

Cocaine-Induced Sleep Disorder

Definition/Diagnostic Criteria

Cocaine-induced sleep disorder refers to a prominent disturbance in sleep that is sufficiently severe to warrant independent clinical attention, is judged to be due to the direct physiological effects of cocaine, and does not occur exclusively during the course of a delirium. Subtypes may include insomnia type, hypersomnia type, parasomnia type (which includes a variety of sleep-related disorders such as confusional arousals, sleepwalking (somnambulism), and sleep terrors (night terrors)), or mixed type (if more than one sleep disturbance is present and none predominates) [1]. The onset of the sleep disorder can occur either during intoxication or during withdrawal. The diagnosis of cocaine-induced sleep disorder is made only when the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and the symptoms are in excess of those usually associated with cocaine intoxication or withdrawal. Typically, cocaine intoxication produces insomnia, while cocaine withdrawal is associated with hypersomnia.

Neurobiology

In addition to changes in the total number of hours slept, chronic cocaine use is associated with significant changes in sleep architecture and deficits in sleep-related cognitive performance (e.g., sleep-dependent learning) [81, 120]. It has been suggested that this may be due to alterations in gamma-aminobutyric acid (GABA) signaling that are the result of adaptation to repeated overstimulation of monoaminergic pathways [81]. Interestingly, while self-reports of sleep quality typically improve following cocaine abstinence, polysomnographic studies have shown that changes in sleep architecture and sleep-related cognitive performance do not improve, at least over the first 3 weeks of abstinence, suggesting that there may be long-lasting deficits in sleep quality that occur as a result of chronic cocaine use and are not necessarily appreciated by the individuals themselves.

Treatment Approaches

Alterations in sleep architecture that occur during prolonged withdrawal from cocaine (reviewed in [81]) include an initial suppression of rapid-eye-movement sleep, followed after about 3 days by a rebound in rapid-eye-movement sleep and an increase in total hours of sleep. After 2.5 weeks of abstinence from cocaine, users have sleep architecture similar to individuals with chronic insomnia—i.e., increased sleep latency, decreased sleep efficiency (the percentage of time spent asleep while in bed), and decreased total hours of sleep. These findings suggest that agents such as tiagabine that improve slow-wave sleep and possibly deficits in sleep-related cognitive performance may be more beneficial than benzodiazepines, which extend sleep by promoting stage 2 sleep [81]. Several of the GABAergic medications that are being tested for treatment of cocaine dependence (topiramate, baclofen,

tiagabine, and vigabatrin) also may be helpful in treating cocaine-induced sleep disorders.

Summary

In sum, cocaine-use-related disorders are associated with severe physical disability (particularly increased risk of cardiovascular disease and cerebrovascular accidents), mental problems ranging from precipitating major psychosis to sleep disorders, and death. Cocaine taking, therefore, is an important cause of preventable morbidity and mortality in the United States and globally. Associated problems of cocaine use such as violent crime and enhancing the spread of HIV/AIDS have a major societal impact. Prevention and education programs, especially among youth, appear to diminish the incidence of cocaine use. Over the last two decades, there has been an explosion of neuroscientific knowledge, and the pharmacogenetic basis of cocaine dependence is being elucidated. In the absence of Food and Drug Administration—approved medications to treat cocaine-related disorders, clinical experience and early results from clinical studies have guided the use of agents to ameliorate these conditions. Presently, self-help and non-pharmacological approaches remain an important component of treatments for cocaine-related disorders.

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Nicotine

Maher Karam-Hage, Jennifer Minnix, and Paul M. Cinciripini

Contents

Epidemiology

Cigarette smoking is the principal cause of premature death and disability in the United States. In 2006 about 438,000 deaths in the United States were caused by cigarette smoking [42]. According to a recent report published by the International Agency for Research on Cancer, tobacco smoking is causally linked to 13 different types of neoplastic disease [95]. However, despite education about the health hazards of smoking and other tobacco control efforts, many smokers continue to encounter extreme difficulty quitting and staying tobacco free long-term.

The latest annual National Survey on Drug Use and Health [164] (covering 20 million non-institutionalized United States residents age 12 years or older) reported that tobacco use has declined in recent years, from the highest rate of 42% in 1965 to the lowest reported rate of 28.6% in 2007. However, in 2007 nearly 42% of the 18–25 year-olds reported using cigarettes in the previous month, a much larger percentage than the 8% who reported using an illicit drug or the 6.9% who were classified as heavy alcohol users.

Surveys with different methodologies and definitions of smoking have produced varying rates of smoking prevalence. For example, the National Health Interview Survey [42] conducted in 2007 reported that 19.8% of the United States population were "current smokers," through rates were substantially higher among those with less than a high school education. Overall, 39.8% of current smokers made at least one quit attempt of at least 24 h in the previous year. The 2008 University of Michigan Monitoring the Future survey found that smoking in the last month among 8th, 10th, and 12th graders was 22.1, 34.6, and 46.2%, respectively [98]. The above numbers highlight the magnitude of the problem with smoking and nicotine dependence, in particular when compared

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_19,

with the lower prevalence of other substances of dependence.

The difficulty in overcoming nicotine dependence is illustrated by the poor success rates among smokers who try to quit. The majority of smokers (~70%) report an interest in quitting, and around 42% have attempted to quit in the previous year. However, fewer than 6% of smokers are abstinent at 1 month after their quit date and fewer than 2% are abstinent 1 year after quitting when they do not receive assistance in smoking cessation [178]. The difficulty in maintaining abstinence is strongly related to affective and cognitive dysfunction, which may persist in some smokers for some time after the initial cessation, as well as post-cessation cigarette cravings [104].

The health consequences associated with smoking tobacco are substantial and life-threatening (see Fig. 1). Reportedly, smoking was the primary causal factor for 30% of all cancer deaths and 80% of deaths related to chronic obstructive pulmonary disease [41]. According to the Center for Disease Control [41] cigarette smoking or exposure to tobacco smoke resulted in 443,000 premature deaths/year and 5.1 million years of potential life lost from 2000 to 2004. The three leading causes of smoking attributable deaths were lung cancer, ischemic heart disease, and chronic obstructive

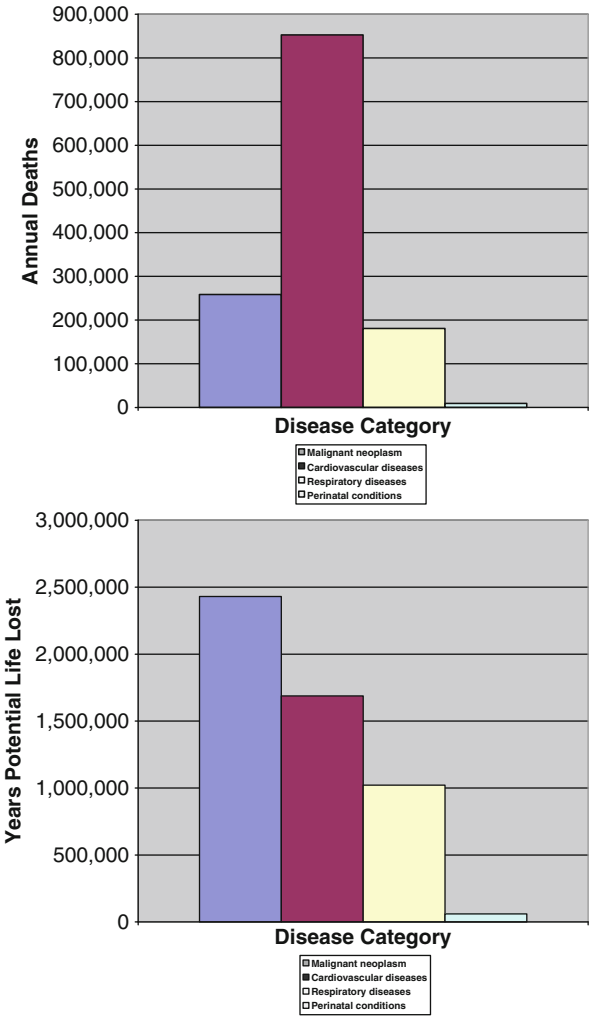

Fig. 1 Smoking-attributed annual deaths and years of potential life lost for the years of 2000–2004 [43]

pulmonary disease. Additionally, an estimated 776 infant deaths attributed to smoking during pregnancy occurred annually from 2000 to 2004. Despite the fact that cigarette use has declined substantially since the 1960s, the number of smoking-related deaths has remained relatively unchanged [43].

Biological, Behavioral, and Cognitive Aspects of Nicotine Dependence

The Reward Pathway

Among the more than 4,000 components of tobacco smoke, 60 or more are known carcinogens [84]. The most studied component of tobacco smoke is nicotine. It is the major psychoactive ingredient in tobacco smoke and the component most associated with tobacco dependence [14]. Like many drugs associated with abuse and dependence, nicotine stimulates a rapid increase in dopamine in the nucleus accumbens and the ventral tegmental area, typically within 10 s after ingestion [135, 136, 143]. Under normal circumstances, the nucleus accumbens and ventral tegmental area are also activated by food, social affiliation, and sexual activity, all of which are linked to survival. The key component of the reward pathway within the mesocorticolimbic system is the neurotransmitter dopamine, whose pathways project from the nucleus accumbens and ventral tegmental area to the prefrontal cortex, the amygdala, and the olfactory tubercle (see Fig. 2). Other neurotransmitter systems such as the gamma-aminobutyric acid system, the glutamate system, and the cholinergic system from those and other areas of the brain are believed to be involved in the activation of the reward pathway, while dopamine appears to be the final common neurotransmitter of this pathway [119].

Nicotine affects the reward pathway by more than one mechanism. In animal studies, dopamine antagonists or the destruction of dopaminergic neurons in the nucleus accumbens results in a decrease of nicotine self-administration in laboratory animals [61]. Nicotine receptors, a sub-type of muscarinic cholinergic receptors are present throughout the central nervous system and exert varying effects

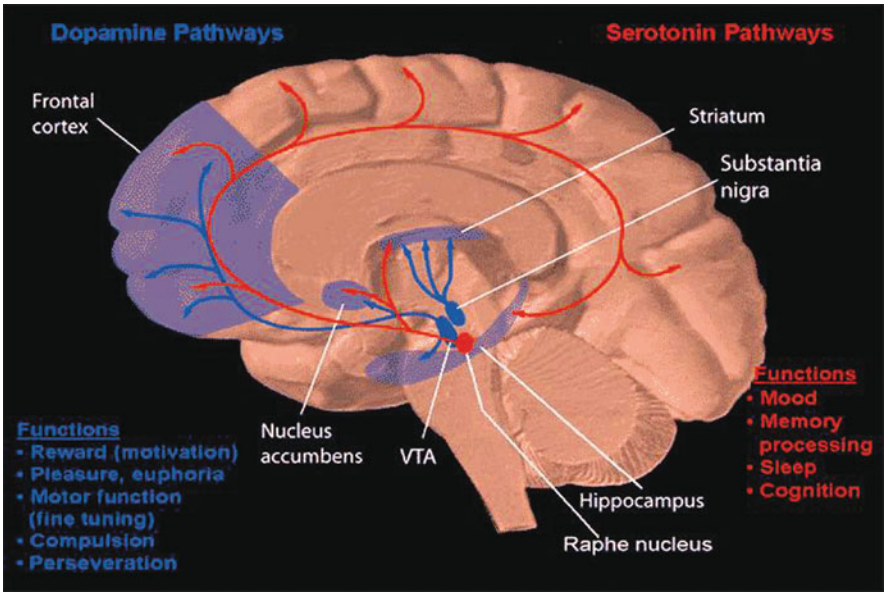

Fig. 2 The reward pathway with projections to the frontal and prefrontal cortex [131]. VTA = ventral tegmental area

(excitatory, inhibitory, or modulatory) depending on their location in the brain. In turn these receptors have an impact on the activity of several neurotransmitters, including dopamine, norepinephrine, serotonin, glutamate, and gamma-aminobutyric acid, and of endogenous opioid peptides. Prior research has focused primarily on dopamine as main determinant of nicotine and other drug addiction [38, 95, 135, 147], but most recently the emphasis is shifting to include most if not all the other major neurotransmitter systems in the brain [181]. Finally, cannabinoid-1 receptors also seem to be involved in nicotine dependence and the activation of dopaminergic neurons in the mesocorticolimbic system [51, 111] highlighting once more the importance of broadening the horizon and scope of our research efforts to include other systems in addition to dopamine and the reward pathway.

Neuronal Adaptation

Most if not all substances of abuse and dependence initially produce desirable and pleasant effects. However, not everyone who uses these substances goes on to abuse them, and not all substance abusers become dependent. Genetic, environmental, and cultural factors may all interact to predispose some individuals to substance abuse and dependence.

The pleasurable sensation produced by reward pathway activation is associated with acute substance use; repeated administration of nicotine over months or years is likely to lead to increased tolerance and withdrawal in the absence of nicotine. Tolerance and withdrawal are the physiologic hallmarks of dependence, and they may be related to neuroadaptive effects occurring within the brain [15]. Interestingly, the chronic use of drugs of abuse appears to cause a generalized decrease in dopaminergic neurotransmission, likely in response to the intermittent yet repetitive increases in dopamine induced by the frequent use of such drugs [180]. Drugs of abuse also increase levels of corticotropin-releasing factor, which is associated with the activation of central stress pathways. In vivo animal studies utilizing microdialysis during withdrawal from ethanol, cocaine, nicotine, or tetrahydrocannabinol showed an increase in extracellular corticotropin-releasing factor [109]. Of interest, the direct injection of a corticotropin-releasing factor antagonist into the amygdala reversed some of the symptoms of withdrawal (i.e., anxiogenic behaviors) [137].

Two neuroadaptive models have been used to explain how changes in reward function are associated with the development of substance dependence: sensitization and counter adaptation. The sensitization model [150] postulates that there is an increased desire for the drug, without necessarily a corresponding increase in pleasure, following intermittent but repeated administration of a drug. This is in contrast to or despite the tolerance to a drug, which would occur later or after continuous exposure to the drug. Sensitization can be thought of as the increase in "wanting" a drug after intermittent but repeated use and can facilitate the transition from occasional use to chronic use and tolerance [149].

The counter adaptation model postulates that the initial positive feelings of reward resulting from the use of a drug are followed by an opposing rather than synchronous development of tolerance that is manifested by the appearance of withdrawal associated with the lack of the substance [175]. Since tolerance takes longer to dissipate than the positive rewarding effects, a cycle of escalating drug use may follow after each cessation and consequent withdrawal. When the neurotransmitter system of the reward pathway is over-activated through escalating drug use, the system may not be able to maintain an increasingly pleasurable response to the drug. This is evidenced in microdialysis experiments that have documented decreases in dopaminergic and serotonergic transmission in the nucleus accumbens after chronic and escalating use [170]. The increase in corticotropin-releasing factor and concomitant decrease in neuropeptide Y during substance withdrawal (including nicotine) are associated with increases in anxiety [154]. In turn during withdrawal the activation of

norepinephrine pathways stimulates additional corticotropin-releasing factor release, possibly resulting in an amplification of arousal and stress and even neurotoxic effects if this amplification of arousal and stress are long-lasting [154].

Other models of nicotine addiction have been proposed, based on mechanisms associated with cognitive control and reinforcement learning [55], particularly the negative reinforcement associated with the reduction in negative affect that may follow smoking after a period of abstinence (withdrawal) [8]. These models are discussed in detail later in this chapter.

Cognitive Impairment

While much of the focus of previous research on nicotine addiction has been related to its effects on reward processes and mesolimbic dopamine neurotransmisssion [38, 95, 135, 143, 147], a growing body of literature suggests that nicotine's noradrenergic and dopaminergic effects on attention, information processing, and affective regulation, elsewhere in the limbic system, may be of considerable importance in understanding the maintenance of dependence. Neurological deficits common to attention and substance use disorders, such as impaired performance, lack of motivation, decreased working memory, and impaired executive function have been well documented [187] in both children and adults [9, 13, 63, 155, 166]. Current lines of investigation suggest that overlapping interrelated brain areas are responsible for explaining the attentional and executive impairments common to the two disorders [44, 68]. The involvement of two areas in particular, the prefrontal cortex and anterior cingulate cortex, highlight the commonalities between drug dependence and attentional disorders, including nicotine and neurophysiological deficits related to cognitive dysfunction.

The prefrontal cortex regulates goal directed behavior, thought, and affect by using working memory to provide representational knowledge about past or future events and integrating this information into a plan for action or to exercise inhibitory control over inappropriate actions or thoughts. In attentional/cognitive disorders these processes are impaired and manifested in symptoms that involve poor attention, planning, impulse control, and monitoring of one's behavior. Studies indicate that the right prefrontal cortex in humans is particularly important in the inhibition of activity (i.e., Stop or Go-No Go tasks) [5]. The orbital and ventral prefrontal cortex may also have a similar inhibitory effect in the affective domain, thus permitting appropriate social behaviors [163, 173]. In attention deficit/hyperactivity disorder for example, the anterior cingulate cortex has been implicated in the regulation of the motivational aspects of attention as well as in the regulation of response selection and inhibition [187]. Thus, researchers have begun to characterize attention deficit/hyperactivity disorder as a disorder with deficits in inhibitory processes involving frontal cortical structures [9]. Notably, there is a significant relationship between a history of attention deficit/hyperactivity disorder and smoking [108]. If a person must mentally manipulate information and make a response, the anterior cingulate cortex (with its connections to the prefrontal cortex) becomes active [134]. This area becomes particularly active in tasks where inhibitory control or divided attention is necessary [148].

The importance of the inhibitory role of these structures in drug dependence has also been highlighted by several researchers. Drug-addicted individuals, including smokers, continue to use drugs even when faced with negative consequences and diminished reward, suggesting an apparent loss of control [149]. The failure to regulate (i.e., inhibit) this drive points to a dysfunction within the prefrontal cortex [181] and related areas, including the anterior cingulate and orbitofrontal cortices [120]. As shown in Fig. 3, the resulting persistence of the behavior is not necessarily due to continued reinforcement by the drug (mesolimbic dopamine) but rather to the enhanced saliency of the drug and drug cues that have been firmly established (learned) in memory during the acquisition of dependence.

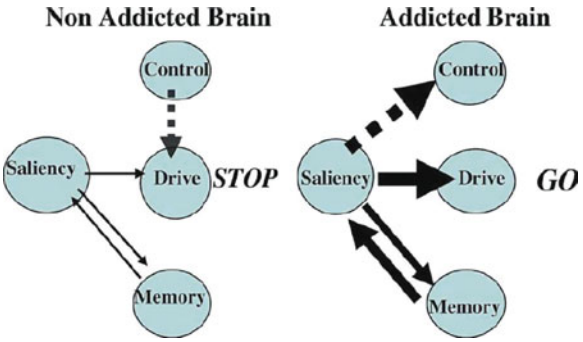

Fig. 3 Addiction model proposed based on results from brain imaging studies documenting abnormalities in brain circuits that involve saliency/reward, motivation/drive, memory/conditioning, and control/disinhibition. These circuits interact with one another and change as a function of experience and context. During addiction, the enhanced saliency value of the drug in the reward, motivation, and memory circuits overcomes the inhibitory control exerted by the prefrontal cortex. A positive feedback loop initiated by consumption of the drug and perpetuated by the enhanced activation of the motivation/drive and memory circuits results in compulsive drug seeking and taking. Reprinted from Volkow et al. [181], with permission from Elsevier

During maintenance of drug dependence these "super salient" drug-related cues, including self-administration, overcome the inhibitory control of the prefrontal cortex that might normally extinguish a response with decreasing hedonistic properties.

Preclinical studies suggest that the impairment in prefrontal cortex function may be related to significant dendritic branching and spine density resulting from repeated drug administration [151], thus amplifying the signal of salient events. Moreover, abstinence from the drug significantly reduces the efficiency of the prefrontal cortex to process information in working memory, thereby interfering with its regulatory function [189]. Such effects might be mediated by the negative affect associated with nicotine withdrawal, and when present, reduce the probability that a smoker may exercise an appropriate coping response and increase the probability of relapse [8, 189]. There is EEG evidence supporting persistent frontal lobe dysfunction among smokers using tasks related to working memory (P300). Neuhaus and colleagues [132] found a hypoactivation of the anterior cingulate, orbitofrontal, and prefrontal cortices among both current and former smokers compared with "never" smokers, suggesting that the dysfunctional activation patterns found in smokers may not completely remit after quitting; a fact that may increase their vulnerability to relapse.

A recent model by Curtin and colleagues [55] attempts to address the conditions under which cognitive control mechanisms affect the processing of motivationally relevant information (i.e., smoking cues) and the execution of situation appropriate behavior. The model holds that once dependence is established, drug use motivation is frequently driven by implicit processes that are largely automatic and outside of the user's awareness. These implicit processes are developed and maintained by negative and positive reinforcement learning. In the case of negative reinforcement, internal states associated with negative affect or drug withdrawal can engage motivational systems and drug use behavior in an attempt to ameliorate these aversive states. With positive reinforcement, environmental cues and positive mood states previously associated with rewarding drug effects can increase approach motivation. The model postulates that these learned associations trigger subcortical, "bottom-up" processes that can influence drug-seeking behavior implicitly by engaging appetitive or avoidance motivational systems. Thus, the drug user may frequently engage in drug use behaviors for reasons that are outside of conscious awareness.

While the Curtin et al. [55] model holds that drug sensitization is largely maintained by the implicit influence of learned associations on motivation, the authors also speculate about circumstances in which drug use comes under explicit or cognitive control. Cognitive control can be defined as the effortful application of attentional resources to meaningful information and tasks [24]. Cognitive control is crucial to learning as it is activated when an organism encounters unexpected outcomes, unfavorable outcomes, or response errors [88]. In this model, cognitive control is important because it is elicited during response conflict, which can occur when the user attempts to regulate the craving and drug-seeking behaviors that result from exposure to conditioned cues. Ultimately, cognitive control is what allows a drug user to engage in less well learned alternatives to drug-seeking behavior when drug craving and approach motivation are activated. However, it is during instances of response conflict and engagement of cognitive control mechanisms, that drug craving will be most acutely experienced by the drug user. If there are clear processing deficits engendered in the management of response conflict (also pertinent to error monitoring in the anterior cingulate cortex), behavioral resistance to the increased craving is also diminished.

Nicotine and Negative Affect

One of the most fundamental aspects of nicotine dependence involves its neuroregulatory function on mood. The relationship of negative affect with the maintenance and cessation of smoking behavior plays a prominent role in current theories of nicotine dependence [8]. In such model, it is theorized that individuals addicted to a substance learn to detect internal cues that negative affect is approaching as drug levels fall within the body. In order to prevent the onset of these negative feelings, the addicted person self-administers the drug, though often this process proceeds without conscious awareness. The longer the individual is without the drug, the more likely these negative feelings are to enter conscious awareness, providing direct reinforcement that taking the drug relieves negative affect (see Fig. 4). This relationship has driven the development of new pharmacological [47, 81, 93] and behavioral [33, 81] approaches to treatment. The experience of negative affect is a significant contributor to the risk of relapse and reports of negative affect reduction are cited by many smokers as an important reason to smoke. Improving the understanding of the psychobiological and genetic mechanisms associated with the modulation of mood by nicotine will help us better understand the mechanisms of nicotine dependence and the relationship between these mechanisms and treatment success.

The term "negative affect" refers to a composite index of many negative mood states, including feelings of depression, dysphoria, irritability, nervousness, etc., and is usually measured by Likert type scales such as the Positive and Negative Affect Scale [183], the Profile of Mood States [123], or other similar adjective checklists [156]. Research on the relationship between negative affect and smoking behavior has included evaluation of the effects of a past history of major depression, which may serve as a marker for vulnerability to future depressed mood, and evaluation of the effects of pre and post-cessation negative affect. A significant shared familial risk of depression and smoking has been identified for heavy and non-heavy nicotine-dependent smokers [96], and a history of major depression [1] has been associated with an increased prevalence of smoking [28, 29, 74, 103], nicotine dependence [28], and greater nicotine withdrawal severity. Some studies have found an inverse relationship between major depression history and quitting success [4, 25, 35, 73, 74, 80, 186] but these findings have not been uniform [30, 72, 87, 126, 133].

Negative affect following a quit attempt has been related to treatment failure and relapse across a variety of treatment modalities [23, 35, 104]. Indeed, the presence of negative affect following cessation has been found to characterize over 50% of all smoking lapses, with 19% of

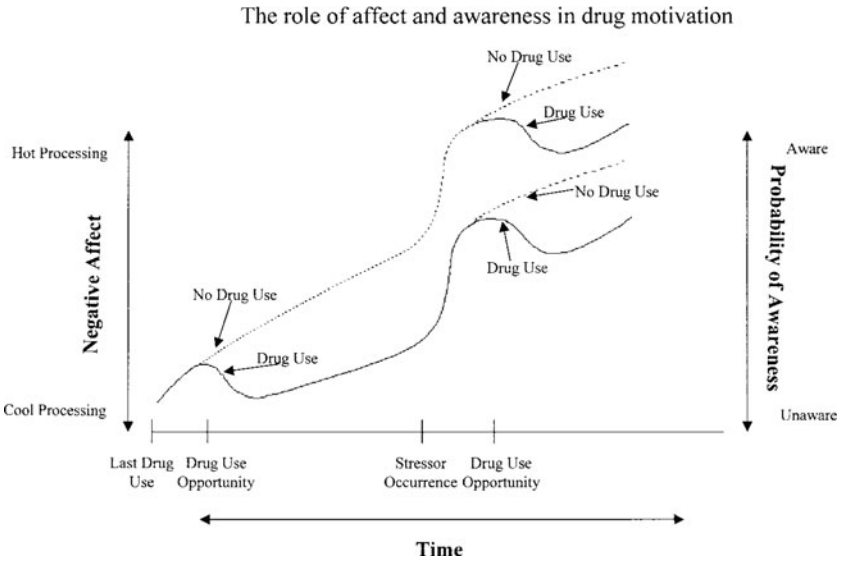

Fig. 4 Affective processing model of negative reinforcement in addiction. The *horizontal axis* represents time since last drug use, and the *vertical axis* represents intensity of the affective response. Affect increases in direct proportion to the amount of time since last drug use. As affect grows, the probability of the affect being consciously available grows as well. Also, as the affect escalates, information processing begins to be dominated by the hot system rather than the cool system. If the drug is used optimally, nascent negative affect will be quelled before it becomes available to consciousness. If drug use is impeded at this point, however, affect may become conscious, and the addicted individual may be aware that negative affect decreases following renewed drug use. Negative affect spurred by exteroceptive stressors can become conscious as well and may be relieved by drug use. Reprinted from Baker et al. [8]

all lapses occurring under conditions of extreme negative mood [156]. Negative affect appears to be the component of nicotine withdrawal that most profoundly influences relapse and the trajectory of nicotine withdrawal symptoms [104, 140, 141]. The expectation that nicotine will produce desirable emotional consequences [185] has also been shown to inversely predict cessation success. In addition to post-cessation negative affect, pre-cessation levels of negative affect [45, 72, 104, 106, 107] have been shown to predict cessation outcome.

When a smoker quits using tobacco, the above biological, cognitive, and behavioral aspects of dependence may increase the risk of relapse. However, many factors are associated with an increased risk for relapse after quitting smoking, including the availability of cigarettes, an increase in psychological stressors and a triggering of conditioning factors (cues). Visual cues can be seeing people smoking or going to a location where one used to smoke or obtain cigarettes. Such factors may trigger residual adaptational changes that occurred in the brain during the period of nicotine consumption and subsequent addiction.

Genetics

Heritability

Recent family, twin, and molecular genetic studies provide compelling evidence of a role for genetic factors governing smoking initiation, continuation and cessation, with estimated heritability rates ranging from 47 to 76% for initiation and 62% for persistence [37, 113, 112, 142, 152, 160]. The concordance rates for smoking, not smoking, and quitting are higher for monozygotic than for dizygotic twins, and the concordance rates for smoking in 82 pairs of identical twins reared apart were 79%. A meta-analysis of data from 8 studies revealed an

estimated heritability rate of 60% for smoking. For the maintenance of dependent smoking behavior, the percent of genetic contribution is about 70% [172]. Three linkage studies of smoking behavior [16, 62, 162] suggest that alleles that influence smoking behavior occur in only a small proportion of families.

Genome-Wide Association Studies of Nicotine Dependence

Recent genome-wide association studies related to nicotine dependence have been published. Uhl et al. [176] used 520,000 single nucleotide polymorphisms using a DNA pooling approach. They prepared pools of DNA from nicotine-dependent European-American smoking cessation trial participants and control individuals. Because in the DNA pooling technique individual genotypes are not available, they compared genotypes from the entire group of nicotine-dependent research participants to genotypes from European-American research volunteers free from any substantial lifetime use of any addictive substance. They performed analyses using smokers versus non-smokers and successful versus non-successful quitters and identified several genes of interest.

A study by Berrettini and colleagues [18] examined nicotine dependence using genome-wide association data from proprietary databases established to study cardiovascular and other common diseases. In this study, nicotine dependence was studied using a single indicator: cigarettes per day where cases were defined as smokers consuming $\geq$25 cigarettes per day and controls were noted as consuming <5 cigarettes per day. Their initial analysis identified a significant relationship (p=0.0006) between a single nucleotide polymorphism in the CHRNA3 region, rs6495308, though the p-value fell below the 10^{-7} expected for genome-wide analysis. Nevertheless, in a replication sample, another single nucleotide polymorphism in this same region, rs1317286, did meet the expected p-value for a relationship with cigarettes per day.

Bierut et al. [19] performed a genome-wide association on 1,050 nicotine-dependent individuals and 879 non-dependent smokers. This was a two-stage study in which DNA pooling was used in the first stage of analyses and 31,960 single nucleotide polymorphisms were selected and genotyped in the nicotine-dependent cases and non-dependent controls. They identified 35 single nucleotide polymorphisms with p-values less than 10^{-6}, however, none of these single nucleotide polymorphisms maintained significance after correcting for multiple testing. However, this study did identify several candidate genes. In a follow-up study, Bierut et al. [20] used data from the Collaborative Study on the Genetics of Alcoholism and contrasted smokers who consumed over 20 cigarettes per day with those who smoked >100 cigarettes in their lifetime but never more than 10 cigarettes per day. The results showed the non-synonymous coding single nucleotide polymorphism of the CHRNA5 gene, rs16969968 (p=0.007), was associated with habitual smoking. Other single nucleotide polymorphisms in this region that were highly correlated with rs16969968 included rs2036527, rs17486278, rs1051730, and rs17487223 (r^2>0.79). A second independent finding noted by these authors in this gene cluster, was an association with rs578776, for which a low correlation with rs16969968 (r^2<0.15) was observed.

There have been 3 recent genome-wide association studies which have identified gene variants in a region on the long arm of chromosome 15 (15q24/15q25.1) as significant contributors to the risk of lung cancer, as well as nicotine dependence. The region of interest encompasses the nicotinic acetylcholine receptor subunit genes CHRNA3, CHRNA5 and CHRNB4, and involves several single nucleotide polymorphisms in strong linkage disequilibrium with each other. These include rs1051730 [3, 89, 167] and rs8034191 [3, 89]. In the case control study by Amos et al. [3] and in a further analysis of these and other data by Spitz and colleagues [161], a significant relationship was noted for gene variants in this region (the "A" variant for rs1051730 in this analysis) associated with lung cancer, nicotine

dependence, and smoking quantity indices in cases and controls, as well as earlier age of smoking initiation and time to first cigarette in controls. A non-significant trend was also noted for an inverse relationship between the adverse allele and duration of cessation. Thorgeirsson and colleagues [167] also found a significant relationship between risk of lung cancer and peripheral artery disease and the "T" variant (TT TG GG) of rs1051730. A significant association was also found between the adverse allele likelihood of being a former smoker and as with the previous study; associations were also noted between the minor allele and smoking quantity, Fagerström Test for Nicotine Dependence scores and symptoms of nicotine dependence from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. Interestingly, the genome-wide association study by Hung and colleagues [92] also noted a significant risk of lung cancer and the variant alleles of rs1051730 and rs8034191 but unlike the other two genome-wide association studies for lung cancer, these authors did not note an association with nicotine dependence: a finding which is at variance with several recent studies of nicotine dependence not involving cancer patients. For example, the rs1051730 single nucleotide polymorphism is in strong linkage disequilibrium (correlated) with the CHRNA5 single nucleotide polymorphism, rs16969968, for which the "A" variant has been shown to increase the risk of nicotine dependence in the studies noted above [20, 153]. This single nucleotide polymorphism also has an r^2 of 0.18 and 0.90 with rs6495308 and rs1317286, respectively, which are two single nucleotide polymorphisms in this CHRNA3-A5 region that have been shown to predict cigarettes per day in heavy smokers in the genome-wide association study by Berrettini and colleagues [18]. Further, in the Thorgeirsson et al. [167] study, the relationship of rs1051730 with Fagerström Test for Nicotine Dependence scores or symptoms on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, was at a level similar to that observed in a candidate gene study using low frequency smokers as controls [153].

Candidate Gene Studies for Nicotine Dependence

An examination of the literature in this area shows that over 60 unique genes have been noted in candidate gene studies of nicotine dependence. Several reviews have been published in this area [39, 117, 118, 127–129] with most concluding that small sample size and replicability pose significant issues in interpreting these results. Additionally, the limited characterization of the phenotype (i.e., simple classification as a smoker or not) may further restrict the information that can be obtained from these studies. Most of the candidate genes studied to date fall into two categories: Nicotine metabolism and central nervous system receptor or neurontransmitter function. These include all the major single nucleotide polymorphisms that have been researched in the smoking literature related to dopamine pathways and nicotinic receptors—for example, DRD2, DOPA, ANKK1, DAT, COMT, CHRNA4, and CHRNB2 (see [70, 89, 94, 153, 191]).

Genome-Wide Studies Predicting Nicotine Cessation Treatment Outcome

Uhl and colleagues [177] recently conducted a genome-wide association study examining successful vs. unsuccessful quitters across three clinical trials: one using nicotine replacement (results from this sample were also previously published by this group [176]); and two using bupropion, in mixed racial samples. The combined sample for all three trials totaled 540 individuals with individual trial samples 266 and 150 for the two bupropion trials and 124 in the nicotine replacement therapy trials. This group of investigators used a DNA pooling strategy and Monte Carlo simulation analysis of gene frequencies to identify single nucleotide polymorphisms that differentiated abstainers and non-abstainers, as well as those that were specific to nicotine replacement therapy or bupropion. In total, they noted several thousand single

nucleotide polymorphisms with nominal significance covering over 100 genes, involved in numerous biological processes ranging from cell adhesion, transcription regulation, intracellular signaling, cell structure and unknown function. While intriguing and suggestive of a pharmacogenetic effect the results from this study are difficult to interpret given the sheer number of "hits" and the complex biological processes involved. Clearly, much more information is needed taking a more traditional approach to genome-wide association techniques to examine both predictors of abstinence and pharmacogenetic effects of smoking cessation medications.

Candidate Gene Studies Predicting Treatment Outcome

There have been a handful of candidate studies examining genetic predictors of nicotine replacement therapy and bupropion. Like the candidate gene studies on nicotine dependence, most of these studies have focused on markers in the dopamine pathway, given the importance of the dopaminergic neurotransmission in nicotine reinforcement. For example, several polymorphisms in the D2 receptor gene (DRD2), including C957T, -141Cins/del and Taq1A (ANKK1), C32806T and a VNTR in the DRD4 (C-521T) have been shown to predict cessation outcome to nicotine replacement therapy [60, 99, 116, 190]. Others have identified genes associated with opioid or serotonergic pathways [58, 115]. With the exception of the study by David et al. [60] most have predicted only end of treatment success. Similarly, many of these same markers (Taq1A, –141Cins/del) [17, 58, 59, 116, 165] and others (COMT, CYP2B6, DAT) [57, 114] have been associated with successful treatment by bupropion, as well as another antidepressant, venlafaxine [46, 47]. One recent candidate gene study took a systems approach to identifying single nucleotide polymorphisms associated with smoking cessation using bupropion [52]. This study involved a population of 217 and 195 smokers receiving bupropion or placebo, respectively. Using a systems-based candidate gene approach this study identified polymorphisms (rs2072661 and rs2072660) within the β_2 nicotinic acetylcholine receptor (CHRNB2) which showed significant association with abstinence rates at end of treatment and at 6-month follow-up in a placebo-controlled trial of bupropion for smoking cessation. The association with the two single nucleotide polymorphisms was very high (r^2=0.96). These effects were independent of treatment but there was some indication that abstinence might be modulated by bupropion. For example, there was a substantial increase in relapse rates for those individuals carrying the minor allele after treatment was discontinued. Subsequent analyses of rs2072661 showed a significant relationship with time to relapse at the 6-month follow-up period and modulation of withdrawal symptoms at the target quit date.

Diagnosis

Nicotine is reported to be among the most addictive of abused substances, especially when consumed through smoking tobacco. After prolonged smoking, the user develops nicotine tolerance and exhibits withdrawal symptoms when nicotine is absent, these are two physiological symptoms of dependence (addiction). Further, nicotine may be responsible for other criteria for dependence: loss of control over smoking (e.g., not being able to reduce or stop smoking; or smoking more than intended), compulsive use (e.g., spending more time using the substance or giving up important events to use the substance), and continued smoking despite adverse consequences (e.g., heart attack, emphysema or cancer). The presence of any three or more of those criteria for at least a year satisfies the definition of "dependence" (classically known as addiction), according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [1] (see Table 1).

A traditional method of assessing nicotine dependence has been the Fagerström Test for Nicotine Dependence, which measures physiological dependence (tolerance and withdrawal)

Table 1 *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for substance dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by *three* (or more) of the following, occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following:
   (a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) Markedly diminished effect with continued use of the same amount of the substance
(2) Withdrawal, as manifested by either of the following:
   (a) The characteristic withdrawal syndrome for the substance
   (b) The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
(3) The substance is often taken in larger amounts or over a longer period than was intended
(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use
(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use of the substance (e.g., chain-smoking), or recover from its effects
(6) Important social, occupational, or recreational activities are given up or reduced because of substance use
(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Specify if:
– With Physiological Dependence: evidence of tolerance or withdrawal (i.e., either Item 1 or 2 is present)
– Without Physiological Dependence: no evidence of tolerance or withdrawal (i.e. neither Item 1 nor 2 is present)

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Table 2 Items and scoring for Fagerström test for nicotine dependence

Questions	Answers	Points
(1) How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6–30 min	2
	31–60 min	1
	After 60 min	0
(2) Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.?	Yes	1
	No	0
(3) Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
(4) How many cigarettes/day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	31 or more	3
(5) Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
(6) Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

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reliably well (the first item of the scale in particular; see Table 2), but does not reliably measure some of the other dimensions of nicotine dependence (especially the behavioral ones). Most research studies have used the total Fagerström Test for Nicotine Dependence score of equal to or greater than 4 as a cutoff to include people in; as a synonymous of physiological dependence to nicotine [138, 146]. The Wisconsin Inventory of Nicotine Dependence [144] is

a more recently developed multi-dimensional scale of nicotine dependence. It is more comprehensive in scope than the Fagerström Test for Nicotine Dependence and includes measures of cognitive enhancement, negative reinforcement, positive reinforcement, automaticity, affiliative attachment, loss of control, behavioral choice/amelioration, craving, cue exposure/associative processes, social/environmental goals, taste/sensory processes, weight control, and tolerance.

Smoking and Psychiatric Comorbidities

There is substantial evidence to suggest that smoking is closely linked with several psychiatric comorbidities, suggesting shared biological pathways between nicotine dependence and these psychiatric conditions. For example, current smoking rates among those with no mental illness, lifetime mental illness, and past-month mental illness has been reported as 22.5, 34.8, and 41.0%, respectively. Remarkably, smokers with a mental disorder in the past month reportedly consumed 44.3% of all cigarettes smoked in this nationally representative sample [110]. Several studies have demonstrated a positive relationship between alcohol, substance abuse and other psychiatric disorders and smoking [10, 22, 31, 54, 74, 82, 110, 188]. For example, the lifetime prevalence rate of alcohol dependence or drug abuse is estimated at 23–30% among adult smokers [11, 26]. Among non-dependent and dependent current smokers, lifetime rates of mood and anxiety disorders have been reported as 12–26.7%, and 33.5–46.5%, respectively [26]. Similarly, as shown in Table 1, among tobacco-dependent smokers, 12-month prevalence of any mood or anxiety disorder was 21–22%, respectively, [79]. There is also an elevated risk of first onset of major depression, panic disorder, and generalized anxiety disorder among smokers [27, 30, 32, 97, 103]. In the area of cognitive dysfunction, odds ratios comparing "ever" with "never" smokers were positively related to the number of attention deficit/hyperactivity disorder symptoms. Among those reporting regular smoking over their lifetime, an inverse relationship between number of attention deficit/hyperactivity disorder symptoms and age of onset, and a positive relationship between symptoms and number of cigarettes smoked, has also been observed [108].

Treatment

The United States Department of Health and Human Services, in concert with other public health agencies, has provided general guidelines for the treatment of tobacco use and dependence. The guidelines were initially published in 1996 (summarizing 3,000 publications), updated in 2000 (adding 2,000 publications), and further updated in 2008, when information was added from about 2,700 newer publications and 10 key recommendations were included [69] (Table 3).

The chance for recovery from nicotine dependence is maximized when a comprehensive biological, psychological, and social (biopsychosocial) assessment is done. Such assessments, which should account for the smoker's motivation for change, can guide both psychosocial therapy and pharmacologic treatment. Pharmacologic treatments are used as adjunctive to psychosocial therapy. When psychosocial and medication treatments are provided in concert the odds of quitting smoking are doubled. However, medication alone can often alleviate some of the effects of nicotine withdrawal, decrease cravings for tobacco use, and decrease the risk of relapse.

Non–nicotine-based medications such as sustained-release "bupropion-SR" (Zyban or Wellbutrin-SR) and varenicline (Chantix) have been shown to reduce cravings and nicotine withdrawal symptoms when used as aids to quitting smoking. Bupropion-SR and varenicline are first-line therapies for tobacco dependence, while nortriptyline (Pamelor) and clonidine (Catapres) are considered second-line (see Table 4).

Table 3 Ten key guideline recommendations

The overarching goal of these recommendations is that clinicians strongly recommend the use of effective tobacco dependence counseling and medication treatments to their patients who use tobacco, and that health systems, insurers, and purchasers assist clinicians in making such effective treatments available.

1. Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments exist, however, that can significantly increase rates of long-term abstinence.
2. It is essential that clinicians and health care delivery systems consistently identify and document tobacco use status and treat every tobacco user seen in a health care setting.
3. Tobacco dependence treatments are effective across a broad range of populations. Clinicians should encourage every patient willing to make a quit attempt to use the counseling treatments and medications recommended in this guideline.
4. Brief tobacco dependence treatment is effective. Clinicians should offer every patient who uses tobacco at least the brief treatments shown to be effective in this guideline.
5. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Two components of counseling are especially effective, and clinicians should use these when counseling patients making a quit attempt:
   - Practical counseling (problem solving/skills training)
   - Social support delivered as part of treatment
6. Numerous effective medications are available for tobacco dependence, and clinicians should encourage their use by all patients attempting to quit smoking—except when medically contraindicated or with specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents).
   - Seven first-line medications (5 nicotine and 2 non-nicotine) reliably increase long-term smoking abstinence rates: Bupropion SR, Nicotine gum, Nicotine inhaler, Nicotine lozenge, Nicotine nasal spray, Nicotine patch, Varenicline
   - Clinicians also should consider the use of certain combinations of medications identified as effective in this guideline.
7. Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of counseling and medication, however, is more effective than either alone. Thus, clinicians should encourage all individuals making a quit attempt to use both counseling and medication.
8. Telephone quit line counseling is effective with diverse populations and has broad reach. Therefore, both clinicians and health care delivery systems should ensure patient access to quit lines and promote quit line use.
9. If a tobacco user currently is unwilling to make a quit attempt, clinicians should use the motivational treatments shown in this guideline to be effective in increasing future quit attempts.
10. Tobacco dependence treatments are both clinically effective and highly cost-effective relative to interventions for other clinical disorders. Providing coverage for these treatments increases quit rates. Insurers and purchasers should ensure that all insurance plans include the counseling and medication identified as effective in this guideline as covered benefits.

Reprinted from *Treating Tobacco Use and Dependence: 2008 Update* [69], U.S. Department of Health and Human Services Web site

Table 4 Food and drug administration—approved dosage and prescription availability for pharmacologic agents for smoking cessation

Cessation agent	Dosage	Label indication and use	Availability in United States	OR of efficacy (95% CI)
Nicotine gum	2 and 4 mg	2 mg ≤25 cig/day and 4 mg ≥25 cig/day; one piece every 1–2 h for weeks 1–6, one every 2–4 h for weeks 7–9, and one every 4–8 h for weeks 10–12	OTC; traditional, mint, and orange flavors, generic available	1.66(1.52–1.81)[a]
Nicotine patch	21, 14, and 7 mg	≥10 cig/day: 21 mg for 6 weeks, then 14 mg for 2 weeks; then 7 mg for 2 weeks, ≤10 cig/day: 14 mg for 6 weeks, then 7 mg for 2 weeks	OTC; clear and skin color; generic available	1.81(1.63–2.02)[a]
Nicotine nasal spray	10 mg/mL, 0.5 mg/squirt	2 squirts (one dose) per hour, minimum 8 doses/day, maximum 40 doses/day; recommended up to 3 months	Prescription only, 100 mg/bottle; no generic	2.35(1.63–3.38)[a]
Nicotine oral inhaler	10 mg/cartridge, 4 mg delivered	6–16 cartridges/day up to 12 weeks, then gradual reduction for another 12 weeks; usually individualized	Prescription only, 168 cartridges/box; no generic	2.14(1.44–3.18)[a]
Nicotine lozenges	2 and 4 mg	If first cig is ≤30 min after waking, use 4-mg lozenge; if ≥30 min, use 2-mg lozenge; use one every 1–2 h for 6 weeks, then one every 2–4 h for 3 weeks, then one every 4–8 h for 3 weeks; minimum 8 lozenges/day, maximum 20 lozenges/day	OTC; mint and cherry flavors; no generic	2.05(1.62–2.59)[a]
Bupropion-SR	100 and 150 mg	150 mg every morning for 3 days, then 150 mg twice daily; recommended for 3 months	Prescription available; generic available	1.94(1.72–2.19)[b]
Varenicline	0.5 and 1 mg	0.5 mg every morning for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily up to 3 months; if successful may extend another 3 months	Prescription only; no generic	3.09(1.95–4.91)[c]; 2.66(1.72–4.11)[d]

Cig cigarettes, *FDA* United States Food and Drug Administration, *OTC* over the counter, *OR* odds ratio; *CI* confidence interval

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[a]Odds ratio/comparative efficacy for nicotine replacement therapies with control (placebo), as reviewed by Silagy et al. [157]

[b]Odds ratio for overall bupropion-SR efficacy, as reviewed by Hughes et al. [91]

[c]Odds ratio for varenicline efficacy compared with placebo by Gonzales et al. [76]

[d]Odds ratio for varenicline efficacy compared with placebo by Jorenby et al. [101]

Pharmacologic agents for nicotine dependence may be grouped into three categories: nicotine agonists (i.e., nicotine replacement therapies), nicotine antagonists (bupropion and mecamylamine), and nicotine partial agonists (cytisine and varenicline).

Nicotine Agonists

Nicotine replacement therapies were the first pharmacologic treatments to be offered for smoking cessation. The quit rate among smokers who take a nicotine replacement therapy is double that of smokers who do not [102]. Some nicotine replacement therapies are available by prescription only, and some are available over the counter. The United States Food and Drug Administration has approved the following nicotine replacement therapies for smoking cessation: polacrilex gum (over the counter); patches (16- or-24 h; by prescription and over the counter); nasal spray (by prescription only); buccal inhaler (by prescription only); flavored gum (over the counter); and lozenges (over the counter). Table 2 provides more detailed information on nicotine replacement therapies.

In a recent review on nicotine replacement therapies, Silagy et al. [157] identified 123 trials on nicotine replacement therapies, 103 of which involved a comparison between a nicotine replacement therapy and a control (placebo) or a non-nicotine replacement therapy control. The Silagy group reported that the overall odds ratio for abstinence with nicotine replacement therapies compared with control (placebo) was 1.77 (95% confidence interval, 1.66–1.88). In addition, they reported that combinations of nicotine replacement therapies were more effective than any nicotine replacement therapy alone, and they offered the following conclusions: (1) 8 weeks of patch therapy is as effective as longer courses of patch therapy, and there is no evidence that tapering therapy is better than abruptly ending therapy; (2) wearing a patch only during waking hours (16 h/day) is as effective as wearing a patch for 24 h/day; (3) gum may be offered on a fixed-dose or as-needed basis; (4) highly dependent smokers (e.g., those who need to smoke within 30 min of waking) and those who have been unable to quit with 2-mg gum can be offered 4-mg gum, and (5) the effectiveness of nicotine replacement therapies appears to be largely independent of the intensity of psychosocial therapeutic support provided to the smoker. Lastly, the review stated that practitioners should give the client brief advice on how to quit and an overview of ways to improve the effectiveness of treatment.

Two considerations in offering combined nicotine replacement therapies are the client's previous success with a nicotine replacement therapy and the extent of nicotine dependence. If someone has had prior success quitting on one type of nicotine replacement therapy, using the same product again is recommended, assuming that the person is interested in nicotine replacement therapies instead of non–nicotine-based medications. Client education and management of expectations are key aspects of the clinical visit before treatment begins. This is especially true for combination approaches, such as the simultaneous use of two nicotine replacement therapies or of bupropion and a nicotine replacement therapy. Clients may hesitate to use such combinations since all nicotine replacement therapy labels still have a warning against combining nicotine replacement therapies as well as against continuing to smoke after starting a nicotine replacement therapy. To note, both the combination of nicotine replacement therapies and using nicotine replacement therapies with concurrent smoking are deemed safe by more recent research [67]. Results from several studies demonstrate the safety of combining nicotine replacement therapies; other studies have explicitly used nicotine replacement therapies (gums, inhalers, or patches) even if participants continued to smoke. Using nicotine replacement therapies in this way have helped reduce the number of cigarettes smoked each day by as much as 50% in participants who were not motivated to quit. Those studies pointed out a lack of significant nicotine toxicity or major adverse events [21, 65, 184].

Nicotine Antagonists

Bupropion

The Food and Drug Administration approved bupropion-SR (Amfebutamone) for the treatment of tobacco dependence in 1991 under the new trade name Zyban. Bupropion-SR therapy is typically started 1–2 weeks before the planned quit date at a dosage of 150 mg per day for 3–7 days. The dosage should then be increased to 300 mg/day (divided into two doses). Bupropion-SR was originally approved as an antidepressant it is considered an atypical antidepressant because it does not have a clearly known mechanism of action. Its pharmacodynamic properties include inhibition of norepinephrine reuptake and a modest inhibition of dopamine reuptake [6]. These properties are thought to contribute to bupropion-SR's antidepressant and antismoking action. In addition, recent studies [158] have suggested that bupropion-SR acts as a non-competitive antagonist on high-affinity (alpha4beta2) subnicotinic acethylcoline receptors. One of bupropion-SR's metabolites, (2S, 3S)-hydroxybupropion, has been hypothesized to be an even more powerful antagonist at alpha4beta2 nicotine receptors than bupropion-SR itself. Therefore, (2S,3S)-hydroxybupropion may also reduce nicotine reward, withdrawal symptoms, and cravings [56].

Bupropion-SR is contraindicated in individuals with a family history or personal history of seizure and in those who have ever had a significant head trauma that resulted in a loss of consciousness for more than 10 min. Patients with anxiety, insomnia, dry mouth, or tremors may experience a worsening of these symptoms with bupropion-SR. In those with elevated liver enzyme levels, bupropion-SR metabolites may accumulate and lead to toxicity.

Hughes et al. [91] analyzed the efficacy data on bupropion-SR as the sole therapy in a recent meta-analysis of 31 clinical trials that included more than 10,000 smokers. The meta-analysis found that individuals taking bupropion-SR were twice as likely as those taking a placebo to achieve long-term tobacco abstinence (odds ratio = 1.94; 95% confidence interval, 1.72–2.19). Bupropion-SR also has been shown to be effective in several special clinical populations such as schizophrenic [66] or depressed [34] individuals, veterans [12], smokers with post-traumatic stress disorder [85] and in primary care settings [130].

The addition of a nicotine replacement therapy to bupropion-SR therapy is believed to produce immediate relief from nicotine withdrawal, at least in the immediate post-cessation period. However, a large controlled trial showed that the combination of bupropion and one form of nicotine replacement therapy (the patch) was more effective than the either alone at the end of treatment; but it was not more effective than bupropion-SR alone at the one year follow-up [100]. Bupropion-SR can offer unique advantages for smokers who also have depression or attention deficit/hyperactivity disorder because it may alleviate some of the comorbid symptoms. It may also be an advantageous treatment choice in individuals who are overweight or afraid of gaining weight after they quit smoking as it seems to help in attenuating the weight gain associated with smoking cessation [125]. Bupropion seems to have a subtle but important positive effect on sexual dysfunction, especially if the dysfunction is related to the use of serotonin reuptake inhibitors [49].

Although other antidepressants and anxiolytics have not generally been found efficacious for smoking cessation [91], bupropion's antidepressant actions may make it a particularly attractive choice for smokers vulnerable to negative affect or among those with some level of affective and/or cognitive impairment. For example, in one study relative to placebo, bupropion has been shown to be effective among smokers with a history of depression [159], although absolute cessation rates among depression history positive and negative smokers may not differ [91]. Apart from smoking, bupropion has long been indicated for the treatment of depression, and recent studies have shown additional benefits including prevention of the recurrence and

improved efficacy for depressed individuals with concomitant anxiety (see Clayton [48]), as well as a favorable outcome for the treatment of cocaine addiction when combined with behavioral treatment [145]. Direct tests of bupropion with depressed smokers have not been carried out since those with concurrent depression are typically excluded from smoking cessation pharmaceutical trials. Similarly, given concerns about bupropion's seizure potential during alcohol withdrawal, it has not been directly used in the treatment of smokers with alcohol use disorders; (although other antidepressants with similar noradrenergic properties have shown efficacy in the treatment of depressed alcoholics (see Torrens et al. [171]).

Mecamylamine

Mecamylamine, a nicotine receptor antagonist, is used as an experimental therapy for smoking cessation. The addition of mecamylamine was shown in preclinical and clinical studies to increase the efficacy of nicotine patch therapy from 27.5–29% to 47.5–58%. However, a more recent multi-site controlled study reported that the increase in efficacy was not statistically significant [75].

Mecamylamine produces unpleasant side effects, such as postganglionic effects (e.g., orthostatic hypotension) and strong anticholinergic effects (e.g., dry mouth and constipation), which have limited its use to either clinical or laboratory research settings.

Nicotine Partial Agonists

Varenicline

Varenicline (trade name Chantix) is the first pharmaceutically designed compound with partial agonist effects at nicotine receptors to become available in the market. Varenicline is a selective partial agonist that stimulates the alpha4beta2 nicotine cholinergic receptors and consequently stimulates dopamine release in the nucleus accumbens, though to a lesser extent (40–60% less) than nicotine itself. By binding to nicotine receptors throughout its relatively long half-life (24 h), varenicline displays antagonistic properties as well. As it prevents the full stimulation of the receptors that ensues when nicotine is co-administered [50]. Because of these properties, varenicline may provide relief from withdrawal symptoms (an agonist effect) while blocking the rewarding effects of nicotine (an antagonist effect) [168]. Animal studies also have shown that varenicline acts as a full agonist of the alpha-7 nicotine cholinergic receptor. Though this property has no clear benefit for smoking cessation [124], it may have benefits for individuals with chronic mental disorders (e.g., schizophrenia).

Clinical trials have shown varenicline to be more effective than bupropion-SR or placebo for smoking cessation with a resulting odds ratio of 3–1 compared to placebo (Table 4). Two randomized double-blind clinical trials have compared varenicline (2 mg), bupropion (300 mg), and placebo. One showed overall continuous abstinence rates from the end of treatment through 1 year of 21.9, 16.1, and 8.4%, respectively [76]; and the other, 23, 14.6, and 10.3% [101]. In all these comparisons, continuous abstinence rates were significantly higher for varenicline than for bupropion or placebo even at 1 year follow-up with medication. In a combined analysis of the two trials, varenicline resulted in significantly higher continuous abstinence rates at 1 year than either placebo or bupropion (all p-values < 0.05) [77]. In this pooled analysis, varenicline nearly tripled the odds of quitting smoking compared with placebo even when using continued abstinence as a measure during the last 4 weeks of medication treatment (odds ratio $= 3.09$; 95% confidence interval, 1.95–4.91; $p < 0.001$). An additional 12 weeks of varenicline therapy (a total of 24 weeks) was given to those who abstained from smoking at some point during the first 3 months of varenicline therapy. After re-randomization to varenicline or placebo in a double blind design, the carbon monoxide-confirmed continuous

abstinence rate was significantly higher for the varenicline group than for the placebo group for weeks 13–24 (70.5% vs. 49.6%; odds ratio [OR], 2.48; 95% confidence interval [CI], 1.95–3.16; $p < 0.001$) as well as for weeks 13–52 (43.6% vs. 36.9%; OR, 1.34; 95% CI, 1.06–1.69; $p = 0.02$) [169]. Furthermore, those who received varenicline reported significantly less cravings and diminished withdrawal symptoms throughout the trial [36].

The most common adverse effects of varenicline are nausea, which occurs in up to 30% of individuals (approximately twice the rate of nausea as in those taking a placebo), flatulence, and abnormal dreams. Recently, the Food and Drug Administration (FDA) has received a large amount of reports indicating increased depressive symptoms, occurrence or increase in suicidal ideation, and difficulty with coordination. The FDA have requested from the manufacturer further analysis of existing data and prospective studies to clarify the relationship to the medication and the magnitude of such occurrences. It is currently recommended that individuals stop the medication and advise their health care provider immediately if they develop changes in behavior or any of the above symptoms [179]. For many patients, the prospect of using varenicline, a new option, seems to motivate them to quit smoking, especially for those who have not succeeded with older smoking cessation medications. It is possible that combining varenicline with bupropion-SR would provide better smoking cessation efficacy, although two trials are under way no data on this combination have been published.

Cytisine

Cytisine (also known as Tabex) is a nicotine-like alkaloid derived from the plant species *Laburnum anagyroides*. Little was known about cytisine in the United States until the fall of the Soviet Union in the 1990s. Most studies of cytisine for smoking cessation were open-label trials and the controlled studies were not done so rigorously. Further, most of the studies were from Bulgaria and none were published in the English-language literature, making it difficult for investigators in the United States to form a definitive scientific opinion on the efficacy of cytisine for smoking cessation [174]. A recent review and meta-analysis of two double-blind, placebo-controlled studies of cytisine (Tabex) reported a pooled odds ratio for smoking cessation of 1.83 (95% confidence interval, 1.12–2.99) at 3 and 6 months, while another double-blind, placebo-controlled trial resulted in an odds ratio of 1.77 (95% confidence interval, 1.29–2.43) at 2 years of follow-up [64].

Other Medications

Clonidine, a second-line pharmacotherapy, has exhibited modest efficacy in smoking cessation trials. Its superiority to placebo has been reported in two meta-analyses that included a total of 13 placebo-controlled clinical trials, with odds ratios of quitting smoking of 2.4 (1.7–3.28 95% confidence interval) and 2.0 (1.3–3.0 95% confidence interval) [53, 78].

Several tricyclic antidepressants, which inhibit the reuptake of norepinephrine and serotonin, such as nortriptyline (a second line pharmacotherapy), might facilitate smoking cessation either alone or in combination with behavioral treatment. There are 6 well-designed, controlled studies showing nortriptyline's effects on smoking cessation with an odds ratio of 2.1 compared to placebo [90]. However, tricyclic antidepressants have significant disadvantages, including anticholinergic burden, cardiac side effects, and potential for lethal overdose.

Other potentially useful medications that are not Food and Drug Administration approved at this time for smoking cessation include [71]: (1) rimonabant (Acomplia®), a cannabinoid-1 receptor blocker, (2) Quitpack® (a combination of mecamylamine plus bupropion-SR) and (3) topiramate (Topamax®).

A novel treatment approach currently under development is active immunization against nicotine via vaccination. The proposed mechanism of action is inducing the formation of

antibodies against nicotine, which binds nicotine in the blood stream and consequently prevents it from crossing the blood-brain barrier [86]. This would prevent the direct and active effects of nicotine on the acetylcholine nicotinic receptors in the brain, potentially attenuating its effect [139] on the reward pathway, thought to be central in developing nicotine addiction. Since nicotine is a small non-immunogenic molecule it must be bound to a carrier protein in order for the immune system to detect and form antibodies against it [7]. Candidate nicotine vaccines have been developed using different antigens [86], they are in different stages of testing [121] and include: (a) NicQb (by Cytos Biotechnology): A virus-like particle nicotine conjugate, inducing specific antibodies of the immunoglobulin G isotype (long-term response, i.e., antibodies) but not immunoglobulin E isotype (immediate reaction, i.e., allergy response) [122]; (b) NicVAX (by Nabi Pharmaceuticals): A detoxified pseudomonas aeruginosa r-exoprotein A [182]; (c) Ta-Nic (by Celtic Pharma): A cholera toxin-B subunit as a carrier protein for nicotine [40, 137]; (d); and a newer NicAb (being developed at University of Minnesota) based on a bivalent antigen mix: detoxified pseudomonas aeruginosa r-exoprotein A plus a keyhole limpet hemocyanin, resulting in an enhanced antibody response [105]. Clinical testing for these products is in various stages of development at this time.

Non-pharmacologic Treatments

Behavioral treatment delivered by a variety of clinicians (e.g., physicians, psychologists, nurses, pharmacists, and dentists) has been shown to increase abstinence rates when "the five A's" are applied [69]: (1) Ask if they smoke; (2) Advise them to quit; (3) Assess motivation for change; (4) Assist if they are willing to change; (5) Arrange for follow-up.

More than 100 studies have validated the use of multimodal behavioral therapies (includes a combination of approaches such as supportive, cognitive behavioral, and motivational techniques) for smoking cessation, either alone or in combination with pharmacologic therapies. Multimodal behavioral therapies without pharmacologic agents achieve double the quit rates compared with controls that come for research visits, with 6-month efficacy ranges between 20 and 25%. While more intensive treatments usually translate into higher abstinence rates, not every smoker requires the same amount of intervention.

Summary

Long term tobacco use, usually resulting in nicotine dependence, is the leading cause of preventable disease and death in the United States and worldwide. Nicotine addiction activates the reward pathway and consequently the prefrontal cortex in a similar way to other addictions. Familial traits and genetics are responsible for as much as 60% of the variance for nicotine dependence, several single nucleotide polymorphisms and specific chromosomes have been implicated. Smoking cigarettes is a very fast and effective tool for nicotine delivery and nicotine dependence is a multifaceted syndrome consisting of biological, behavioral, and cognitive components. After a cessation attempt the emerging negative affect (anxiety, depression, irritability, etc.) has been found to correlate with relapse to smoking. Therefore, the treatment of nicotine dependence often requires an integrated approach that includes behavioral and motivational therapy in addition to medication. The diagnosis of nicotine dependence is usually made clinically, however there are several scales that can be used to quantify the level of dependence, such as the Fagerström Test for Nicotine Dependence and the Wisconsin Inventory of Nicotine Dependence. After more than two decades of research and development, health professionals can now turn to an arsenal of efficacious pharmacotherapies to treat smoking cessation. These agents often double the odds for quitting over placebo and in some cases almost triple the odds of quitting over those of placebo. Indeed, many smokers have benefited from these treatments and quit successfully.

However, despite these advances, many smokers relapse and unfortunately the long-term abstinence rates among smokers who are interested in quitting smoking remain low despite the best efforts and pharmacological treatment.

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Marijuana: An Overview of the Empirical Literature

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Introduction

Marijuana (also referred to as cannabis) is a drug that is derived from the flowers, stems, leaves, and seeds of the hemp plant (*Cannabis sativa*). The need for public health awareness and evidence-based clinical care for marijuana use and its disorders remains a major health care priority in the United States and beyond. Indeed, marijuana has been the most widely used illicit substance in the United States for the past 30 consecutive years [66], with approximately 25 million people in the United States (8.6% of the population) having used marijuana in the past year [67]. An estimated 10% of persons who have ever used marijuana will become daily users [64]. Lifetime marijuana dependence is estimated at 4% of the general population, a rate that is the highest of any illicit drug [3, 4]. These rates of marijuana use, abuse, and dependence in the United States represent a significant public health concern considering that several well-documented negative consequences have been associated with daily or weekly drug use (e.g., increased risk of severe medical disease, increased risk taking behavior, and clinically significant life impairment) [9, 81, 109].

The overarching aim of the present chapter is to provide an overview of marijuana use and its disorders. The chapter is organized into seven sections. First, we describe the prevalence of marijuana use and its disorders. Second, we clarify the nature of marijuana use in terms of its pharmacokinetics and acute intoxication features. In the third section, we describe the

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_20,

classification of marijuana use and its disorders using the current diagnostic nomenclature. Fourth, we describe the motivational bases for use of the drug. In the fifth section, we provide a synopsis of some problems associated with marijuana use and its disorders, including health problems, social problems, and psychological disturbances. Sixth, we provide a summary of the scientific work focused on marijuana, the reasons for its use, and users' relative success in quitting. In the final section, we describe some practically oriented clinical issues for primary care medical practitioners to consider in terms of the recognition and treatment of marijuana use and its disorders.

Prevalence

Marijuana has been the most widely used illicit substance for 30 consecutive years in the United States [65], with approximately 25 million people in the United States (8.6% of the population) having used marijuana in the past year [67]. An estimated 10% of persons who have ever used marijuana will become daily users [64]. Lifetime marijuana dependence is estimated at 4% of the general population, a rate that is the highest of any illicit drug [3, 4]. Rates of conditional dependence, defined as the risk for developing dependence among those who have ever used the drug, indicate that marijuana is associated with a high rate of dependence potential [4]. For example, the relative risk of experiencing marijuana dependence given use of the drug in the past year is estimated to be 7% among adults, which is only slightly lower than that for cocaine (12%) and greater than that observed for alcohol (5%) [69]. Furthermore, greater levels of use are related to an increased risk for dependence. Studies suggest that the rate of dependence is 20%-30% among those persons using marijuana on a regular (weekly) basis [49]. Moreover, marijuana use problems have increased in certain parts of the world, with 35% of adult marijuana users in the United States currently meeting criteria for marijuana abuse or dependence, compared with 30% 10 years earlier, representing an increase of approximately 730,000 individuals [26].

Of special relevance to clinical practitioners, many treatment and community studies have examined prevalence rates of marijuana use among different samples suffering from a variety of medical and psychological problems. For example, one study found that among those seeking treatment for psychosis, approximately 23% currently used marijuana, with about half of that group currently "misusing" the drug [47]. This study examined the "misuse" of marijuana rather than abuse or dependence. As a result, the precise percentage of those abusing or dependent on marijuana in this study is not known. Another community-based study found that approximately 16% of those with spinal cord injury used marijuana [117]. Other work found that marijuana use accounted for as much as 25% of the primary drug problems of individuals seeking residential drug treatment [38]. Similarly, among adolescents seeking outpatient services for marijuana abuse or dependence, approximately 38% reported suffering from depression and 29% reported acute levels of anxiety [37]. These studies suggest that marijuana use: (1) may be overrepresented among certain "vulnerable" populations and (2) is a primary clinical concern.

Nature of Marijuana Use: Pharmacokinetics and Acute Intoxication Features

Pharmacokinetics

Marijuana can be consumed via smoking (e.g., hand-rolled cigarettes, water pipes, non-water pipes) or ingestion (e.g., mixed into foods or used in the process of brewing tea). Marijuana shares some qualities with tobacco in that it is composed principally of plant material, often is used via smoking routes (e.g., pipes, joints), and contains a myriad of chemical compounds. Unlike tobacco, however, the active

agents in marijuana are cannabinoids (unique to the marijuana plant). There are at least 60 different cannabinoids in marijuana, although the pharmacokinetics of the vast majority of these compounds is largely unknown [6]. Of these, the most well-known, and arguably important, cannabinoid is tetrahydrocannabinol, which is believed to be the most potent psychoactive agent in the cannabinoid plant [110]. The tetrahydrocannabinol content of plants from a range of sources and strains varies dramatically [86]. With a focus on improved plant breeding and improved growing techniques, the tetrahydrocannabinol content of marijuana has increased dramatically in a short period of time. As one illustrative example, tetrahydrocannabinol content from a typical marijuana cigarette (joint) in the 1960s was 10 mg, whereas estimates suggest that it currently is around 1 g (or 150–200 mg) [6]. Given that marijuana effects are dose dependent (i.e., greater amount or potency yields greater effect) [110], the significantly increased potency of marijuana available in the current time period relative to the past is a major public health concern and is important to understanding the current and historical prevalence rates of use, abuse, and dependence.

Since the discovery of a cannabinoid receptor within the brain in the late 1980s, researchers have been able to explicate the process by which tetrahydrocannabinol acts on the brain. Currently, there is evidence of three potential cannabinoid receptors, only one of which is located within the brain (the cannabinoid-1 receptor) [110]. When tetrahydrocannabinol is inhaled into the body via marijuana smoking, it passes from the lungs into the bloodstream [56]. Once in the blood, tetrahydrocannabinol attaches to cannabinoid receptors, such as the cannabinoid-1 receptor, adding to or reducing the naturally occurring endogenous ligands for these receptors (e.g., anandamide) [36]. The cannabinoid-1 receptor, in particular, has been found to mediate both neurochemical and behavioral properties of these cannabinoids including tolerance [110]. It also is noteworthy that tetrahydrocannabinol and other cannabinoids move rapidly into fat and other bodily tissues but are relatively slowly released from these tissues back into the bloodstream [61]. Eventually, cannabinoids are cleared from the body via urine and fecal matter [110].

Acute Intoxication Features

In general, marijuana consumption produces a mild, relatively short period of intoxication (being "high"). More specifically, marijuana can produce a range of acute psychosensory experiences including perceptual distortions (e.g., hallucinogenic properties), relaxation, anxiety, acute paranoia, inhibition, and so on [63]. Periods of intoxication depend on use patterns and potency, but tend to last for at least a few hours [21, 87, 91]. Marijuana intoxication also impairs cognitive and psychomotor performance with complex, demanding tasks [50, 98]. There is a dose-dependent relation between marijuana use and psychomotor and cognitive impairment, with higher doses being associated with more impairment for more demanding tasks [6, 50]. Although cognitive impairment for hours after using marijuana is a well-replicated phenomenon in laboratory studies [98], there has been consistent debate about the permanent cognitive effects of using marijuana [6]. Some recent work suggests that individuals who have used marijuana over long periods of time demonstrate impaired performance on a variety of neuropsychological tests (e.g., attention, memory, and processing complex information) even when not acutely intoxicated [51]. These negative cognitive effects appear to be present months and even years after successful cessation [98]. Overall, pre-existing cognitive deficits or disease may be exacerbated or complicated by regular marijuana use.

Classification of Marijuana Use and Its Disorders

The current diagnostic criteria for problematic patterns of marijuana use, according to the *Diagnostic and Statistical Manual of Mental*

Table 1 Criteria for marijuana abuse

A. A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:
   1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home.
   2. Recurrent substance use in situations in which it is physically hazardous.
   3. Recurrent substance-related legal problems.
   4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

B. The symptoms have never met the criteria for marijuana dependence.

Table 2 Criteria for marijuana dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period [2]:

1. Tolerance, as defined by either of the following:
   (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following:
   (a) the characteristic withdrawal syndrome for the substance
   (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Disorders, 4th edition, include abuse and dependence [2] (see Tables 1 and 2 for the diagnostic criteria for marijuana abuse and marijuana dependence, respectively). Marijuana abuse is a pattern of marijuana use that includes significant and unpleasant consequences associated with frequent use. This pattern needs to have occurred within a 12-month period. Some of the consequences associated with marijuana abuse include multiple legal problems, repeated use in physically hazardous situations, and recurrent social and interpersonal problems as a result of use. What differentiates substance abuse from dependence is that abuse only includes harmful consequences of frequent use, whereas dependence indicates compulsive use, tolerance, or withdrawal [2]. As with diagnosis of other substance use disorders, it is also important to note that marijuana abuse cannot be diagnosed if marijuana dependence criteria are met. This important distinction highlights the putative more severe nature of marijuana dependence.

There are relatively few empirical data, however, pertaining to the validity of distinguishing among marijuana use, abuse, and dependence [48]. Moreover, for a long period of time, scholars did not uniformly endorse or support a marijuana dependence syndrome [16]. Current research has partially laid these earlier questions to rest in that heavy users of the drug tend to report problems controlling their use, despite noted negative consequences, and experience withdrawal and other adverse symptoms when discontinuing use (see [51] for a review). In fact, the best estimates suggest that approximately 1 out of every 10 individuals who use the drug become dependent on it at some point in the future [4], a pattern of data consistent with alcohol use problems, but markedly lower than that found with tobacco [4].

To date, researchers have employed standardized interviews to index marijuana diagnoses in a manner identical to those for other types of substances (e.g., alcohol, tobacco). At the

same time, in contrast to the relatively recent emerging perspective that classification of marijuana along the nosological lines of use, abuse, and dependence is the optimal and most accurate approach [16], it has been more common historically to denote marijuana use variability by asking respondents to indicate their level of use (e.g., frequency) over a specified period of time [33]. From this perspective, having participants specify the frequency, and perhaps quantity, of marijuana use also can be a common assessment method [24]. Collectively, then, deciding upon whether nosological classification and/or a use-oriented assessment protocol (i.e., volume and frequency) is indicated may depend on the specific clinical need or research question being posed and the theoretical basis for it.

Motivational Bases of Marijuana Use

Researchers and clinicians also have increasingly found merit in applying motivational models to understand and clinically intervene with marijuana use and its disorders. This work has built from the motivational study of alcohol [28, 31, 106, 107] and tobacco [62, 88, 90, 120] use. At the most basic level, such an approach recognizes that there are a number of distinct motives for using marijuana that can vary both between and within individuals [27]. That is, two individuals may use marijuana for different reasons, and one individual may use for multiple types of reasons. Motivational models predict that distinct motives may theoretically be related to particular types of problems [27]. For example, specific motives may play unique roles in various aspects of use (e.g., addictive use, withdrawal symptoms, craving) or problems related to use (e.g., psychological disturbances, risk-taking behavior). Thus, enhancing efforts to explicate marijuana use motives empirically will presumably facilitate, as it has for alcohol and tobacco use [27, 88], the nature of marijuana use and its disorders as well as linkages between marijuana use and its clinically important correlates.

Recognizing the practical importance of theoretically delineating and empirically measuring marijuana use motives, Simons and colleagues developed the Marijuana Motives Measure [96, 97]. Studies have evaluated the factor structure of the Marijuana Motives Measure: one focused on young adults in the United States ($n = 161$ [97]); one focused on young adults and adolescents in France ($n = 114$ [22]), and the most recent one focused on young adult marijuana users in the United States ($n = 227$ [122]). Using a combination of exploratory factor analytic and confirmatory factor analytic approaches, the Marijuana Motives Measure demonstrated a multidimensional measurement model across extant work—specifically, a five-factor solution denoting Enhancement, Conformity, Expansion, Coping, and Social motives for marijuana use, each with satisfactory levels of internal consistency [22, 97, 122].

Existing motivation-oriented work on marijuana is important in terms of informing the understanding of how and why marijuana use may be related to certain patterns of substance use and psychological problems. For example, greater levels of Coping, Enhancement, Social, and Expansion motives for marijuana use have each been found to be concurrently significantly associated with frequency of past-30-days marijuana use [10, 22, 96, 97]. These associations between motives for use and frequency of use do not appear to be attributable to other alternative factors such as amount of time being a marijuana user or other types of concurrent substance use [10]. However, the exact directional relation between marijuana motives and patterns of marijuana use remains underexplored. For example, it is not known whether specific marijuana motives explain variance in marijuana use patterns when controlling for the shared variance with other motives (e.g., the explanatory value of coping motives when controlling for shared variance with other marijuana use motives). Still, it is noteworthy that other work suggests that specific motives may be relevant to the understanding of psychological vulnerability. For example, coping motives for marijuana use, but not other motives, have been significantly predictive of

negative affect, anxious arousal, and anhedonic depressive symptoms [83]. These types of findings may have important theoretical implications for a better understanding of previous research linking marijuana use to affect-based psychological vulnerability.

Negative Correlates of Marijuana Use and Its Disorders

Historically, marijuana has been viewed by some as a "less severe" or "soft" drug [100]. In contrast, scientific study has provided a corpus of empirical evidence that marijuana use and its disorders are associated with a number of clinically significant problems [68]. Indeed, there are several empirically documented negative consequences of frequent or problematic marijuana use (typically defined as weekly or daily use). These negative effects are evident in physical, social, interpersonal, and, more recently, psychological realms. In this section of the chapter, we describe some examples of work pertaining to possible negative correlates of marijuana use.

Health-Related Problems

Perhaps the foremost negative effect linked to various types of marijuana use is its impact on physiological processes, particularly the cardiovascular and pulmonary systems. On the one hand, as would be expected, many of these effects are similar to those typically found with tobacco. On the other hand, due to the potentially greater level of carcinogenic properties of marijuana relative to tobacco [99], among certain subpopulations of users (e.g., those using marijuana more frequently), the negative medical effects of this drug are, perhaps, even more clinically noteworthy. For example, frequent marijuana use is associated with increased risk of severe respiratory illnesses, especially chronic bronchitis [9]. Other work has shown that when compared with individuals who do not use marijuana or tobacco, or with tobacco smokers who have no marijuana use history, the lung function of those who use marijuana regularly is significantly poorer [41].

There also has been a series of important large-scale prospective studies documenting the negative effects of marijuana over time on pulmonary functioning (e.g., [94, 111, 112]). Though the results across investigations are not fully consistent, they converge on the observation that greater duration of marijuana use is related to increased bronchitis symptoms (e.g., coughing, wheezing [111]). There also are studies of the relations between marijuana use and cancer. Most investigations suggest that there is an increased risk of lung cancer among more frequent users of the drug [20]. Controlled studies of these cancer-related negative effects of marijuana use, however, are largely underrepresented in the literature. In addition to the increased risk for lung cancer, it is noteworthy that some research suggests that marijuana use may be related to impaired immune system functioning, but these investigations, again, have not been consistently replicated [25, 58, 71]. Upon close inspection of these studies, it becomes clear that some of the inconsistencies of these investigations may be related to problems in the measurement of marijuana use and individual differences in use. A similar set of issues is evident for linkages between marijuana use and impaired reproductive effects. Non-human research suggests that heavier marijuana use is related to impaired reproduction capacity [51], but controlled evidence among humans is currently lacking [20].

It should be noted that although the vast majority of research has focused on elucidating putative negative health consequences or correlates of marijuana use, there has been scientific and clinical interest in possible health benefits of the drug. Namely, marijuana has been suggested to improve certain disease symptoms (e.g., by decreasing eye pressure, involuntary movement, and perceived pain) and to stimulate appetite [57, 58]. Although this body of work is complicated, the strongest evidence of possible health

benefits for marijuana use appears to be focused on increasing appetite, decreasing nausea and vomiting, preventing systemic weight loss, and possibly improving pain tolerance [58].

Social Problems

In addition to the potential risk of a number of negative physical consequences, adverse social consequences related to certain types of marijuana use have been reported (e.g., frequent users such as those who use on a daily or weekly basis). Lynskey and Hall [78], for example, reviewed evidence suggesting that marijuana use was a contributing factor to impaired educational attainment, and others have found that marijuana use leads to reduced workplace productivity [74], as well as impaired judgment within hours after marijuana use (e.g., among airline pilots [75]). In all of these studies, a consistent pattern emerges: the greater the amount of use (measured in frequency of use or severity of use), the greater the impairment. The specific mechanism(s) underlying these use-related effects are as yet theoretically and empirically unspecified.

As another example, marijuana use has been shown to be related to other social problems. For example, one cross-sectional study found that those who are dependent on marijuana compared with those who are not demonstrate greater levels of clinically significant impairment in life activities (e.g., work or school performance [103]). Additionally, quantity of marijuana use and acute intoxication have been related to general risk-taking behavior and impaired judgment. For instance, marijuana use has been linked to fatal traffic accidents and general driving impairment [40], even after statistically controlling for the variance accounted for by alcohol use [43]. Other work suggests that frequent or more severe marijuana use may lead to using more severe forms of other drugs (e.g., widely publicized, but sometimes controversial, "gateway theories" of the developmental nature of substance use patterns) [85]. One overarching limitation to the vast majority of work linking certain types of marijuana use to social and interpersonal functioning, and even future use of other substances, is that there is a dearth of (controlled) prospective evaluations. Thus, conclusions drawn from extant work should be viewed conservatively.

Psychological Problems

There have been a variety of psychological problems associated with marijuana use and its disorders. Perhaps the most well-known psychological problem(s) associated with marijuana use and its problems has been psychotic-spectrum disorders. There are numerous lines of empirical evidence that have provided robust evidence of an association between marijuana use and psychotic-spectrum disorders. Indeed, case reports of marijuana use have documented that such drug use can precede the onset of certain psychotic-spectrum disorders such as schizophrenia at higher rates than expected by chance of psychosis among "regular" marijuana users [11]. Although the directional nature of the marijuana-psychotic-spectrum problem association has been the subject of consistent intellectual debate (e.g., [52]), one position has been that the use of marijuana may actually increase the risk of psychotic-spectrum disorders [11]. Consistent with this marijuana-to-psychotic symptoms/disorders perspective, the acute effects of marijuana use have been found to contribute to the elicitation of psychotic episodes and exacerbations of such symptoms among previously afflicted persons (e.g., the recurrence of psychotic symptoms [80]). Other work has found that intravenous tetrahydrocannabinol administered to antipsychotic-treated patients with schizophrenia and non-psychiatric controls exacerbated positive schizophrenic symptoms in the patient sample and induced positive symptoms in controls [39]. Neuroimaging studies also have found similarities between neural networks impaired by marijuana use and those known to be implicated in the etiology of schizophrenia (see [77] for a review). Finally, in

a meta-analytic review of the existing empirical literature, Semple and colleagues [93] concluded that the early use of marijuana increased the risk of schizophrenia or a schizophrenia-like psychotic illness by approximately three-fold. Although a model indicating that marijuana may lead to psychotic-spectrum disorders provides only one possible way in which these factors may be related, it documents the importance of understanding marijuana in the context of severe mental illness.

In another area of research, scientific activity has been focused on addressing marijuana's relationship to depressive symptoms or problems [46]. The interest in this line of inquiry appears to have been historically fueled by the clinical observation that regular (e.g., on a daily or weekly basis) marijuana users often reported a "lack of motivation" for completing day-to-day activities (e.g., going to school [115]). The depression-marijuana literature has sometimes identified statistically significant relations between marijuana use and depressive symptoms and disorders [23]. However, the most recent work in this domain has indicated that the strength of such marijuana-depressive associations may be relatively weak, and markedly attenuated, or even nonexistent, after controlling for "common" variables such as gender [34]. As one illustrative example, Brook and colleagues [13] completed a study that involved a two-time (1- to 2-year interval) prospective study of Colombian adolescents (n = 2,226; 48.2% female) who were 12–17 years old. Findings indicated that marijuana use in early adolescence did not significantly predict later depressive symptoms (time 2) after controlling for distress and interpersonal functioning in earlier adolescence (time 1). This work, when considered in the context of the psychotic-spectrum research, noted earlier highlights that marijuana should not be considered to have the same types of linkages with all forms of mental illness.

Another stream of more recent work has begun to address the relations between marijuana use and anxiety symptoms and disorders. This work was initially stimulated by the observation that marijuana use may acutely promote heightened levels of anxiety symptoms and elicit panic attacks under certain conditions or among certain individuals [57, 113, 115]. For example, when a person is intoxicated from using marijuana, they may experience acute paranoia, escalating anxiety symptoms, and perhaps a panic attack. This type of experience makes intuitive sense in that marijuana can elicit a wide range of acute sensory-oriented experiences and distortions that may be perceived as out of the person's control and could be interpreted as threatening by some persons fearful of such internal stimuli and experiences. Some evidence appears consistent with this perspective. For example, Hathaway [55] found that among weekly users of marijuana (n = 104), approximately 40% reported having had at least one panic attack related to such use. These prevalence rates are noteworthy in light of lifetime rates of panic attacks among the general population of approximately 5–8% [72]. Another study found that, after covarying cigarettes per day, alcohol use, and negative affectivity, the interaction between marijuana use and anxiety sensitivity (fear of anxiety and related internal sensations) is related to increased levels of anxiety symptoms among marijuana users who also use tobacco [119]. Thus, certain individual differences such as anxiety sensitivity may be important to consider in understanding the linkages between marijuana use and anxiety states and disorders.

Another study involving a representative sample (n = 4,745) found that a lifetime history of marijuana dependence, but not use or abuse, was related to an increased risk of panic attacks after covarying the effects of polysubstance use, alcohol abuse, and demographic variables [118]. In a more recent investigation, Zvolensky and colleagues [121] prospectively evaluated marijuana use, abuse, and dependence in relation to the onset of panic attacks and panic disorder. Participants at the start of the study were adolescents (n = 1,709) with a mean age of 16.6 years (SD = 1.2; time 1) and were reassessed 1 year later (time 2) and then again as young adults (time 3; mean age = 24.2 years, SD = 0.6). Results indicated that adolescent-onset marijuana use and dependence were significantly

prospectively associated with increased odds for the development of panic attacks and panic disorder. However, marijuana use or dependence was not *incrementally* associated with the development of panic after controlling for daily cigarette smoking. These recent findings underscore the importance of considering the role of cigarette smoking in the context of marijuana use in regard to understanding panic vulnerability.

Marijuana: Motivation to Quit, Reasons for Quitting, and Success in Quitting

Though historically and presently presumed by some key segments of the general public to be "relatively harmless" [5], it is important to point out that marijuana has many cardinal features of addiction similar to more "hard drugs". Indeed, for many individuals who use marijuana, tolerance to the drug develops and, presumably, contributes to more frequent or heavier use patterns or dosing with more potent ("more pure tetrahydrocannabinol") forms of the drug [50]. For example, non-human research and, more recently, a smaller human empirical database suggest that marijuana discontinuation among regular users produces an internally consistent withdrawal pattern (see [17] for a review). Disrupted sleep, nightmares, nausea, anxiety, tension, irritability, sweating, and chills are common withdrawal symptoms [15, 18, 17, 53]. Many of these symptoms appear early after drug discontinuation [18], and some may last for weeks beyond the quit day (e.g., disrupted sleep [18, 17]). This withdrawal profile can appear relatively quickly during the course of use (e.g., relative early in the marijuana using career [14, 29, 103, 101]) and may have clinical importance in terms of predicting relapse [19], although current data are not yet developed enough to yield conclusions in this regard. With the recognition that marijuana use and its disorders are common addictive behaviors and can be related to life impairment and a variety of related negative consequences, it is natural to question how motivated users are to quit, what their reasons are for quitting, and what their relative degree of success is in doing so?

Motivation to Quit

Two bodies of empirical evidence indicate that a large number of individuals who use marijuana on a regular basis (e.g., monthly) and who meet a range of diagnostic criteria (from use through dependence) are motivated to quit. The first literature has evaluated treatment-seeking behavior. Here, the Drug Abuse Reporting Program [92] and other reports [95] first documented that a clinically significant number of individuals were seeking therapeutic services for problematic marijuana use. Other large-scale surveys independently replicated such findings [42, 59]. Dennis and colleagues [35] reported that of "the 1.5 million adult admissions to the U.S. public treatment system in 1998, 35% were admitted for treatment of marijuana problems" (p. 9). Such rates are higher than those found for cocaine (32%), opioids (18%), stimulants (9%), and other psychoactive substances (12%) [35]. Additionally, other reports involving national databases have found that the demand for treatment of marijuana use and its disorders doubled between 1992 and 1998 [108]. It also is important to note that marijuana treatment outcome studies have documented that a large number of treatment-seeking marijuana users are *not* current polysubstance abusers [100, 102]. For example, Stephens and colleagues [103] found that 80% of a large, marijuana-dependent sample ($n = 309$) did not report abuse of other substances in the past 90 days and 40% reported never abusing an illicit drug other than marijuana. These data indicate that marijuana represents a significant clinical and public health problem in its own right and commonly prompts treatment-seeking behavior even in the absence of other drug use.

The second body of evidence related to motivation to quit suggests that, despite the notable rates of documented treatment-seeking behavior,

most persons using, abusing, or dependent on marijuana actually attempt to quit on their own [30, 32, 116]. Self-quit behavior is operationally defined as attempts to quit without professional assistance (i.e., enrolling in a formal treatment program that uses pharmacological, psychosocial, or combined therapeutic approaches) [30]. Numerous studies have reported that by young adulthood, many individuals have made multiple marijuana quit attempts on their own. It also is noteworthy that rates of self-quit attempts from marijuana are generally similar to those observed for other substances (e.g., tobacco) [60]. For example, studies of weekly marijuana users have indicated that by age 30, individuals have reported a range of 3–7 quit attempts on their own (e.g., [30, 103]). Although some of these unsuccessful quitters may ultimately seek professional treatment when they continue to fail in their quit efforts, it is not presently clear what percentage will ultimately do so and under what circumstances.

These data are noteworthy for two chief reasons. First, these data suggest that a large proportion of marijuana-abusing or -dependent individuals are interested in and pursue quitting on their own. Second, there is little empirical knowledge about the phenomenology of these quit attempts (e.g., latency to lapse and relapse, withdrawal symptoms) or the mechanisms underlying success or failure in quit attempts among self-quitters not seeking professional treatment. Such knowledge is essential for understanding malleable processes underlying marijuana lapse and relapse versus sustained abstinence and, therefore, will ultimately facilitate future translational efforts to develop innovative marijuana treatment strategies targeting those at high risk for relapse.

Reasons for Quitting

Current marijuana users, ranging from monthly users to those dependent on the drug, report multiple concurrent reasons for quitting [45, 79, 103, 116]. Among adults, worry about physical and psychological effects of marijuana use is the most often cited factor for wanting to quit [79, 116]. For example, Copersinio et al. [30] reported that 60% of non-treatment-seeking adult weekly marijuana users reported worry about health problems (both real and perceived) as a motivating factor for quitting, and 63% desired to quit in order to gain more "self-control" over their lives. In another study, Reilly and colleagues [89] similarly found that anxiety or depressive symptoms were the most commonly reported "negative effects" of marijuana use and the primary reason for quitting among weekly marijuana users ($n = 268$). Others have reported similar findings among both non-treatment seekers [12] and treatment seekers [103]; such findings do not appear to vary as a function of the type of marijuana use problem [12]. Overall, these data suggest that marijuana users typically express multiple reasons for quitting, with the most common reasons pertaining to excessive negative emotional symptoms (e.g., anxiety and depression, worry about negative health effects of marijuana use) and impaired levels of personal self-control associated with regular marijuana use.

Success in Quitting

Individuals attempting to quit marijuana experience marked difficulty whether they make a quit attempt on their own or seek professional (formal) treatment. Numerous survey studies, for example, have documented that current, regular marijuana users (both those who are and are not dependent on the drug) who try to quit on their own report difficulty in remaining abstinent, as indexed by numerous unsuccessful quit attempts [30, 116].

Although self-quit attempts (without professional assistance) tend to be the most frequently employed quit strategy [12], it is striking that even among those who *do* seek professional treatment, relapse to use is a common experience. Indeed, in a critical review of the

treatment outcome literature for marijuana dependence, McRae and colleagues [82] concluded: "studies suggest that many patients do not show a positive treatment response, indicating that marijuana dependence is not easily treated" (p. 369). For example, one large-scale controlled study ($n = 291$) found that 63% of adults receiving two of the best available intervention strategies—motivational individualized intervention or cognitive-behavioral therapy—relapsed to regular use within 4 months [102]. For comparison purposes, the delayed treatment (control) condition reported that 91% of individuals were not abstinent at the 4-month assessment [102]. At 16 months, relapse rates among the active treatment conditions rose to 71 and 72% for the motivational individualized intervention and cognitive-behavioral therapy, respectively [102]. Other studies have reported similar results [29, 100, 104], and more recent clinical trials have extended such work by noting that in addition to full relapse, lapses are highly common and clinically significant. For example, Moore and Budney [84] reported that among marijuana-dependent adult outpatients receiving treatment ($n = 152$), 71% lapsed (defined as any marijuana use) within 6 months, 46% within 3 months, and 24% within 1 month. In the same study, 71% of lapsers ultimately experienced a full relapse (defined as 4 or more days of use per week) [84].

It also should be noted that there have been historically few pharmacotherapy options available for marijuana use disorders. In fact, currently there are no medications approved by the United States Food and Drug Administration for marijuana use disorders, although a number of agents are currently being investigated. See Chapter "Potential Pharmacotherapies for Cannabis Dependence" for further details.

Although marijuana relapse is now a well-documented, prevalent clinical problem, there has been relatively little scientific work focused on predictors of success or failure in attempts to quit using marijuana. The work that has been completed in this regard has been broadly guided by social learning [7], stress and coping [70], and behavioral economic [8] theories of substance use and relapse. These studies have thus far provided a number of initial and important observations: (1) early lapses are predictive of later relapses among adult and adolescent marijuana-abusing or -dependent persons, regardless of whether they receive formal treatment or not [1, 54, 73, 84]; (2) personal stressors (e.g., family conflict) are related to relapse among individuals with marijuana abuse or dependence receiving outpatient treatment [44]; (3) other substance use and peers' substance use (alcohol and other drugs) are predictive of relapse to marijuana use among adolescent marijuana-abusing or -dependent outpatients [73], and (4) the level of self-efficacy (i.e., beliefs regarding one's ability to refrain from use) for abstaining from marijuana use among adults with marijuana abuse or dependence seeking treatment is predictive, albeit modestly in terms of effect size, of later relapse [76, 105].

Marijuana: Overview of Clinical Issues Relevant to Practitioners

Given that marijuana use and its disorders are common and can be associated with a relatively wide variety of negative problems, clinicians such as primary care physicians who interact with patients in non-specialty clinical settings ought to be knowledgeable of basic issues in clinical care for this drug problem. To facilitate this process, we now turn to a discussion of some core clinical competencies by highlighting basic assessment and treatment strategies. This discussion is broadly relevant to clinical practitioners working in medical, dental, and psychological sectors of the health care industry. The topics discussed in this domain are not intended to be exhaustive or indicative of the full range of possible clinically relevant issues. They are, however, intended to offer some initial insight into the basic skills and knowledge that may be required to interact effectively with the marijuana-using population.

Basic Competencies

The most basic level of competency of clinical relevance focuses on simply being aware of the scientifically developed knowledge on the prevalence and impact of marijuana and its disorders. Here, clinicians should initially strive to attain an overall awareness of marijuana use and behavior as it relates to their patient population(s). Specifically, it is important for clinicians to recognize that marijuana use is integrally related to a wide range of negative life problems (e.g., respiratory illness). By obtaining such knowledge of marijuana use and its disorders, the clinician is better equipped to offer patients accurate information about problems related to marijuana use. This information can include psychoeducational "facts" (e.g., how marijuana may impact lung disease), but also may involve strategies designated (through scientific evaluation) as helpful to quitting, such as brief motivational interventions [103]. To gain access to this information, practicing clinicians can consider both informal and formal methods of education. More specific goal-oriented targets can include, but are not limited to, being able, efficiently and capably, to: (1) describe the prevalence of marijuana use and its disorders, (2) describe regional marijuana use patterns, (3) describe the negative physical and psychological consequences of marijuana use and dependence, (4) describe the importance and role of marijuana treatment, particularly those methods based on evidence-based resources, (5) maintain a general awareness of emerging research related to the treatment of marijuana use and its disorders, (6) understand the criteria used for defining marijuana use, abuse, and dependence, and (7) communicate an interest and willingness to consult with other resources when marijuana knowledge may be limited.

A second basic competency skill domain pertains to developing basic assessment and counseling skills for dealing effectively with marijuana use and its disorders. This domain of competence naturally builds from the foregoing description of general knowledge and awareness. This area of work necessarily begins with developing a level of "clinical comfort" with marijuana use topics and being capable of engaging a patient in a discussion focused on this topic. For this reason, the basic competency element in this domain requires counseling skills that strengthen interpersonal connection (e.g., rapport, listening to patient concerns). From the counseling perspective, a variety of core skills are necessary. These include, but are not limited to: (1) having the capacity to be an active listener and demonstrate an empathetic stance regarding clinical care involving marijuana-related issues, (2) being able to communicate the strengths and challenges to evidence-based care treatment approaches for marijuana use and its disorders in a non-threatening manner, and (3) being able to understand basic models of behavior change that pertain to marijuana use and meaningfully communicate levels of "motivational stage and readiness" to clients.

From an assessment perspective, basic competencies are needed in order to understand how to evaluate marijuana use behavior and history adequately. Without this level of proficiency, it will be challenging to document readiness to quit or success in doing so. In the assessment process, there are both historical and current factors to evaluate. The overarching goal is to learn to comprehensively document and obtain accurate information that can be used in a clinically meaningful manner. The assessment process can be usefully divided into two global phases: intake (or initial assessment) and ongoing assessment. For the intake assessment, key variables to assess include: the extent and nature of marijuana use from a lifetime and current perspective; documenting current interest and motivation in quitting; employing evidence-based technologies for documenting marijuana use, abuse, and dependence; identifying (with the client) barriers to quitting currently; identifying strengths in the client or the environment (e.g., social support) for quitting; documenting the nature of past quit history and relative degree of success in such attempts, and personal as well as cultural variables that may impact marijuana use and decisions regarding use. The

intake assessment process should also integrate information about the client's medical and psychological history (e.g., concurrent substance use) in order to understand how such factors may influence the ongoing marijuana use or attempts to quit.

Ongoing assessments require an understanding of each client and the specific variables that need to be regularly tracked in order to accurately and objectively document (and understand) the motivation to quit and marijuana use behavior. Here, there will be differences across individuals, but in most instances marijuana use behavior, ongoing life stressors, and current motivation to quit are possibly important targets. This information can be used to track and understand ongoing efforts to quit. For example, clinicians should take note of each client's specific thoughts related to marijuana use (e.g., belief that marijuana use functions as an effective method of stress management), primary reason(s) for wanting to quit smoking (e.g., health, social stigma), and situations in which marijuana use is most likely to occur (e.g., when drinking alcohol). This information, in turn, can be applied to help educate clients about their specific marijuana use patterns and, ultimately, help them formulate a plan for making a quit attempt that is individualized to their specific needs and life circumstances.

Aside from the individual level of commitment to professional development, it is a reality that most medical care occurs within a context that intersects with other health care professionals. Therefore, enlisting in an integrated manner the systems involved in such clinical work may be a powerful resource for dealing with marijuana use and its disorders. The need for such systems-oriented care is particularly evident given that educational efforts solely focused on the individual have not always been met with large degrees of success in the substance use field (e.g., [114]). Additionally, many individuals seek medical care in medical systems governed by managed care businesses or other third party payers. As a result, changes to a system of medical care can have a major impact in terms of the type and quality of care administered by practitioners working within that system.

Summary

Understanding and treating marijuana use is an important public health priority. Despite the increasing recognition that marijuana use and its disorders are not actually "harmless", the scientific literature pertaining to the etiology and maintenance, assessment, and treatment of marijuana use and its disorders is still in its beginnings. The next decade promises to be an important time to marshal resources in order to bridge major knowledge gaps and translate such developments into promising prevention and treatment approaches.

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Opiates and Prescription Drugs

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Contents

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Classification

Medications derived from papaver somniferum, the opium poppy, have played a central role in medical practice for well over 3,500 years. Sumerian clay tablets, which include our oldest known medical texts, called the opium poppy "Hul Gil", the "Joy Plant". In the Greco-Roman era, poppies were cultivated for their pain-relieving, antidiarrheal, and sedative properties. Today, medications in this class are divided into two groups. Opiates are naturally occurring compounds derived from the active alkaloids of the opium poppy. This group includes morphine, codeine, and thebaine. Opioids are manufactured medications that are classified as either fully synthetic or semisynthetic. Medications in the synthetic opioid group include alfentanil (Alfenta®, Rapifen®), fentanyl, meperidine (Demerol®), methadone (Dolophine®), pentazocine (Talwin®), propoxyphene (Darvon®), and sufentanil (Sufenta®). Included in the semisynthetic opioid group are buprenophine (Buprenex®, Suboxone®, and Subutex®), hydrocodone (Hycodan®), oxycodone (Percodan®), and oxymorphone (Numorphan®), all of which are derived from thebaine. Other semisynthetic compounds derived from the opium poppy are

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_21,

hydromorphone (Dilaudid®) and heroin, which is metabolized to morphine. Both of these drugs are highly abusable. The human body also produces a number of endogenous opioids, such as endorphins, enkephalins, and dynorphins.

Etiology

There is no clearly defined etiology for opiate dependence. Risk is determined by multiple factors including genetics, psychiatric comorbidity, and social and environmental factors, including drug exposure. Twin studies suggest that genetics alone accounts for 45–50% of the risk for opioid dependence. Recent work has identified two sites on chromosome 17 that are associated with an increased risk for drug dependence; one of these sites is connected to severe symptoms of opioid dependence, but not to dependence on other drugs [44]. Further work is needed to identify the specific genes that are associated with the unique risk for opioid dependence.

Epidemiology

Patterns of Use

For most of the twenty first century, heroin was the primary opiate abused in the United States. There were major epidemics after World War I, World War II, and the Vietnam conflict. Among the general population, it is estimated that 10–30% of individuals exposed to licit and illicit opioids may develop symptoms of abuse or dependence. These numbers may be significantly higher in individuals with co-occurring psychiatric disorders, particularly those exposed to sexual abuse or combat trauma. While regular estimates of drug use in adults and adolescents have been available from the Monitoring the Future study and the National Survey on Drug Use and Health, information on drug use disorders has rarely been collected [58, 143]. There was a 16-year gap between publication of the 1990–1992 National Comorbidity Survey data and the 2000 National Survey on Drug Use and Health, which collected 12-month prevalence data on drug use disorders [143]. Depending on the survey and the criteria used, estimates for the lifetime prevalence of any drug dependence disorders have ranged from 0.4 to 7.5% [28, 47, 67, 123].

For many years, it was assumed that the lifetime risk for heroin dependence was relatively low and ranged from 0.4 to 0.7%. In 2006, the National Survey on Drug Use and Health reported that 3.79 million individuals used heroin at least once in their lifetime and 323,000 were classified with either dependence or abuse of heroin. In addition, it was estimated that there were 250,000 individuals in methadone maintenance treatment. From 1984 to 1994, new users of heroin each year ranged between 28,000 and 80,000. From 1995 to 2001, the number averaged over 100,000; in 2006, it dropped slightly to 91,000 [33]. These numbers have been relatively unchanged since 1965.

Incidence of Substance Use Disorders

The most recent national survey, the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions, was designed to collect data on drug use disorders and, for the first time in a national survey, to collect separate data on both illicit drugs and prescribed medications. The National Epidemiologic Survey on Alcohol and Related Conditions surveyed 43,093 adults (18 years of age and older) in the United States, and captured data at the time when the United States' epidemic of prescription opioid abuse was at its peak. The National Comorbidity Survey and the Environmental Catchment Area Survey combined data on heroin and other opiates into a broad "drug abuse" category that also included other illicit drugs, thus making it impossible to get specific data on opiates, or to separate out information on heroin from data on prescribed opiates [28, 57]. The National Epidemiologic Survey on Alcohol and Related Conditions reported the prevalence of 12-month and lifetime drug abuse as 1.4 and 7.7%, respectively, and

the rates of drug dependence as 0.6 and 2.6%, respectively. Rates of abuse and dependence were significantly higher in men vs. women and in Native Americans vs. Whites, Blacks, and Hispanics [28]. The lifetime prevalence of nonmedical prescription opioid drug use was 4.7%. The lifetime prevalence of nonmedical opioid drug use disorders was 1.4%, indicating that approximately 30% of users were at risk for developing an opioid drug use disorder. Men were significantly more likely to progress from use to abuse to dependence than were women, as were Native Americans as compared with Whites. The mean age onset of opioid abuse or dependence was 22.8 years, and the mean age at first treatment was 26.2 years, a lag of 3.4 years. Approximately two-thirds of individuals with opioid use disorders never received treatment [57]. This prevalence of nonmedical opioid use disorders is 2–3 times higher than prior estimates of the prevalence of heroin use disorders.

Abuse of Opioid Analgesics

The abuse of opioid analgesics was traditionally thought to be a relatively small part of the United States' drug problem. While there were few data on the risk for dependence among individuals treated for chronic pain, the risk was assumed to be minimal [115, 119]. During the 1960s, the introduction of pentazocine (Talwin®) triggered a period of abuse after opiate addicts discovered that the injected combination of Talwin® and amphetamines ("T's and Blues") produced a potent euphoric effect. After this problem was identified, the Food and Drug Administration required that the medication be reformulated as a combination tablet of Talwin® and naltrexone (TalwinNX®) [91]. This formulation produced an antagonist reaction in addicted individuals if the tablets were crushed and injected, essentially eliminating significant abuse of this medication. The abuse of other opioid analgesics remained a minimal problem until the introduction of OxyContin® in 1996. From 1970 to 1995, the National Survey on Drug Use and Health reported that the annual number of new nonmedical users of pain relievers ranged from 700,000 to 1,000,000 [143]. In the 5 years following 1996, this number almost tripled to 2,500,000 [33]. These numbers reflect a new epidemic of abuse of pain relievers in the United States (see Fig. 1).

As noted above, prior to 2000, the National Survey on Drug Use and Health reported only drug use data, not data on drug use disorders [28]. In 2005, the National Survey on Drug

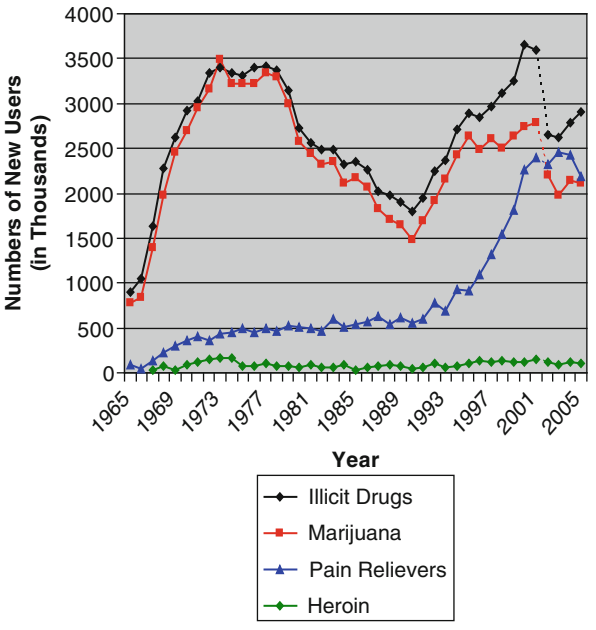

Fig. 1 New drug user patterns, 1965–2005 [33]

Use and Health reported that 4.9% of 12–17 year olds had used prescription pain relievers nonmedically in the past year. This was more than 24 times the reported use of heroin in this group (0.2% vs. 4.9%). In this cohort, past-year dependence or abuse was 1.1% (275,000 individuals) for pain relievers, vs. 0.0% (fewer than 9,000 individuals) for heroin dependence or abuse [143]. In 2006, the National Survey on Drug Use and Health reported that 33,422,000 Americans aged 12 or older admitted to the nonmedical use of pain relievers at least once in their lives and that 12,649,000 had done so in the last year. The survey classified 1,635,000 individuals aged 12 or older with dependence or abuse of pain relievers, as compared with 323,000 individuals classified with dependence or abuse of heroin. There were over 2,150,000 new illicit users of pain relievers in 2006, making the abuse of pain relievers the most common new drug of abuse, ahead of marijuana abuse (2,063,000). In comparison, there were only 91,000 new initiates to heroin use in 2006 (see Fig. 2). The 2006 National Survey on Drug Use and Health estimated that 7,800,000 adults in the United States (3.2% of the total population) were in need of treatment for some type of illicit drug problem; less than 20% of that group received any treatment in 2006. This survey made it clear that the abuse of pharmaceutical analgesics had replaced heroin as the dominant opioid abuse problem in the United States [33].

Risks Associated with the Use of Opioid Analgesics

For many years, pain management specialists had voiced concern about the undertreatment of pain. The pharmaceutical industry also identified a need for less abusable and more potent opioids for pain management. In the 1980s, the Bard Corporation developed a sustained-release technology suitable for morphine. This led to the marketing of sustained-release morphine in England under the brand name of MST Continus®; in 1984, the same medication was introduced in the United States by Purdue Pharma as MS-Contin®. This formulation proved effective in preventing significant abuse, and the medication gained wide acceptance in the American market. The expanding use of opioids for the treatment of severe pain led to an interest in a medication with greater potency, longer duration of action, and low abuse potential. Oxycodone provided the desired potency, but it could not be successfully formulated with the sustained-release technology that had been effective with morphine. This problem

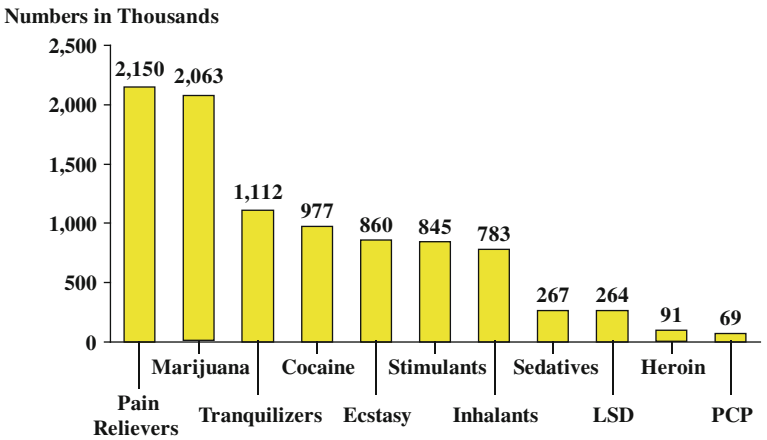

Fig. 2 Past-year initiates for specific illicit drugs among persons aged 12 or older, 2006 (National Survey on Drug Use and Health) [33]. LSD = lysergic acid diethylamide; PCP = phencyclidine

was resolved in 1996 when Purdue introduced OxyContin®, a time-release formulation of oxycodone with an acrylic coating that was designed to dissolve slowly and provide 12 h of pain control, permitting individuals with pain to sleep through the night. This formulation permitted delivery of doses ranging from 10 to 160 mg—doses far in excess of the 30-mg maximum dose previously available in oxycodone tablets. This was a major advance in the management of severe pain. Based on the experience with MS-Contin®, both Purdue and the Food and Drug Administration assumed that this formulation would have low abuse potential, and Purdue was permitted to market the medication as a potent, long-acting narcotic with a lower abuse potential than other opioid analgesics. Consequently, Purdue marketed OxyContin® as a first-line agent for the treatment of non-malignant pain. At that time, there was a general presumption that iatrogenic addiction secondary to the treatment of legitimate pain was a rare event. This assumption was based on a series of articles published between 1977 and 1982, all of which reported a minimal risk of iatrogenic addiction in the treatment of acute pain [90, 115, 119]. This view was reinforced by Portenoy and Foley [118], who found evidence of abuse problems in only 2 out of 38 individuals chronically treated with opiates for non-malignant pain. They concluded that opioid maintenance therapy was safe, except in individuals with a history of drug abuse. In 2000, Joranson et al. reviewed emergency room data from the Drug Abuse Warning Network and found no evidence of an increase in analgesic abuse, despite significant increases in the prescription of opioid analgesics [60].

In the late 1990s, clinicians in rural Virginia and northern Maine reported that young people were crushing OxyContin® tablets and snorting or injecting the drug. This method of ingestion produced a highly euphoric and reinforcing experience; abusers were exposed to very high doses of oxycodone, and many quickly became addicted. There was also a corresponding spike in overdose deaths. Despite growing evidence of addiction and overdose deaths, Purdue executives remained convinced of the efficacy and safety of their medication. By 2000, sales of OxyContin® reached over $1 billion/year and the company was marketing it as a first-line agent for a wide variety of pain syndromes, with recommendations that it be used before lower scheduled narcotics, or even before Ultram®, a non-narcotic [91]. In 2001, the Food and Drug Administration required a new label for OxyContin® that dropped claims about a reduced risk of abuse. By this time it had become apparent that overdose deaths and reports of addictive behavior did not just involve individuals who were illicitly using the drug, but that some people being treated for legitimate pain problems were becoming addicted and finding it impossible to stop their use of the drug. In retrospect, clinicians realized that the bulk of the medical literature claiming a minimal risk of iatrogenic addiction primarily reported on experience using opioids to treat acute pain and that there were few data on the risk of addiction in individuals treated for chronic pain [60]. Similarly, there were no data on the addiction risks associated with the use of long-acting high-potency agents such as OxyContin® for either acute or chronic pain. All of the published research on the abuse risk of chronic opioid treatment preceded the marketing of those medications.

As physicians became aware of the problems associated with OxyContin®, many shifted to oral methadone as a safer alternative for the management of chronic pain. From 1998 to 2006, the number methadone prescriptions for pain in the United States increased from 0.5 million to over 4 million. Unfortunately, there was a linear relationship between opioid-related overdose deaths and the increase in the prescription of pain relievers (see Fig. 3) [113].

Neurobiology

The functions of all the compounds in this class (opiates, synthetic opioids, and endogenous opioids) are mediated through a variety of receptors in the central and peripheral nervous

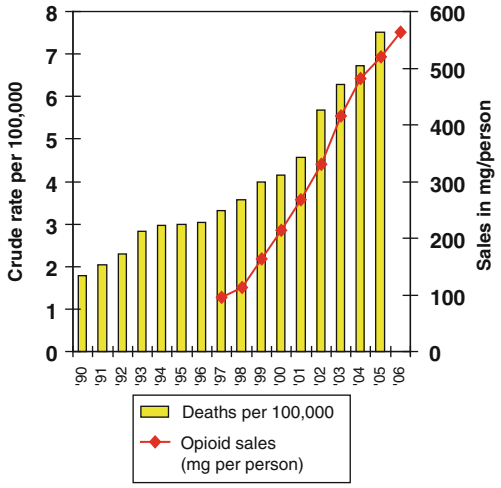

Fig. 3 Deaths per 100,000 related to unintentional overdose and annual sales of prescription opioids by year, 1990–2006 (L. J. Paulozzi, Centers for Disease Control Congressional Testimony, United States Senate Subcommittee on Crime & Drugs, Committee on the Judiciary and the Caucus on International Narcotics Control, March 12, 2008; adapted from [113])

system. The mu, delta, and kappa opioid receptors are well defined, and genes encoding for these receptors have been cloned [25, 26, 39, 64]. The mu receptor was named because of the affinity of morphine for this receptor. Full agonists at the mu receptor activate the receptor, are highly reinforcing, and include the most abused types of opioids. There are two primary subtypes of the mu receptor. Subtype 1 (mu_1) apparently mediates analgesic effects. Subtype 2 (mu_2) is likely responsible for the symptoms associated with opioid overdose (including respiratory depression) and withdrawal. Agonists at the mu receptor include morphine, methadone, and beta-endorphin. These compounds also have agonist activity at the delta receptor (named because of their presence in the vas deferens). The primary agonists at the delta receptor are met-enkephalins and leu-enkephalins.

Another group of receptors were named kappa because of their affinity for the opioid agonist ketazocine. Kappa receptors bind endogenous dynorphin and are thought to mediate spinal cord analgesia. They are also involved in the psychotomimetic and dysphoric effects seen in overdoses of pentazocine and other kappa-active synthetic opiates. Opioid antagonists (naloxone and naltrexone) are synthetic derivatives of oxymorphone and act primarily at the two mu receptor sites, though they also have some antagonist activity at the kappa receptor (see Fig. 4).

There is another group of medications that have mixed agonist-antagonist properties. For example, pentazocine acts as a kappa agonist and as a weak mu antagonist. Butorphanol has mixed kappa and mu agonist properties and

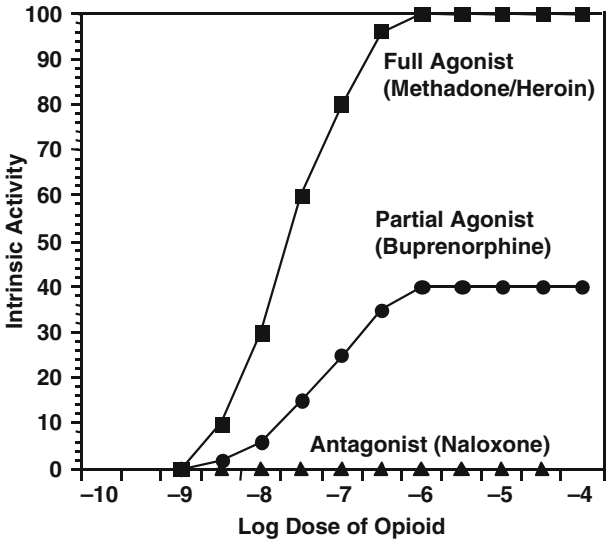

Fig. 4 Intrinsic activity: full agonist (methadone), partial agonist (buprenorphine), and antagonist (naloxone) [adapted from Fig. 2-1, Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opiate Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 40–3939. Substance Abuse and Mental Health Services Administration, Rockville, MD, 2004]

weak antagonist properties. Buprenorphine is classified as a partial opioid agonist at the mu and kappa receptors and an antagonist at the delta receptor. While it binds tightly to the mu receptor, it only partially activates the receptor (see Fig. 4). There appears to be a plateau effect that limits activation to about 50% of receptor activity and prevents the respiratory depression seen with full mu receptor agonists; interestingly, the analgesic effect of buprenorphine does not seem to be limited by the plateau effect [31]. When a partial agonist is administered in the presence of a full agonist, the partial agonist either displaces the full agonist or prevents its binding to the receptor. As a result, the partial agonist acts as an antagonist to the full agonist [151].

More recently, a new receptor named the orphanin/nociceptin receptor or opioid receptor-like receptor has been identified [30, 95]. Orphanin/nociceptin is an endogenous opioid-like neuropeptide that acts as an agonist at the opioid receptor-like receptor. It has an inhibitory effect on synaptic transmission and appears to be involved in memory, learning, attention, and pain perception [110]. Despite the structural similarity between the opioid receptor-like receptor and the three "classical" opioid receptors, most opioids lack affinity for the nociceptin system [54], and it is not affected by opioid antagonists. The function of the nociceptin/opioid receptor-like receptor system in pain control needs further clarification, and other functions are still a matter of speculation, though investigation suggests that it has a role as a down-regulator of immune function [42]. It is also known that activation of the opioid receptor-like receptor causes motor impairment, suggesting that development of opioid receptor-like receptor agonists would be difficult.

The abuse potential of opioids can be predicted by three sets of characteristics. Drugs with a shorter half-life have a greater abuse potential (heroin > methadone). Drugs with higher lipophilicity cross the blood-brain barrier more rapidly and are more likely to be abused (heroin > morphine > methadone). Finally, those drugs with a faster route of administration have a higher abuse potential (intravenous injection > subcutaneous injection > oral ingestion). Heroin (di-acetyl-morphine) has two acetyl groups that render it very lipophilic, enabling it to cross the blood-brain barrier more rapidly than morphine, thereby making it a preferred drug for injecting opioid abusers [112, 136].

Biological Effects of Use

The primary acute effects of opioids are euphoria, analgesia, decreased consciousness and respirations, vomiting, and constricted pupils. Codeine is also effective as a cough suppressant, and morphine is used to treat cardiac-related pulmonary edema. Analgesia and euphoria are produced directly through agonist effects at the mu receptor and indirectly through activation of the dopaminergic reward system in the nucleus accumbens. In overdose situations, consciousness is depressed to levels of non-responsiveness, the pupils are pin point, and there is marked suppression of autonomic functions with decreased pulse, blood pressure, and respiration, leading to lethal respiratory depression. The skin becomes cyanotic, and skeletal muscles become flaccid. Pulmonary edema occurs in 50% of cases. Physical tolerance can develop within 1–2 weeks with repeated dosing, requiring increased doses to maintain the original opioid effect. Tolerance develops more rapidly with shorter-acting opiates and with binge patterns of use, but is very slow to develop in individuals maintained on methadone. Interestingly, there is no down-regulation of mu receptors in methadone recipients [70], supporting the observation that most neurophysiologic functions return to normal with methadone maintenance treatment [76, 77]. With chronic use, physical dependence develops and users manifest a characteristic withdrawal syndrome if the dose is reduced or stopped (see below). In some animal models, physical dependence has developed in the absence of tolerance, suggesting that these are dissociable phenomena [121]. Tolerance develops

more quickly to opiate side effects than to the analgesic effect. Chronic opiate use leads to reduced dopaminergic tone and decreased binding capacity at the D2 dopamine receptor [8, 78, 148, 149]. Once tolerance develops, opiates are required to maintain an altered homeostatic set-point within the hypothalamic-pituitary-adrenal axis and within the pathways that govern memory and hedonistic desires [75]. Abnormalities in the hypothalamic-pituitary-adrenal axis may persist for over 1 year following opioid detoxification. A relative endorphin deficiency is also present during chronic opiate abuse and during the prolonged opiate withdrawal syndrome, but endorphin levels normalize during methadone maintenance treatment [73, 77, 135]. Despite the development of tolerance, pupillary constriction, constipation and sweating may persist indefinitely. Long-term users report lethargy, decreased libido, and diminished sexual function; men have below-normal testosterone levels, and women may develop amenorrhea and have difficulty conceiving.

In physically dependent individuals, there is a characteristic withdrawal syndrome when opioids are reduced or stopped abruptly. Symptoms begin within 6–12 h following the last dose of a short-acting opiate such as heroin. Early stages are characterized by anxiety, nausea, muscle aches, and abdominal cramps. This progresses to yawning, rhinorrhea, lacrimation, sweating, piloerection (gooseflesh, "going cold turkey"), dilated pupils, diarrhea, insomnia, and elevated temperature, heart rate, blood pressure, and respirations. In the most severe stage, the syndrome includes severe craving, abdominal cramps, diarrhea, and painful cramps and muscle spasms ("kicking the habit"). Many of the acute symptoms of opiate withdrawal are driven by an overactive catecholaminergic system located in the locus coeruleus, and by dopaminergic neurons located in the ventral tegmental area. The syndrome is most severe in individuals dependent on short-acting opiates such as heroin, but it clears in 4–7 days. Withdrawal from long-acting opioids, such as methadone, is less severe but can last for 14 days or more. Withdrawal symptoms from the partial agonist buprenorphine are slightly less severe than those caused by methadone and last 5–7 days, making it the preferred opioid for use in medically supervised withdrawal (see Fig. 5 and Table 1). Following withdrawal, many addicts experience a prolonged state of dysphoria that may last for months.

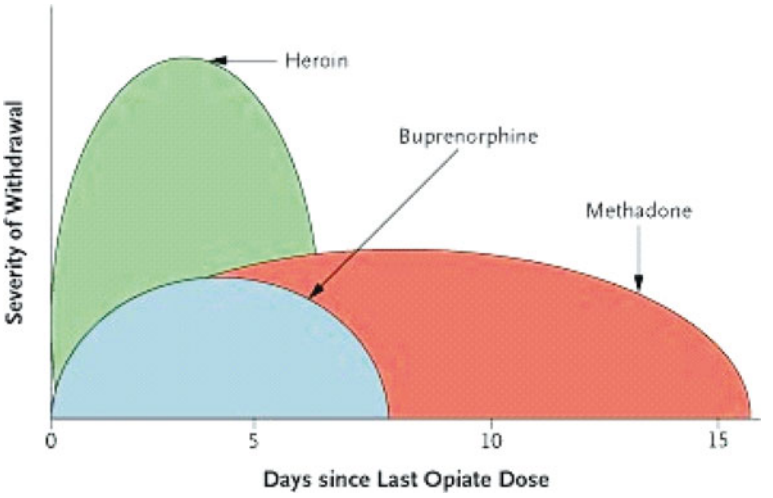

Fig. 5 Comparison of spontaneous withdrawals (Heroin > Buprenorphine > Methadone Withdrawal). The graph illustrates the severity of opioid-withdrawal symptoms after abrupt discontinuation of equivalent doses of heroin, buprenorphine, and methadone. Copyright © 2004 Massachusetts Medical Society. All rights reserved [72]

Table 1 Characteristics of spontaneous opioid withdrawal

Drug	Onset	Peak	Duration
Heroin	6–12 h	~ 3 days	4–7 days
Buprenorphine	1–3 days	~ 4 days	5–7 days
Methadone	1–2 days	~ 7 days	12–14 days

Psychological Effects of Use

In non-tolerant users, opioids produce sedation, analgesia, and, in some cases, euphoria and a profound sense of well-being. This is often described as being "high" or "on the nod." Many users also report an antidepressant effect from opioids. As use becomes more frequent, users cycle between states of euphoria and normality (see Fig. 6).

Regular use eventually leads to physical tolerance, a state where progressively higher doses are required to produce the desired experience of euphoria. Eventually the individual becomes physically dependent and starts to experience withdrawal symptoms whenever the euphoria wears off. Drug craving becomes progressively more severe, and higher doses are required to prevent the development of withdrawal. In this later stage of dependency, users rarely feel normal and typically cycle between states of low-level intoxication and withdrawal (see Fig. 6). Large doses of opiates are needed to eliminate withdrawal symptoms, and it may be difficult for the addict to achieve any state approaching normality, let alone euphoria. At this stage, addicts are chronically irritable and depressed. Individuals maintained on stable doses of long-acting opioids such as methadone, levo-alpha acetyl methadol, or buprenorphine become tolerant to any sedative effects, and they generally report the absence of craving, euphoria, or withdrawal symptoms. They often feel more alert and energized following their daily dose. However, many individuals on maintenance treatment fail to develop tolerance to the side effects of constipation and sweating.

Diagnosis

The diagnoses of opiate dependence and abuse are established using the standard *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision criteria for substance abuse or dependence [4]. Clients may present with the typical symptoms of either opiate intoxication or withdrawal described in the sections below titled "Opiate Overdose" and "Opiate Withdrawal Syndromes". A urine toxicology examination should be obtained on all clients to confirm current use and to screen for the abuse

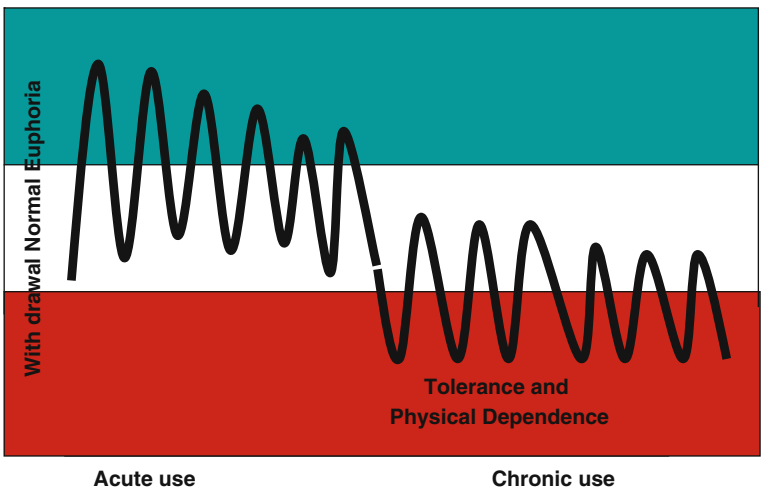

Fig. 6 Natural history of opioid dependence. Courtesy of Daniel P. Alford, MD

of other substances (see Section "Psychiatric Comorbidity"). All clients require a medical evaluation to screen for HIV/AIDS, hepatitis, and other blood-borne infections. Chronic users are likely to present with track marks and other signs of injection drug abuse, though some individuals addicted to pain relievers may have no history of intravenous drug use and may present no abnormal findings on physical examination.

Confusion exists between the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision category of opioid dependence and the common condition of physiological dependence. Physical dependence occurs whenever there is ongoing use of opiates for medical treatment. Physically dependent individuals may manifest both tolerance and withdrawal symptoms, but they show no symptoms of craving or loss of control, and the majority are able to taper off opiates with little or no difficulty. A few individuals, particularly those treated with high-potency opioids, may experience prolonged and severe withdrawal symptoms and will require a much more gradual medication taper. For some clients (between 3 and 30%), long-term treatment with opiates may trigger an iatrogenic addiction. They may experience euphoria when initially treated, and then go on to develop craving and loss of control of their medication use, eventually meeting full *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision criteria for dependence [4]. When evaluating these clients, it may be useful to look for the presence of the "4 C's" commonly associated with addiction: *C*raving, *C*ompulsive use, loss of *C*ontrol, and *C*ontinued use despite apparent harm [3]. Clinical experience suggests that individuals at highest risk for abusing pain medications are those with a prior history of alcoholism or other substance abuse, and with co-occurring psychiatric disorders, including antisocial personality disorder.

Psychiatric Comorbidity

Dependence on alcohol and other classes of drugs is common in the majority of opiate addicts and has a significant impact on the outcome of treatment. There is also a high rate of comorbidity between all of the drug use disorders and other psychiatric disorders. With few exceptions, the National Epidemiologic Survey on Alcohol and Related Conditions data showed positive and significant correlations between drug use disorders, alcohol use disorders, nicotine dependence, and antisocial personality disorder [28]. As Kessler noted in his reviews of the literature on the epidemiology of comorbidity of mental and substance use disorders, the available data have consistently shown that comorbid disorders are more chronic and have a significantly more persistent and severe course [65, 66, 68]. Unfortunately, methodologic limitations in the original National Comorbidity Survey, the Environmental Catchment Area Survey, and the National Comorbidity Survey Replication make it difficult to get specific comorbidity estimates regarding opiate use, abuse, and dependence [53, 57]. While the National Comorbidity Survey found an odds ratio of 2.4 for comorbidity between any lifetime alcohol or drug use disorder and any lifetime *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised mental disorder [67], there were no drug-specific data available in that study. Responses on opiates, cocaine, cannabis, and hallucinogens were combined under a single category of drug use disorders [5]. Both the National Comorbidity Survey and the Environmental Catchment Area Survey relied on data collected prior to the recent epidemic of the abuse of pain relievers; nor did these surveys distinguish between heroin abuse and the abuse of prescribed medications.

Data specific to comorbidity in opiate addiction are relatively limited. Clinical studies have reported that a range of 55–74% of opiate addicts in treatment have an affective disorder [102]. Brooner et al. [17] evaluated 716 opiate abusers seeking methadone maintenance treatment and reported that 47% of the sample met criteria for other psychiatric disorders. The most common diagnoses were antisocial personality disorder (25.1%) and major depression (15.8%). Rosen and colleagues recently evaluated a group of 140 methadone maintenance participants over the age of 50. In this sample, 57.1% had at least one other psychiatric disorder in the previous

year. The most prevalent disorders in this cohort were major depression (32.9%), post-traumatic stress disorder (27.8%), and generalized anxiety disorder (29.7%); women had higher levels of depression than men (43.8% vs. 27.2%) and had twice the prevalence rate of panic disorder and agoraphobia [139]. As indicated above, depression and anxiety disorders are common in this population and are associated with increased severity of substance use disorders and poorer treatment outcome [17, 125]. Other substance use disorders are also common in individuals dependent on opiates. Brooner et al. [16] evaluated 68 methadone maintenance participants enrolled in an HIV education program. Among this group, lifetime rates for abuse or dependence were as follows: cocaine 55.9%, sedative/hypnotics 53%, marijuana 47.1%, and alcohol 47.1%. Forty-eight percent of the sample met criteria for a non-substance use psychiatric disorder, the most common being antisocial personality disorder (29%) and major depression (19%). Individuals with other psychiatric disorders also had a greater number of substance use disorders and a more severe clinical course.

The association between heroin abuse and antisocial personality disorder reflects an overlap of genetic and psychological factors. Individuals willing to initiate heroin use are often impulsive, and typically see themselves as non-conformists, or risk-takers, and in defiance of social convention. Their use of heroin is not surprising given the illegality of heroin and the commonly acknowledged social deviation associated with intravenous drug use. The National Epidemiologic Survey on Alcohol and Related Conditions study showed strong associations between drug use disorders, other substance use disorders, and antisocial personality disorder [28]. The authors suggested that this association is related to the unique genetic factors that underlie these groups of disorders.

As compared with earlier national epidemiologic surveys, the National Epidemiologic Survey on Alcohol and Related Conditions study provided more specific information on opiate dependence and other co-occurring psychiatric and substance use disorders. Individuals identified in the National Epidemiologic Survey on Alcohol and Related Conditions who were dependent on one type of prescription medication were highly likely to have clinically significant drug use disorders for both illicit drugs and other classes of nonmedical prescription drugs. There was a high comorbidity for mood, anxiety, personality, and other substance use disorders, including nicotine and alcohol. The specific odds ratios for comorbidity between opioid use disorders and other conditions were: other nonmedical prescription drug use disorder (80.1), other illicit drug use disorder (28.1); alcohol use disorder (11.4), nicotine dependence (6.7), any mood disorder (4.6), bipolar I disorder (4.9), any anxiety disorder (3.0), panic with agoraphobia (4.3), any personality disorder (4.9), and antisocial personality disorder (8.1), respectively. These conditions were all diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria, required the criteria of "clinical significance", and ruled out conditions considered to be substance-induced [57].

Co-occurring Psychiatric Disorders and the New Opioid-Dependent Population

Recent studies suggest that some features of psychiatric comorbidity and opiate addiction have changed during the last decade. The availability of cheap, high-quality heroin has meant that most initiates begin by snorting the drug; some become addicted yet never progress to intravenous use. Members of this group minimize the risk of non-intravenous drug use. They see snorting heroin as relatively socially acceptable and do not see themselves as socially deviant (and indeed are probably less antisocial than earlier generations of heroin users). Similarly, abusers of pain relievers are even less likely to see their behavior as dangerous or antisocial (they naively assume that "legal" drugs are both safe and less likely to lead to addiction). Data from the 2006 National Survey on Drug Use and Health showed that more than 56% of the abusers of pain relievers obtain the drug free from friends or

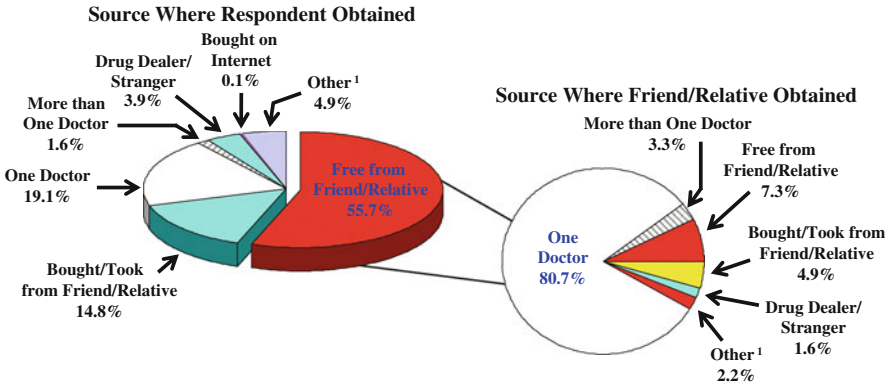

Fig. 7 Source where pain relievers were obtained for most recent nonmedical use among past-year users aged 12 or older, 2006 (National Survey on Drug Use and Health) [33]. Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown. [1]The "Other" category includes the sources: "Wrote Fake Prescription", "Stole from Doctor's Office/Clinic/Hospital/Pharmacy", and "Some Other Way"

relatives; a few purchase or take drugs from friends, and less than 3.9% purchase from "drug dealers" [33] (see Fig. 7).

This type of distribution system reinforces the perception that the illicit use of these drugs is normative. It is only after these individuals become physically dependent and have escalating habits that they are forced to seek out illicit suppliers. At some point they may recognize that heroin is cheaper than opioid pharmaceuticals and they may then switch to snorting and/or intravenous heroin use. As the severity of their opioid dependence progresses, they are also likely to manifest symptoms of a substance-induced personality disorder, with both dependent and antisocial features. Such substance-induced antisocial traits typically resolve when these individuals become engaged in addiction treatment, but they may reappear during periods of relapse.

Iatrogenic Addiction

There is a growing and less well-defined group of individuals who are iatrogenic opioid addicts. Since the mid 1990s, careless and over-enthusiastic prescribing of highly potent opioid analgesics has placed many individuals at increased risk for addiction. Of particular concern are veterans returning from combat in Iraq and Afghanistan who may be suffering from both combat stress and physical injuries requiring treatment with potent opioids. Comparison of prescription opioid abusers and heroin abusers shows higher levels of chronic pain, depression, and benzodiazepine use among the abusers of prescription opioids [13, 96]. They are also less likely to use illicit non-opioid drugs or to inject drugs [137]. As compared with heroin addicts, this group is more likely to have had psychiatric treatment, yet have fewer family problems, be more socially stable, and have fewer illegal sources of income [13, 29]. They also tend to resist referrals for methadone maintenance and are likely better candidates for naltrexone treatment or office-based buprenorphine treatment [40].

The abuse of other substances is also less common in this population as compared with heroin addicts [137]. Alcohol abuse or dependence has been a long-standing problem among individuals on methadone maintenance. Marijuana use is also very common, though clinicians have disagreed over the clinical significance of this behavior. During the 1980s, cocaine abuse became rampant among opiate abusers. While this problem has declined among the general population, it remains epidemic among

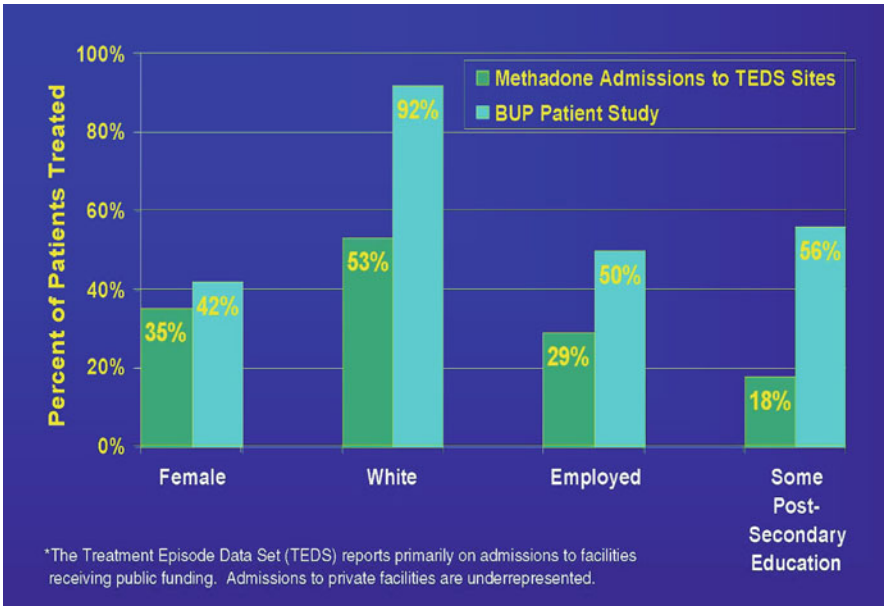

Fig. 8 Methadone recipients* and buprenorphine (BUP) recipients study sample: demographic differences [144]

heroin addicts. The concurrent abuse of all of these substances continues to be a problem among those on methadone maintenance; however, clinicians report less frequent problems of this type in clients treated with buprenophine in the office-based setting. Dobler-Mikola et al. reported on the first 6 months of methadone maintenance treatment for 103 participants and noted that 51% continued to use cocaine and 61% continued to use heroin [36]. In contrast, Mintzer et al. reported that 54% of Suboxone® recipients at 6 months were clean from all drugs [93]. In a separate study, Fiellin et al. reported that the self-reported frequency of opiate use dropped from 5.3 days/week to 0.4 days/week during a 6-month buprenorphine maintenance trial; 50–57% of the participants had at least one cocaine-positive urine test during the 6-month trial [41].

The demographics of this new opioid-dependent population are more apparent in individuals being treated with buprenorphine. The Substance Abuse and Mental Health Services Administration was required by the legislation (Drug Addiction Treatment Act of 2000) that authorized the office-based use of buprenorphine to complete a national survey reviewing demographic data on buprenorphine recipients who were being treated in that setting. As compared with individuals on methadone, this study indicated that buprenorphine recipients were younger, included higher percentages of Whites and women, and were far more likely to be employed and have higher levels of education (see Fig. 8) [144].

Clinicians have generally reported that these clients are less deteriorated, appear much less socially deviant, and are more typical of the general population. On average, addicted individuals enter buprenorphine maintenance treatment 5 years earlier than methadone maintenance clients enter treatment. They are significantly less likely to have used needles and consequently have a much lower incidence of hepatitis C and HIV disease.

Clinical Management

Opiate Overdose

Opiate overdose is a life-threatening emergency. Patients typically present with depressed

consciousness, depressed respirations, and miotic pupils. With meperidine (Demerol®) overdoses, the pupils may not be miotic. Similarly, with severe hypoxia, or in overdoses with multiple classes of drugs, the pupils may be dilated. It is also common to see hypotension and diminished heart rate and occasionally pulmonary edema. The patient should be checked for venous sclerosis (track marks), but these may be missing in younger addicts who may be taking prescription medications orally or may be inhaling or smoking heroin. A drug overdose should be suspected in any comatose individual, and serum toxicology and blood glucose should be obtained immediately.

The primary goal of treatment is to sustain or restore vital functions and to immediately reverse the overdose with an opioid antagonist.

1. Immediately assess the adequacy of airway, breathing, and circulation (A, B, & C). Initiate intubation and resuscitation, and support vital functions as needed.
2. Establish an intravenous line and administer 50% dextrose/water solution.
3. In cases of suspected recent oral drug ingestion, gastric lavage should be initiated. Care must be taken to avoid aspiration; patients should be intubated if there is evidence of respiratory depression.
4. Naloxone (Narcan®) 0.2–0.4 mg intravenously will begin to reverse the effects of an opiate overdose within 1 min. If there is no response to the initial dose, repeat doses may be administered every 2–3 min. If there is no response after a total dose of 10 mg naloxone, it can be assumed that the coma is not solely caused by an opiate. The patient should then be evaluated for other causes of coma, including the ingestion of other drugs, trauma, and diabetic coma.
5. All overdose patients should be hospitalized and monitored for a minimum of 24 h, particularly if an ingestion of multiple drugs is suspected.
6. Patients who have overdosed on long-acting opioids such as methadone or propoxyphene need to be monitored for 24–48 h. Since the antagonist effects of naloxone will last for only 30–90 min, such patients should be monitored in an intensive care unit and placed on an intravenous naloxone drip.
7. Patients who present with symptoms of interstitial pneumonia, pulmonary congestion, or edema should be treated with oxygen, and with intubation and assisted ventilation if required. In these circumstances, cardiac function is normal and there is no change in heart size. Treatment with diuretics and digitalis will be ineffective and should be avoided.
8. Any overdose patient should have a psychiatric evaluation and should be referred for substance abuse treatment. Physicians need to stress the importance of further treatment and strongly encourage attempts to curb or eliminate further drug use. Whenever possible, opiate overdose kits containing intranasal naloxone and instructions for managing overdoses should be provided to all drug-abusing individuals and their friends and families.

Opiate Withdrawal Syndromes

The withdrawal syndrome for short-acting opiates (heroin or morphine) begins 6–12 h after last use. Early symptoms include opiate craving, anorexia, anxiety, and irritability. These are coupled with clinical signs of increased respirations and blood pressure, sweating and yawning, lacrimation, rhinorrhea, piloerection (gooseflesh), tremor, and dilated pupils. After 48–72 h, the symptoms progress to include nausea, vomiting, diarrhea, insomnia, tachycardia, abdominal cramps, and involuntary muscle spasms and limb movements. Observable signs subside over 5–7 days, but a prolonged state of craving, depression, irritability, and dysphoria may persist for months.

The signs and symptoms associated with withdrawal from long-acting opioids such as methadone or propoxyphene are similar to those described above, but they may not begin until 24–48 h after the last dose and may last for

3 weeks or more. Individuals detoxifying from methadone also complain of deep bone pain that may last for weeks. As with individuals withdrawing from short-acting opiates, there is a similar protracted withdrawal state. Buprenorphine has a withdrawal syndrome similar to other long-acting opioids, but it is usually less intense and of shorter duration (see Fig. 5) [72].

Opiate Detoxification

Similar to the treatment of other withdrawal syndromes, the primary objective is to substitute the short-acting drug of abuse with a longer-acting drug in the same class and gradually taper at a rate that prevents severe withdrawal and avoids intoxication or excessive sedation. The preferred medications for opiate detoxification are oral methadone and sublingual buprenorphine [71, 117]. Clinical experience suggests that methadone is preferred for less motivated individuals with larger opiate habits, or for individuals with histories of polydrug abuse or significant psychiatric comorbidity. Buprenorphine is preferred for highly motivated individuals with smaller habits. In circumstances where opioids are not available, the alpha-adrenergic agonist clonidine may be substituted. Clonidine moderates autonomic withdrawal symptoms but does not control insomnia, restlessness, craving, or dysphoria. In combination with methadone, it may permit more rapid detoxification with lower doses of opioids. However, clonidine alone is not an adequate treatment for the withdrawal syndrome. Addicts rarely prefer clonidine, and relapse rates are higher than those seen with other medications [45, 82].

Before starting withdrawal medication, the client should have a thorough physical with urine toxicology and a complete drug and medical history. Except in those who are currently on medication-assisted treatment with either methadone or buprenorphine, it is almost impossible to estimate accurately the person's level of dependence. Clients' reports are often misleading, and it is highly dangerous to estimate the quality and quantity of street drugs. Even when clients are transferred from maintenance programs, the clinician must always contact program staff to verify the dose before starting treatment. The only safe way to avoid an inadvertent overdose is to document the presence of mild opiate withdrawal before initiating treatment. This is best done using a standard opiate withdrawal scale such as the Clinical Opiate Withdrawal Scale or the Objective Opiate Withdrawal Scale [52, 152]. Once clients score in the mild to moderate withdrawal range on the Clinical Opiate Withdrawal Scale, they can be given an initial dose of 20 mg methadone orally or 4 mg buprenorphine sublingually.

For younger individuals with minimal habits, it is prudent to start with 10 mg methadone or 2 mg buprenophine. Clients should be periodically monitored with a withdrawal scale and can be redosed in 2–4 h if withdrawal symptoms do not subside. If 10–20 mg methadone was effective as an initial dose, it may be repeated in 12 h if necessary. In no circumstance should the total 24-h dose exceed 40 mg methadone or 12 mg buprenorphine. If symptoms progress on the second treatment day, the total daily dose may be increased to 60 mg methadone or 16 mg buprenorphine, but doses in this range are rarely necessary in inpatient settings. Once symptoms are adequately controlled, the dose should be tapered at a rate that prevents further withdrawal and minimizes distress. Methadone can be decreased 5 mg/day or a maximum of a 20% dose reduction per day. Inpatient methadone detoxification can usually be completed in 5–7 days [117]. Buprenorphine can be decreased at the rate of a 50% dose reduction per day, though a more gradual reduction spread over 13 days has a better outcome and was significantly more effective than clonidine [82]. A recent review compared buprenorphine detoxification treatment with clonidine and methadone [45]. Compared with clonidine, buprenorphine-treated clients stayed in treatment longer (particular in outpatient detoxification), had fewer withdrawal symptoms, and were more likely to complete treatment. There was no significant difference in outcome comparing methadone to

buprenorphine in severity of withdrawal or completion of treatment, but withdrawal symptoms resolved more quickly in buprenorphine-treated individuals.

While detoxification can be accomplished on either an inpatient or an outpatient basis, the best results are seen with very prolonged outpatient tapers, or with a 1- to 2-week inpatient detoxification followed by long-term residential care. Brief (3- to 4-day) inpatient detoxification treatment has a very high relapse rate, averaging 90–95% within 1 year. Better outcomes are seen with multiyear maintenance treatment followed by gradual outpatient detoxification. Yet, in the best of circumstances, there is an 80% relapse rate within 1 year [7]. Since the fatality rate for active opiate dependence ranges from 8 to 20% per year, addicts need to understand the risks when detoxification is not followed by long-term residential treatment.

Other protocols for detoxification have involved a rapid inpatient clonidine taper combined with a transition to narcotic antagonist treatment utilizing naltrexone or naloxone. Naltrexone is used to precipitate withdrawal, and then increasing doses of clonidine are used to suppress withdrawal symptoms as naltrexone is quickly increased to antagonist maintenance levels [107, 127]. While this approach provides a quick and cost-effective model for detoxification, there is no evidence that it produces higher levels of long-term abstinence as compared with other detoxification approaches [46]. "Ultra-rapid" detoxification protocols have been proposed utilizing escalating doses of naltrexone given under general anesthesia or heavy sedation [14]. O'Connor and Kosten reviewed the existing literature on rapid and ultra-rapid detoxification and concluded that the studies were inadequate because of the small numbers of subjects included, variations in protocols utilized, lack of randomized design and/or control groups, and lack of long-term follow-up [106]. Well-designed, long-term studies are necessary to demonstrate that these procedures have greater efficacy over standard detoxification protocols beyond the short-term detoxification period [138]. In addition, deaths have been reported during the 16–40 h following ultra-rapid detoxification [63]; for this reason alone, ultra-rapid detoxification procedures cannot be recommended.

Other medications have been proposed for opiate detoxification, but none have been studied adequately. Proposed agents include *N*-methyl-*D*-aspartate receptor antagonists, such as dextromethorphan and memantine, and the serotonin type 1A receptor agonist buspirone. Buydens-Branchey et al. compared placebo with a methadone taper vs. two dose levels of buspirone. There was no significant difference noted between the subjects treated with a methadone taper and those treated with either buspirone dose [19].

Opiate Pharmacotherapy

Naltrexone

Naltrexone is an orally effective mu-opioid antagonist that was approved for the treatment of opiate dependence in 1984. It has a high receptor affinity that prevents the binding of most other opioids [105] (see Fig. 4); its long half-life permits thrice-weekly dosing. Unfortunately, client compliance has been very poor, and side effects of anxiety and dysphoria may be problematic. It is rarely effective with most addicts but has worked well in highly motivated individuals under external monitoring [131]. The recent development of a 30-day depot formulation holds promise for improved efficacy and has renewed interest in the use of this medication [27].

Methadone

Methadone was developed as an analgesic during World War II. It is a full agonist at the mu and delta receptors (see Fig. 4) and acts as an *N*-methyl-*D*-aspartate antagonist [50]. In 1965, Dole and Nyswander reported its successful use as a maintenance medication for

chronic opiate addiction. It is a highly lipophilic, long-acting, and orally effective medication that controls craving and opiate withdrawal with a single daily dose. In company with counseling and other supportive services, up to 70% of addicts are able to eliminate their opiate use [7, 37]. Clients demonstrate no euphoria, mental dulling, or motor impairment. Long-term methadone dosing normalizes brain endocrine physiology and re-establishes normal activity along the hypothalamic-pituitary-adrenal axis [75]. Federal regulations limit maintenance treatment to highly regulated methadone clinics, and individuals must document a 1-year history of addiction and a current state of physiologic dependence to qualify for maintenance treatment. Successful treatment requires adequate dosing (60–120 mg daily), strong ancillary services delivered by professionally trained therapists, and long-term, if not indefinite, treatment [7, 20, 88, 142]. Methadone has typical opiate side effects and does not appear to have significant hepatotoxicity.

Methadone should not be started in maintenance clients until opiate withdrawal has been documented, and the starting dose should not exceed 30 mg orally, with a maximum of 40 mg as the total first-day dose. In individuals with significant persistent withdrawal symptoms, the dose may be increased to 50 mg on the second day, but from that point forward, dose increases should be held to a maximum of 10 mg/week. Recent reports of prolonged QTc waves and torsade de pointes have raised concerns about the safety of methadone, particularly in doses over 100 mg. Deaths have been reported among individuals being treated for pain when doses were increased rapidly. Because of its long half-life, methadone may quickly accumulate to toxic levels if individuals are not given adequate time to develop tolerance to previous doses. Electrocardiograms should be obtained before starting treatment and should be repeated regularly in those receiving doses over 100 mg. Methadone is metabolized by the CYP4503A4 system. Drugs that induce that system, such as phenytoin, rifampin, or efavirenz, may reduce methadone levels and precipitate withdrawal. Similarly, drugs that inhibit the CYP4503A4 system, such as cimetidine or the macrolide antibiotics, will increase methadone levels.

Levo-Alpha Acetyl Methadol

Levo-alpha acetyl methadol is an orally effective, long-acting derivative of methadone that has been approved for maintenance treatment. Because of its long half-life, it can be dosed thrice-weekly [100]. Despite clinical efficacy [59], levo-alpha acetyl methadol was never widely accepted by methadone clinics or opiate addicts. It has particular utility in individuals who are rapid metabolizers of methadone and have traditionally been difficult to stabilize on methadone. After the Food and Drug Administration required a black-box warning because of the risk of death associated with prolonged QTc intervals and torsade de pointes, the manufacturer voluntarily withdrew levo-alpha acetyl methadol from the market.

Buprenorphine

Buprenorphine, a partial agonist at the mu-opiate receptor, was approved by the Food and Drug Administration in 2002 for the treatment of opiate dependence. Its effectiveness has been demonstrated in a number of double-blind, placebo-controlled trials [59, 61, 81, 141]. Buprenorphine is available in a sublingual formulation, either alone (Subutex®) or in a combination tablet with naloxone (Suboxone®). As a partial opiate agonist, it binds tightly to opiate receptors but does not fully activate the receptor. Because of this "ceiling effect", there is no significant respiratory depression regardless of the dose of buprenophine ingested (see Fig. 4). For this reason, it has been recognized as an unusually safe opioid. This property, coupled with a slow onset of action and the combination formulation with naloxone (to reduce the illicit intravenous use of the medication), was thought to limit the abuse potential of the medication. Both the Food and Drug Administration and the

Drug Enforcement Administration approved its use in office-based settings, without the regulatory limitations placed on methadone maintenance treatment. The introduction of office-based buprenorphine treatment has been a major public health success [144]. As anticipated, the availability of maintenance treatment in private office settings has attracted a large population of addicted but higher-functioning individuals. There are currently over 300,000 individuals on buprenorphine maintenance in the United States, compared with 275,000 individuals on methadone maintenance. Individuals are attracted to the greater flexibility of office-based treatment and to the lesser intensity and shorter duration of withdrawal symptoms with buprenorphine as compared with methadone. It should be noted, however, that there is no evidence that buprenorphine detoxification is associated with any less of a long-term relapse rate than is seen with methadone. It is critical that all maintenance clients be engaged in individual or group counseling and/or 12-step programs. Pharmacotherapy without ancillary services is rarely effective [49, 88, 97].

Federal regulations limit practitioners of office-based buprenorphine treatment to 30 active clients and require a waiver for a second Drug Enforcement Administration number based on American Board of Psychiatry and Neurology certification in addiction psychiatry, certification in addiction medicine by the American Society of Addiction Medicine or the American Osteopathic Association, or completion of an 8-hour training course. To qualify for treatment, clients must be at least 16 years old and must meet *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for opiate dependence. In comparison with methadone, this permits the treatment of younger people with short addiction histories. These individuals are more likely to primarily abuse pain relievers, not heroin, and many have never used intravenous drugs. As a group, they are less likely to be HIV positive, to have hepatitis C, or to have criminal records, and are more likely to be employed and to have had some college education. Clinicians have reported that most of their buprenorphine recipients are highly motivated and respond very positively to treatment [97, 144].

Treatment initiation with buprenorphine requires careful attention to its antagonist-like properties. Because of its high affinity for the opiate receptor, buprenorphine will displace most other agonists. However, as a partial agonist, it does not fully activate the receptor. The net result is that the addict experiences this action as an antagonist effect. Severe but relatively brief withdrawal may be precipitated whenever buprenorphine is taken in the presence of a full agonist. To initiate buprenorphine treatment successfully, the clinician must, therefore, determine that the client is currently opiate free. This is best done by counseling the client to abstain from opiates for at least 24 h and by documenting the presence of opiate withdrawal using withdrawal scales such as the Clinical Opiate Withdrawal Scale. Once the individual demonstrates mild to moderate withdrawal on the Clinical Opiate Withdrawal Scale, he or she may safely take the first buprenorphine dose. It is recommended that an initial dose of 4 mg sublingually be given under observation in the clinician's office and that the client be observed for an additional 2 h to ensure that there is no precipitated withdrawal. Supplemental doses can be given if withdrawal symptoms persist, with a maximum recommended first-day dose of 8 mg. The dose can be raised in 2- to 4-mg increments over the next 2–3 days to a dose that eliminates any further withdrawal symptoms and craving. The usual maintenance dose ranges between 12 and 16 mg sublingually daily. Urines should be monitored regularly. Higher doses should be considered if craving and opiate use do not cease within 1–3 weeks. Because of the ceiling effect, there is no pharmacological justification for daily doses over 32 mg.

Novel Anticraving Medications

While agonist replacement and antagonist treatments have demonstrated efficacy in reducing craving for opiates, other pharmacologic agents

have also been investigated. Only a small number of studies have been conducted with these medications, and further studies are needed to determine their efficacy. A 12-week randomized, placebo-controlled trial showed that baclofen recipients remained in treatment longer, but baclofen did not reduce the rate of positive urines [6]. In a small trial, pentazocine-dependent individuals were given either naltrexone alone or gabapentin and naltrexone. Participants given gabapentin and naltrexone reported less craving during and shortly after detoxification than those given naltrexone alone [79]. In another small, 12-week trial, methadone maintenance participants who were given magnesium had fewer positive urines for opiates than those given placebo [86]. Although topiramate has been investigated for its use in detoxification [157, 158], there are no trials to date that have tested its efficacy in reducing craving for opiates.

Psychosocial Treatment

A variety of psychosocial treatments have been used to treat substance use disorders. While pharmacotherapy is an important component of treatment, non-pharmacologic strategies remain crucial for the overall success of treatment. Although most of these treatments are not specific to opiate dependence, this section will review the psychosocial treatments in common use.

Outpatient Drug-Free Programs (Post-Detoxification Treatment)

A variety of individual and group psychotherapies may be very helpful in modifying clients' behaviors and lifestyles. Commonly used individual psychotherapies include cognitive behavioral therapy, contingency management, motivational enhancement therapy, and 12-step facilitation. In addition, various group therapies are also frequently utilized, including family therapy and intensive outpatient group treatment.

Relatively few randomized trials have been conducted to examine the effects of psychosocial treatments for opiate dependence in the outpatient drug-free post-detoxification setting. Nevertheless, a recent meta-analysis of controlled trials for psychosocial treatments concluded that contingency management and cognitive behavioral therapy for opiate dependence produced effect sizes that are low-moderate to high-moderate, comparable to the effect size of pharmacologic treatment for anxiety disorders [38].

Cognitive behavioral treatments are among the most frequently employed interventions that are empirically tested across a broad range of substances, including opiates [22]. Cognitive behavioral therapy attempts to help clients learn the various feelings, thoughts, behaviors, and situations that raise the likelihood of drug use, and to help them cope more effectively with negative emotional states. Individuals are also taught to avoid triggers and situations that promote drug use. Typically, cognitive behavioral therapy approaches place an emphasis on functional analysis of drug use as well as skills training [22]. There have been several studies that have reported positive results utilizing cognitive behavioral therapy, but not in a drug-free context [9, 80, 122]. A recent study also showed positive results with exposure therapy in a drug-free setting, a behavioral technique aimed at reducing cue reactivity by exposing abstinent individuals to drug-related cues while preventing their conditioned responses [87]. Community reinforcement approaches, also based on operant conditioning theory, have been shown to be helpful for clients on methadone maintenance treatment, who have been shown to reduce their use of illicit opiates if given alternate reinforcers—i.e., take-home methadone [1, 140].

Contingency management is a generic behavioral intervention based on the principle of operant conditioning, using primarily positive reinforcements to promote abstinence [55]. A common strategy involves the use of a voucher that can be used to purchase retail items in the community if therapeutic goals are met—i.e., negative urines [129]. There are two randomized

trials to date that have shown positive results when contingency management is used in conjunction with naltrexone [23, 24]. One study examined voucher reinforcement for heroin and cocaine users in an outpatient drug-free program but did not show any significant difference with the no-voucher group [62]. This finding is consistent with other studies that have found an increased likelihood of negative results when treating individuals with polysubstance dependence [38]. A meta-analysis examining all the studies that utilized voucher-based reinforcement therapy or related monetary-based incentives to treat substance use disorders concluded that overall voucher-based treatments were superior to control treatments [83].

Motivational enhancement interventions include the various strategies that attempt to increase clients' motivation to change their drug use, reduce ambivalence, and increase commitment to abstinence [35]. This approach uses the "stages of change" model to help identify where clients are in the recovery process and to help them progress more rapidly. Motivational interviewing is the most frequently utilized interviewing style that attempts to increase motivation for change [92]. No studies have been conducted for opiate-dependent individuals in a drug-free setting. One study has been conducted with participants in a methadone program, but it did not contain all the components necessary to qualify as motivational enhancement therapy and did not show any reduction in opiate use as compared with controls [133].

Twelve-step facilitation is a manualized, evidence-based treatment with a large research base that can be integrated with other therapies that the client is receiving [126]. It is a technique used to help clients engage in and maximize their response to 12-step meetings. Twelve-step facilitation was initially created for Project MATCH and was shown to be as effective in reducing alcohol use as was motivational enhancement therapy and cognitive behavioral therapy [101]. However, there are no studies that have examined the efficacy of 12-step facilitation specifically for opiate-dependent individuals in a drug-free setting.

Group therapy is the most widely used psychosocial treatment for substance use disorders [15]. Since users may be less likely to trust clinicians and others in a position of authority, group treatments utilizing family members, peers, and other users can dilute the negative countertransferences that users experience. Groups can be offered in a wide variety of settings (inpatient, outpatient, and residential), target specific populations (such as gay men and lesbians, women with post-traumatic stress disorder, combat veterans, or individuals with bipolar disorder), and can have a variety of theoretical approaches (12-step, cognitive behavioral therapy, and interpersonal). Groups can provide relief from the tremendous shame and isolation that clients experience, as well as provide a safe environment for obtaining support, confirmation, and advice [15]. Furthermore, groups can correct disturbed interpersonal interactions by establishing a healthy and mutually supportive attachment to others [43]. Several studies have examined group therapy for opiate users in the setting of agonist maintenance treatment (see the section below titled "Outpatient treatment in the setting of methadone and buprenorphine maintenance").

Family therapy includes treatments that involve family members of the substance user. It is designed to help the family manage and cope with the distress caused by the negative consequences of drug use [109]. A particularly well studied family therapy is behavioral couples therapy, which is designed for married or cohabiting couples [108]. This treatment works to promote a cohesive relationship and better communication with family members, which in turn can lower the risk of relapse.

McLellan et al. have defined "intensive outpatient programs" as programs that offer at least 9 h/week of structured programming and "partial hospital programs" as programs that offer at least 20 h of services per week [88]. In one study, compared with individuals in "traditional" outpatient treatment, which offers no more than 4 h of programming per week, clients in intensive programs received more addiction-focused treatment but fewer medical and employment-focused services. At the 6-month follow-up,

both groups had notable improvements in substance use, health, and social functioning [88]. In another study, graduates from an intensive program were more likely to be abstinent from drugs at the 6-month follow-up and less likely to be incarcerated than those who did not complete the program [150].

Drug Courts

Drug courts are being increasingly utilized to offer treatment in place of incarceration [128]. Standard features of drug courts include regular and close monitoring of progress by the judicial officer, urine drug testing, coordinated aftercare plans, and dismissal or reduction of charges upon successful completion of treatment [128]. While not specific to opiate users, an extensive meta-analysis revealed that drug court participants had lower re-arrest and conviction rates than those who did not participate [146].

Outpatient Treatment in the Setting of Methadone and Buprenorphine Maintenance

Individuals maintained on methadone or buprenorphine clearly benefit from additional psychosocial interventions. In a study by Woody and colleagues, methadone maintenance clients who received professional treatment (cognitive or supportive-expressive therapy) showed greater improvements than those individuals who received only drug counseling [154]. The greater benefit was found to be sustained at the 12-month follow-up, and similar results were replicated in a community sample [155]. A recent meta-analysis of psychosocial treatments combined with agonist maintenance treatment concluded that the addition of psychosocial support to standard methadone maintenance treatment significantly reduces the use of heroin during treatment [2].

There has been one study published to date that specifically tested the benefit of cognitive behavioral therapy combined with buprenorphine maintenance treatment [97]. Although the participants were dually dependent on cocaine and opiates, those who attended more therapy sessions had significantly more negative urines for opiates and cocaine. Although the study duration was only 70 days, the results appeared to support previous data that showed beneficial effects of buprenorphine and cognitive behavioral therapy for maintenance clients [61]. Kakko et al. [61] compared buprenorphine maintenance with placebo; all subjects received weekly group cognitive behavioral therapy and weekly individual counseling. One-year retention in treatment was 75% in the buprenorphine group and 0% in the placebo group. While not the primary hypothesis of the study, these results suggest that 6 days of medication treatment followed by placebo coupled with cognitive behavioral therapy and individual counseling was a very ineffective treatment for chronic opioid dependence [61]. In another study, standard methadone maintenance treatment was compared with methadone maintenance plus weekly group therapy. At 6 months, the group therapy clients had significantly less drug use than the control group [134].

Therapeutic Communities

Therapeutic communities for substance use disorders are based both in the community and in prisons, and include a variety of short- and long-term residential and ambulatory programs that provide medical, mental health, vocational, educational, family counseling, legal, and administrative services [32]. The general goal of therapeutic communities is to promote abstinence, change antisocial behaviors, and develop prosocial attitudes and skills by living together with others in a structured environment [156]. Features that differentiate therapeutic communities from other residential treatments are their coordination of a comprehensive range of treatment services in one setting, use of the community itself as the therapist and teacher, and a view that holds that the individual, not the drug, is the

essence of the disorder [32]. Another element of therapeutic communities is the "encounter", a variety of peer-led supportive/confrontational sessions, aimed at giving members feedback from others on whether they are meeting community expectations of recovery [32].

A recent meta-analysis examining the efficacy of therapeutic communities showed that there is little evidence that therapeutic communities offer significant benefits compared with other residential treatments, or that one type of therapeutic community is better than another [139]. However, the authors also acknowledged that the analysis may be biased and that firm conclusions cannot be drawn.

Therapeutic communities have been frequently utilized in correctional facilities [153]. One meta-analysis demonstrated that substance-dependent prisoners treated in therapeutic community programs have lower recidivism rates compared with those without treatment [114]. Another study examined prison-based psychosocial treatments and reached a similar conclusion [94]. Optimal results were seen when inmates participated in prison-based therapeutic communities that were followed by community-based aftercare [56, 84].

Conclusions Regarding Psychosocial Treatment

Although relatively few studies have been conducted exclusively with opioid-dependent individuals, the psychosocial therapies described above have been shown to be effective in this population and are critical in the overall treatment of addiction. A wide variety of these treatments can be offered to suit the needs of individual clients. While no one psychosocial intervention has been shown to be superior to another, the evidence taken as a whole clearly favors incorporating psychosocial therapies, with or without pharmacologic treatments. In addition, the efficacy of pharmacologic therapies is clearly improved when combined with psychosocial treatments.

Managing Co-occurring Psychiatric Disorders

The Incidence of Co-occurring Psychiatric Disorders

The incidence of co-occurring psychiatric disorders in individuals with opiate dependence ranges from 13 to 85% (see Table 2). The lifetime prevalence for any drug use disorder is 37.5% in individuals with bipolar I disorder [47]. There is also a high lifetime prevalence of post-traumatic stress disorder in those with substance use disorder although clients may initially deny a post-traumatic stress disorder history. Individuals with post-traumatic stress disorder may only be willing to discuss this problem after they have developed a more trusting relationship with their clinician. Villagomez et al. reported a lifetime post-traumatic stress disorder prevalence of 20% in women and 11% in men [147]. The prevalence is even higher in adolescents with substance use disorders, with a 24.3% incidence in boys and a 45.3% incidence in girls [34]. Similarly high rates of co-occuring disorders are reported in older methadone clients [130]. These findings indicate that all opioid-dependent individuals should be screened for other psychiatric disorders on admission. Severe problems such as suicidal or homicidal ideation, or psychosis, require immediate assessment and consideration for hospitalization. Less severe symptoms of anxiety and depression are very common in individuals entering treatment; many of these symptoms are substance-induced and will clear once the client's substance use is under control. Appropriate diagnosis is difficult when clients are either intoxicated or in withdrawal. The first goal of treatment is, therefore, to stabilize the addiction.

Table 2 Lifetime prevalance in opioid-dependent individuals [132]

	Men (%)	Women (%)
Affective disorders	70.7	85.4
Anxiety disorders	13.2	25.4
Phobic disorder	8.2	13.9

Substance-Induced Disorders vs. Independent Disorders

Once the individual has achieved abstinence or has been stabilized on methadone or buprenorphine, a more comprehensive psychiatric evaluation should be done to determine whether there are any persistent psychiatric symptoms. The first step in this evaluation is to separate substance-induced psychiatric disorders from independent psychiatric disorders. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision criteria for a substance-induced disorder require that symptoms occur during, or within 30 days of, intoxication or withdrawal, and that the symptoms can be presumed to be related to substance use. If symptoms persist 30 days beyond substance use, they are presumed to reflect an independent psychiatric disorder [4]. Independent psychiatric disorders are more likely if there is a family history of psychiatric disorders. These symptoms do not diminish with sobriety, and they typically continue with little change during prolonged periods of abstinence. The age of onset for most psychiatric disorders is in the early teens and typically precedes the development of any substance use disorder by 5–10 years. A careful longitudinal history will clarify the sequence of symptoms and will help to separate an independent psychiatric disorder from any substance-induced psychopathology. It is difficult to make this assessment in the presence of active substance use. Unless there is a clear history that confirms the presence of other psychiatric disorders, treatment should focus primarily on the addiction.

Managing Co-occurring Psychiatric Disorders

In the case of co-occurring psychiatric disorders, a more comprehensive treatment plan is required to address both conditions. Treatment is most effective if the psychiatric treatment is integrated into the substance abuse treatment program. All involved clinicians should work in close collaboration to ensure coordinated care. Treatment elements need to be integrated throughout the entire course of treatment, from assessment, to initial detoxification or stabilization, and through aftercare [18]. Substance abuse clients will respond to most standard evidence-based forms of psychiatric treatment, including psychotherapy and pharmacotherapy [145]. However, standard treatments for psychiatric disorders cannot be expected to treat the substance use problem. Sobriety from all substances of abuse must remain a primary treatment goal and will require active participation in addiction treatment. Structured psychotherapy approaches are most effective, particularly cognitive behavioral therapy. The "seeking safety" treatment model developed by Najavits for treating co-occurring post-traumatic stress disorder and substance use disorders is particularly useful for managing addicted individuals with a range of psychopathology [98].

There are few published data on the treatment of co-occurring depressive disorders in opioid-dependent individuals; most of the available data come from studies on methadone maintenance clients. In a placebo-controlled trial, Nunes et al. demonstrated efficacy for imipramine in the treatment of depressed methadone maintenance clients [103]. Results with selective serotonin reuptake inhibitors in this population have generally been negative [116], though two studies reported improvement in depression in methadone recipients using sertraline [21, 51]. Kosten et al. failed to demonstrate efficacy for desipramine in the treatment of depressed buprenorphine-maintained subjects, and warned against using this combination of medications [74].

While it is common practice to prescribe selective serotonin reuptake inhibitors and other antidepressants to treat anxiety disorders in individuals with substance use disorders [111], including those maintained on methadone and buprenorphine, there are few data to demonstrate efficacy in this specific population. McRae et al. have demonstrated efficacy for buspirone in

the treatment of anxiety disorders in methadone recipients [89]. Short-acting benzodiazepines are typically avoided in this population because of concerns about abuse and toxicity [11]. However, Bleich et al. demonstrated efficacy for the long-acting benzodiazepine, clonazepam, in the treatment of anxiety disorders in methadone recipients with a prior history of benzodiazepine abuse [10]. There has been particular concern about prescribing benzodiazepine for individuals maintained on buprenorphine, related to reports of overdose deaths in France secondary to the intravenous injection of combinations of buprenorphine and high-potency benzodiazepines [12, 69, 104]. Despite these concerns about the risks of benzodiazepine use in opioid addicts, a comprehensive review of the literature has shown efficacy for the treatment of generalized anxiety disorder, panic disorder, and agoraphobia and probable efficacy for social phobia, with little evidence of added risk for medication abuse or increased relapse [120]; also see [111].

There are relatively few data on the treatment of schizophrenia and co-occurring opioid dependence. The incidence of schizophrenia is thought to be relatively low in this population, though the Environmental Catchment Area Survey reported a 47% lifetime prevalence for any substance use disorder in this population [123]. Alcohol use disorders are the most common substance use disorders seen. Methadone clinics report a very low incidence of psychosis. In general, individuals with schizophrenia and co-occurring opioid dependence are poorly compliant with medication, do not respond well to typical antipsychotics, and show high rates of relapse and hospitalization. However, this population has responded positively to treatment with the atypical antipsychotics, particularly clozapine. It has been speculated that clozapine (a weak D_2 blocker, but a potent noradrenergic A_2 blocker) may normalize mesolimbic dopamine circuits and thus reduce craving for opiates and other drugs of abuse [48].

When considering pharmacotherapy for any psychiatric disorders, caution is required to avoid the use of abusable medications, especially short-acting benzodiazepines. Treatment should always begin with non-abusable medications with proven efficacy for the specific condition. Clients need to be monitored closely to ensure sobriety and compliance with treatment. Depressed clients can be treated with most of the standard antidepressants. When treating anxiety disorders, attention should be given to psychological therapies and coordinated pharmacotherapy. Benzodiazepines should be used with caution and should not be prescribed unless the individual has failed to respond to adequate trials of antidepressants or buspirone. If required, long-acting benzodiazepines are preferred to the more abusable shorter-acting drugs such as alprazolam. Atypical antipsychotic medications may be particularly effective in this population, though quetiapine should be used with caution because of its abuse potential. Any client who fails to respond to treatment should be monitored closely to ensure medication compliance and to rule out any relapse to substance use.

Primary Prevention

In the last two decades, prevention activities in the United States have focused on interdiction and on public education with a primary abstinence message, “Just say no.” The gradual decline in the use/abuse of marijuana, cocaine, and heroin [33, 58] suggests that this approach may have had a positive impact on the use of some illicit substances. However, the recent epidemic of the abuse of prescription pain relievers and a corresponding increase in opioid-related overdose deaths indicate the need to reassess prevention techniques. Young adults, in particular, seem to have interpreted the messages against illicit drugs to imply that licit drugs are safe and non-addictive. The medical community has also underestimated the addictive risks involved in the use of opioids to treat acute and chronic pain. There is clearly a need for a national education campaign to inform the public and physicians about the risks associated with prescription pain relievers and the availability of effective treatment [28]. Physicians have not

been well trained in the management of pain or in the safe prescription of potent opioids with long half-lives. In 2008, the Center for Substance Abuse Treatment of the Substance Abuse and Mental Health Services Administration launched a major campaign to improve physician education in these areas. Other efforts are under way to improve medical school curricula and residency training to achieve a better understanding of the addictive disorders and to improve substance use disorder screening and the management of individuals at risk for substance use disorders [85, 99, 124]. Food and Drug Administration approval of a variety of alcohol anticraving medications and the availability of buprenorphine for the office-based treatment of opioid dependence have opened a new era for the medical treatment of substance use disorders. Corresponding changes in physician education are necessary if these new treatment options are to achieve their full potential. Physicians and the public need education to destigmatize substance use disorders, and to improve general awareness of the effectiveness of addiction pharmacotherapy and manually guided therapies such as cognitive behavioral therapy, motivational enhancement therapy, and 12-step facilitation.

Epidemiologic evidence has consistently shown that primary psychiatric disorders strongly predict the later development of substance use disorders, with a range of 5–10 years between the onsets of the two conditions. This presents a clear opportunity for primary prevention. Kessler has estimated that the effective early treatment of psychiatric disorders would prevent as much as 50% of all substance dependence disorders [66]. Needle exchange programs provide another opportunity for prevention of disease and outreach to opiate abusers. A large percentage of new cases of hepatitis C are a direct result of injection drug users sharing hypodermic needles. In order to prevent the spread of hepatitis C and HIV, needle exchange programs were developed to provide sterile needles and associated injection supplies at no cost. Sometimes the dirty needles must be exchanged for clean needles. These programs also typically offer a variety of other services, such as “bleach kits”, HIV testing, condoms, and referrals to treatment.

Conclusion

As with other chronic relapsing medical disorders, physicians and other clinicians have important roles to play in long-term treatment approaches that integrate appropriate pharmacotherapy with psychotherapy and self-help interventions. Routine screening, particularly for adolescents and young adults, client education about the risks and benefits of potent pain relievers, conservative management of less severe pain syndromes, and early and aggressive treatment of depression and anxiety disorders all will play a role in reducing the incidence of opiate use disorders. Once patterns of opiate misuse or abuse are identified, referrals for treatment, including appropriate pharmacotherapy, and long-term management approaches hold the most promise for successful control and amelioration of the problems associated with opiate dependence.

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Clinical Aspects of Methamphetamine

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Contents

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Introduction

Methamphetamine, which was developed in 1893, is a synthetic stimulant that affects regions of the central nervous system and other major organ systems. Until 1951, no prescription was necessary to obtain methamphetamine or other amphetamine-containing products. Prescriptions for variants of these drugs were freely dispensed in the 1960s, and methamphetamine abuse and dependence increased during this period. "Crank" or "crystal", different versions of methamphetamine, became popular in the 1960s, and "ice", a smokable derivative of methamphetamine, emerged in the late 1980s in Hawaii. The evolution of methamphetamine use between 1988 and 2008 has varied. The early to mid 1990s witnessed escalating problems with methamphetamine throughout many parts of the United States; however, the highest rates of use were in the Western region of the country, particularly in suburban and rural communities. The primary reason for the growth of methamphetamine use was the wide availability of pseudoephedrine, the primary precursor of methamphetamine, which is contained in many over-the-counter cold medications including Sudafed®, Nyquil®, and Claritin-D®. Methamphetamine was manufactured and distributed by small mom-and-pop type "kitchen

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_22,

chemists," as well as larger syndicates and drug cartels. Extended use of methamphetamine has severe physical and mental effects on the user. Those exposed to methamphetamine production sites, including children, can suffer serious health consequences from explosions, fires, and toxic gases and wastes. Consequently, methamphetamine abuse and dependence has had a substantial impact on the treatment, health care, criminal justice, and social welfare systems. From 2003 to 2006, the federal government and many states imposed strict pre-cursor control laws that restrict the retail sales of medications that contain pseudoephedrine. These efforts have substantially reduced the availability of methamphetamine and increased its price in many areas of the United States.

From the early 1990s through 2005, numerous indicators indicated steady increases in the use of methamphetamine. However, in 2007, 529,000 persons aged 12 or older were current users of methamphetamine, a reduction from 731,000 in 2006 [96]. Similarly, the Community Epidemiology Work Group of the National Institute on Drug Abuse recently reported that methamphetamine indicators from law enforcement (arrests and seizures) and emergency room data from 20 of 22 metropolitan areas, showed either a stable or downward trend of methamphetamine use during 2006 and 2007 [53]. Similarly, treatment admissions for methamphetamine, which increased dramatically from the 1990s to 2005, showed a decline in 2006.

While methamphetamine use peaked and has seemed to stabilize in many parts of the United States, global trends remain highly problematic. Epidemiological data from several countries, including regions of Southeast and East Asia (i.e., Thailand, Cambodia, Indonesia, Malaysia, and the Philippines), Canada, Australia, South Africa (i.e., Cape Town), and parts of Europe (e.g., Czech and Slovak republics) indicate that methamphetamine production, trafficking, and use are steadily increasing [18, 30, 54].

Neurobiological Impact of Methamphetamine

Although individuals initiate use of methamphetamine for a variety of psychological and socio-cultural reasons, once methamphetamine has been ingested, profound changes occur in the structure and chemistry of the brain. Methamphetamine blocks the reuptake of released dopamine in the synaptic clefts, resulting in increased levels of dopamine in the synapse of neurons in the nucleus accumbens and other areas of the mesolimbic region of the brain [104]. The chronic and long-term use of methamphetamine results in lower levels of dopamine receptors that are associated with increased dependency, i.e., loss of control and compulsive drug use [83]. Methamphetamine use also results in a significant loss of dopamine transporters (used as markers of the dopamine terminal), which is associated with slower motor function and decreased memory, attention, and cognitive functioning, such as inhibitory control [55, 63, 88]. Furthermore, methamphetamine increases cytoplasmic concentration of dopamine, which promotes oxidation products that are toxic to the nerve terminals [31, 72, 83]. The neurotoxicity of methamphetamine is further accentuated by its prolonged half-life and, therefore, long duration of action.

Recent investigations into the neurobiological phenomena associated with methamphetamine dependence have employed magnetic resonance imaging and functional magnetic resonance imaging, as well as positron emission tomography and single photon emission computerized tomography. Brain imaging studies have provided delineated depictions of brain activity during methamphetamine intoxication and in early phases of abstinence following methamphetamine withdrawal, yielding potential therapeutic targets for prospective medications and even for behavioral therapies. In brief, the research has documented abnormalities in cortical and limbic systems, deficits in dopaminergic and serotonergic neurotransmitter systems,

deficits in gray matter, and variations in glucose metabolism compared with nonusers of methamphetamine [1]. Changes in glucose metabolism have been shown to be associated with severity of psychiatric symptoms [14]. Imaging studies of methamphetamine-abusing individuals have also revealed greater activity in the amygdala and less activity in the infralimbic cortex among methamphetamine abusers than in non-using individuals, as well as changes in glial cell proliferation or metabolism and in neural integrity [1].

Other findings include reduced concentrations of the neuronal marker N-acetylasparate and total creatine in the basal ganglia, and the striatum has been shown to be considerably affected by methamphetamine use, with lower levels of dopamine transporters and lessened dopamine receptor availability [85], indicating compromises that manifest in cortical regions that control executive function [1]. In chronic methamphetamine abusers, there are structural changes including greater cortical volume and changes in the hippocampus that relate to cognitive deficit [98]. Increased striatal volume and decreased striatal metabolism have been found and postulated to be a function of increased water content or as result of inflammation [13].

A number of investigations have explored longer-term abstinence and neurobiological changes after cessation of methamphetamine abuse, showing some recovery but not full reversion to a normal state over a period of several months of abstinence. After protracted abstinence, methamphetamine abusers showed increased metabolism in the thalamus, similar to controls, whereas recently abstinent methamphetamine abusers had lower metabolism in both the striatum and thalamus [104]. Furthermore, after methamphetamine cessation and recovery over time, there appears to be some improvement in dopamine transport function [103]. Sekine and colleagues [86], for example, found that serotonin transporter density generally decreased as the years of methamphetamine use increased and serotonin transporter density was correlated inversely with aggression scale scores.

Implications of neurobiological findings for treatment approaches, both pharmacotherapies and behavioral therapies, include the need to improve cognition in order to facilitate learning among methamphetamine-experienced subjects, whose weakened ability to concentrate may be attributable, at least in part, to errors and differential activity in the anterior and middle cingulate gyrus and insula [49]. Recent research has confirmed that methamphetamine-abusing individuals can be compromised in terms of responses to external stimuli, lessening their ability to meaningfully participate in or benefit from behavioral therapies. New knowledge from such studies will lead to potential therapeutic targets for interventions designed to facilitate cessation of methamphetamine use and reduce relapse.

Acute and Chronic Health Effects of Methamphetamine Abuse and Dependence

Euphoria, increased blood pressure, elevated body temperature, and rapid heart and breathing rates are commonly experienced acute effects of methamphetamine use. Other immediate clinical symptoms include reduced fatigue, reduced hunger, increased energy, increased sexual drive, and increased self-confidence. Depending on the nature and extent of abuse, negative acute physiological effects can include intense stomach cramps, shaking, bruxism, disrupted menstrual cycles, “formication,” or the sensation of insects creeping on the skin, and insomnia [73]. Heavy and long-term chronic methamphetamine use can result in many life-threatening medical illnesses and disabilities [65].

Cardiopulmonary consequences are common among methamphetamine abusers. Chest pain, hypertension, shortness of breath, and tachycardia are common in emergency room cases involving methamphetamine toxicity

[80]. Also seen in emergency rooms among methamphetamine abusers is acute coronary syndrome. Turnipseed and colleagues [101] documented acute coronary syndrome in 25% of methamphetamine abusers admitted for chest pain, possibly resulting from myocardial ischemia and its attendant risk of arrhythmias and cardiogenic shock [105]. Cardiovascular symptoms, including irregular heartbeats have developed in more than half of the methamphetamine abusers studied by Beebe and Walley [3]. Cardiomyopathy related to methamphetamine use may be reversible; however, this is dependent on cessation of drug use [41]. Pulmonary edema was found in over 70% of methamphetamine-related deaths [44]. Damage to small blood vessels in the brain can result in stroke, paralysis, and brain damage [68, 104].

"Meth mouth" and other oral complications are common among chronic methamphetamine abusers, even though the contribution of level of methamphetamine abuse to their etiology is questionable. Oral health problems most often seen among methamphetamine abusers include rampant caries, tooth fracture, and periodontal disease (e.g., gingivitis, periodontitis) [89, 90]. In addition to caries and gingivitis, methamphetamine abusers often present with tooth wear and temporomandibular joint syndrome related to bruxism, which may be a reaction to anxiety and restlessness, especially during early abstinence [17].

Skin excoriations or cutaneous ulcers are common among methamphetamine abusers, notably occurring in response to reported sensations of bugs crawling below the skin and subsequent scratching [5]. Self-inflicted wounds have been documented among methamphetamine abusers, postulated to occur in presence of dopaminergic agonism that manifests in a similar manner to motor stereotypies and hyperkinetic movements [42]. In addition to consequences such as those above and cellulitis and abscesses resulting from injection of methamphetamine, users and associates are prone to severe burns and chemical injuries that occur during manufacture of the drug [81].

Many users suffer from neurocognitive impairments [50, 93] and psychiatric comorbidity, particularly severe psychosis, depression, and suicidal ideation [56, 109]. A recent examination of methamphetamine-related emergency department admissions indicates that among the 15,038 emergency room-related visits from February 2006 to June 2006, 353 were methamphetamine related, with the top four medical reasons reported related to mental health (18.7%), trauma (18.4%), skin infections (11.1%), and dental diagnoses (9.6%) [34].

Methamphetamine Use, Sexual Behavior, and Communicable Diseases

Methamphetamine use is highly prevalent among men who have sex with men [91]. Several surveys show consistently high rates of methamphetamine use among men who have sex with men [45]. In the Young Men's Survey of men who have sex with men (ages 15–22) in seven U.S. cities, 32% (Los Angeles), 28.5% (San Francisco), and 28.2% (Seattle) of young men who have sex with men reported methamphetamine use in the previous 6 months [97]. A number of studies among methamphetamine-dependent populations of men who have sex with men indicate strong associations between methamphetamine use and the sexual transmission of infectious diseases, including HIV/AIDS and other sexually transmitted infections (such as syphilis) compared with men who have sex with men who do not use methamphetamine [46].

Studies of methamphetamine users in general also show strong associations between methamphetamine use and HIV risk [62, 79, 87]. A recent study by Rawson and colleagues [76] found that male and female methamphetamine users tend to engage in frequent sexual activity, to have multiple, anonymous sexual partners, and to report low rates of condom use

and high rates of unprotected anal and vaginal sex. Men tend to report that their sexual thoughts, feelings, and behaviors became associated with methamphetamine use and that methamphetamine use made them obsessed with having sex and led to their engagement in riskier sexual acts (i.e., anal sex) [79]. Although both men and women methamphetamine users report increased sexual desire while under the influence of methamphetamine, men tend to experience greater sexual enhancements and desires that have been linked to more unusual and riskier sexual acts [9].

Studies of methamphetamine users in general also show strong associations between methamphetamine use and communicable disease risk, including HIV, hepatitis A, B, C, and other sexually transmitted infections, due to risky sexual and drug use practices [67]. Risky drug use practices among methamphetamine users, including injection and drug-sharing behaviors (e.g., sharing water for needle or pipe preparations and/or to rinse syringes/pipes and cotton) have also significantly increased the risk of infectious diseases [26, 27, 32, 40, 47, 62, 75, 76, 79, 87, 102].

Affected Populations

Youth

While national trends concerning methamphetamine use by youth under the age of 24 have been equivocal, in some geographic regions there is an indication of significant problems associated with methamphetamine use by this population. State and local data from treatment programs reveal that methamphetamine use among youth is a major problem [10]. The Phoenix House, a large treatment center in Southern California, revealed that admissions for methamphetamine accounted for approximately half of the center's youth admissions in 2005–2006, doubling since 2002. When examining methamphetamine youth admissions by age, data indicate that youth represent the highest proportion; however, methamphetamine use among younger youth (12–17 years old) is also problematic [75]. Treatment admission data from Los Angeles County indicate increased admission rates for female methamphetamine-abusing youth, particularly Latinas [25, 75]. The literature on clinical risk factors associated with methamphetamine use among youth suggests that methamphetamine-abusing youth tend to have past histories of physical and sexual abuse/trauma, family history of substance abuse, and current psychological problems, including affective emotional and conduct disorders [61, 66, 75, 108]. Risky sexual behaviors, including violence and aggression, as well as multiple sex partners and unprotected sexual intercourse, have also been implicated among methamphetamine-abusing youth [2, 107].

Women

Research indicates that women are using methamphetamine at rates relatively equal to men [37]. Almost half (46%) of national admissions to publicly funded treatment are adult female methamphetamine users, compared with 31% of admissions for other drugs (i.e., heroin, alcohol, marijuana) [96]. Studies show that women tend to progress faster to drug dependence, suffer more adverse consequences [29], and present for treatment with greater psychological distress [4], compared with their male counterparts. A large body of literature comparing drug-dependent women with drug-dependent men indicates that women are more likely than men to report extensive histories of trauma, neglect, and abuse [57]. In fact, between 70% and 85% of women who develop methamphetamine dependence have reported a history of sexual and physical abuse [8, 60, 73]. Such histories have been linked to an increased likelihood of domestic violence in adult relationships, chronic addiction, criminal activity, homelessness, and psychiatric co-occurring illness [58].

In a recent study, Messina et al. [59] reported that methamphetamine-dependent women offenders tend to have had significantly greater exposure to childhood abuse and household dysfunction than have methamphetamine-dependent men and more often reported sexual abuse in adolescence and as an adult.

Methamphetamine-Using Pregnant Women and Their Children

Methamphetamine use among pregnant women, in particular, is a major public health problem in the United States. Compared with non-methamphetamine-using pregnant women, pregnant methamphetamine-using women had a 3.5 times greater likelihood of having a lower birth weight child and pre-term births [94]. Winslow and colleagues [106] indicated that the use of methamphetamine by pregnant women has been linked to placental abruption, intrauterine growth retardation, and preterm birth. To date, there is limited research on the impact of prenatal methamphetamine exposure on the developing fetus. Smith and colleagues [95] recently examined the neurobehavioral effects of prenatal methamphetamine exposure (as measured by meconium assay and self-report) in a longitudinal follow-up study and found that exposure to methamphetamine was associated with increased physiological central nervous system stress. First-trimester methamphetamine use was related to elevated stress abstinence, and third trimester methamphetamine use was associated with poor quality of movement. When parents use or produce methamphetamine, the potential consequences for their children include asthma or other respiratory ailments. Children in the vicinity of small-scale methamphetamine manufacture in residential settings can suffer burns. The explosive, corrosive, and toxic chemicals involved in methamphetamine production and their by-products can affect children and others even after clandestine labs have been dismantled.

Criminal Offenders

The number of incarcerations and other problems within the criminal justice system among methamphetamine-dependent individuals have increased, which supports the strong association between methamphetamine dependence and participation in illegal behaviors [22]. Since 2002, the criminal justice system has been the top referral source for methamphetamine treatment [12]. The latest national statistics indicate that a large proportion of admissions for primary methamphetamine/amphetamine abuse across the country was from the criminal justice system (49%), compared with 34% for other categories of drugs [96]. In California, more than half of drug-abusing offenders diverted from the judicial system to treatment in lieu of incarceration were primary methamphetamine users [21].

Methamphetamine-dependent offenders seeking treatment may require different treatment options and plans tailored to their special characteristics [12]. It has been suggested that drug courts may be an effective tool for promoting successful treatment outcomes for methamphetamine-dependent offenders [39]. Drug courts are governed by a number of key components, including the integration of treatment with criminal case processing; early identification and prompt placement of eligible drug offenders into the program; provision of a continuum-of-services treatment plan; alcohol and drug testing; and ongoing judicial interaction [100]. A recent study examined the treatment response of methamphetamine-dependent individuals within a drug court setting and found that drug court participation was associated with better rates of engagement, retention, completion, and abstinence compared with methamphetamine users who did not participate in a drug court treatment setting [52]. Follow-up analyses revealed that participants who were enrolled in the drug court intervention used methamphetamine significantly less frequently compared with methamphetamine users without drug court supervision.

Clinical Management of Methamphetamine Users

Managing Methamphetamine Intoxication

Acute agitation from methamphetamine intoxication is most often the condition that leads users to seek medical attention, and "talking down" the patient in a calm environment is a first course of action. Addressing possible methamphetamine toxicity may involve emetics or lavage to remove methamphetamine pills, but toxicity from intravenous or smoked routes of administration may necessitate the use of charcoal and medications such as ammonium chloride or quelidrine to hasten clearance of methamphetamine from the gastrointestinal tract and the circulatory system. No medications are available to reverse methamphetamine overdose. Either a benzodiazepine or an antipsychotic may be used in extremely agitated individuals who pose a threat to others. A standard approach is provision of haloperidol in 5 mg by mouth or parenteral repeated doses, frequently in combination with 1–2 mg of lorazepam and 1 mg of the anticholinergic cogentin. Also useful are intramuscular injections of 2 mg lorazepam, 5 mg haloperidol, or both, administered in several doses over a 12-h period and with patient evaluation for 12 h.

Managing Acute Methamphetamine Psychosis

Symptoms of methamphetamine-induced psychosis can be difficult to differentiate from those of other disorders that may pre-date drug abuse, and so a definitive diagnosis is required before commencing treatment. Methamphetamine abusers frequently report auditory hallucinations, which is more typical of schizophrenia, in addition to visual (flashing lights, peripheral artifacts), olfactory, and tactile sensations. Symptoms of methamphetamine psychosis include: persecutory delusions, ideas of reference, hallucinations (visual and auditory, olfactory, tactile), relative clear sensorium, stereotypy and compulsive acts, anhedonia and depression, blunt affect, poverty of speech, and being prone to excited delirium and violence.

Methamphetamine-induced acute psychosis, which generally is transient, can require use of either a benzodiazepine or an antipsychotic, both of which should be halted when acute symptoms have resolved. Low-dose antipsychotics between psychotic episodes may be useful, but there is no empirical guidance on the efficacy or appropriateness of such treatment. Such agents are contraindicated for adolescents and young adults, in whom methamphetamine-induced psychosis has increased more than five-fold from 1993 to 2002 [15]. Treatment of this population should follow the treatment described above for intoxication.

Managing Chronic Methamphetamine Psychosis

Symptoms of persistent or chronic methamphetamine psychosis are often so similar to those of schizophrenia that some clinicians may regard them as clinically equivalent conditions, although a good case is made for methamphetamine *producing* a persistent psychosis that resembles schizophrenia [70]. Regardless of the causal direction or association, the symptoms of schizophrenia and of persistent methamphetamine psychosis are not readily distinguishable, and the treatment for this condition remains basically the same as in recent practice (see Table 1).

Managing Methamphetamine Withdrawal

Methamphetamine withdrawal symptoms consist of severe fatigue, cognitive impairment,

Table 1 Managing chronic methamphetamine psychosis

Preventing relapse of psychosis symptoms:
- Clients with chronic methamphetamine psychosis that were given small doses of Haldol® did not have further recurrences of psychosis symptoms, whereas those not medicated did [84].

Benzodiazepines versus antipsychotics for methamphetamine psychosis:
- Relapse of psychosis symptoms has been inhibited by use of antipsychotic medication, but relapse has not been prevented by use of benzodiazepines.
- Beneficial effects of early antipsychotic treatment must be weighed in the context of possible adverse effects from such medications.

Long-term use of antipsychotics for persistent psychosis:
- Possibly deleterious long-term effects of antipsychotics indicate a need for caution in adults; likely negative effects on brain development in youths argue against use of antipsychotics.
- Adverse effects in adults may outweigh possible benefits.

feelings of depression and anxiety, anergia, confusion, and paranoia. For the majority of individuals experiencing acute withdrawal/early-phase abstinence, most symptoms resolve within 2–10 days. Rest, exercise, and a healthy diet may be the best management approach for most people in withdrawal. Those with heightened agitation and sleep disturbance may respond to benzodiazepines, but acute depression and anhedonia associated with early abstinence generally resolve without intervention. Clinicians should be aware of possible dehydration and hyperthermia. Drug craving may be addressed via behavioral treatments or periods of residential care.

In the process of dealing with near-term abstinence, clients who exhibit severe paranoia, episodes of psychosis, powerful craving for methamphetamine, and protracted dysphoria and anhedonia will present challenges for the clinician. Furthermore, certain groups of individuals present for treatment with special concerns, as detailed below:

- *Female methamphetamine users*—higher rates of depression, often with histories of sexual and physical abuse; responsibilities for children.
- *Injection methamphetamine users*—very high rates of psychiatric symptoms; severe withdrawal syndromes; high rates of hepatitis.
- *Homeless, chronically mentally ill individuals*—high levels of psychiatric symptoms at admission and during treatment.
- *Individuals under the age of 21*—antipsychotic medications and other mediations should be avoided or used with caution.
- *Men who have sex with men*—at very high risk for HIV, hepatitis, and other sexually transmitted diseases.

Methamphetamine Use and Co-occurring Disorders

Many methamphetamine-dependent individuals present for treatment with symptoms of psychiatric problems [109], although distinguishing the degree to which these symptoms can be attributed to methamphetamine use versus underlying mood disorders is often difficult. In a recent examination of predictive factors associated with diagnosing methamphetamine-dependent individuals with major depression, Glasner-Edwards and colleagues [23] identified having a lifetime history of suicide attempts and current depressive symptoms (as measured by the presence of a Beck Depression Inventory score of 20 or above) as two robust predictors.

Clinically, suicidal behavior has been a major concern regarding methamphetamine-dependent individuals [109]. Some research has implicated methamphetamine-related intoxication, withdrawal, and psychiatric symptoms in elevating users' risk of depression and suicide [48]. A recent study documents injection drug use, current depressive symptomatology, and a clinical history of psychiatric problems as significant risk factors for suicidal behaviors in methamphetamine-dependent users [24].

Treatment Outcomes with Methamphetamine Users

A body of literature has been developed on treatment outcome evaluations for methamphetamine abuse. Engagement in treatment, retention in treatment for at least 90 days, abstinence during treatment, and treatment completion have been consistently shown to successfully predict positive treatment outcomes with methamphetamine-dependent populations [33, 35]. Risk factors for poor treatment outcomes have been identified as daily methamphetamine use, injection methamphetamine use, having less than a high school education, young age at treatment admission, having a disability [6], polydrug use [7], childhood trauma and abuse [60], and having an underlying psychotic disorder [24] or major depression [23]. Treatment participation and active recovery efforts, including frequent 12-step program participation, have been associated with successful treatment outcomes [36]. Research has also shown that women and men respond to treatment similarly in terms of retention and completion, although women tend to have slightly better treatment outcomes, including more improved relationships with family and fewer medical problems as compared with men [8, 37].

Few studies to date have examined the longitudinal impact of treatment, including patterns of use and psychosocial outcomes. In a recent longitudinal examination of outcomes over a 10-year period, Hser and colleagues [36] found that quitting was predicted by current treatment and self-help participation among stimulant users (including methamphetamine and cocaine users), and that cessation of drug use was less likely among methamphetamine users with an early drug-use onset, relative to cocaine or heroin users.

Treatment Approaches for Methamphetamine Abuse and Dependence

The majority of studies investigating the effectiveness of treatment for stimulant addiction have focused on cocaine abuse and dependence, with fewer studies on methamphetamine. Despite differences between the two stimulants in individual health, psychological, and cognitive effects, both groups tend to show comparable responses to psychosocial behavioral treatments [16, 38, 51].

Evidence-based behavioral treatment for methamphetamine-dependent individuals *does* work as documented by the authors and colleagues [77, 92]. Treatment has profound effects, including reductions in methamphetamine use during treatment, increased treatment retention, decreased use of other drugs, decreased criminal involvement, and reduced high-risk sexual practices among gay and heterosexual users [71, 74].

Behavioral Therapies for Methamphetamine Abuse and Dependence

Cognitive Behavioral Therapy

Cognitive behavioral therapy is a short-term, focused approach to help substance users become abstinent and avoid relapse. The underlying assumption is that learning processes play

an important role in the development and continuation of substance abuse. Key elements of cognitive behavioral therapy are:

- Functional analyses of substance abuse
- Individualized training in recognizing emotional states
- Exercises, such as thought stopping and managing thoughts about drug use
- Coping skills, problem-solving, planning for emergencies, and refusal skills
- Examination of the client′s cognitive processes related to substance use
- Identification and debriefing of past and future high-risk situations
- Encouragement and review of extra-session implementation of skills
- Practice of skills within sessions.

Cognitive behavioral therapy promotes abstinence via skill training, including learning and practicing strategies for: (1) reducing availability and exposure to drugs and related cues, (2) fostering resolution to stop drug use by exploring positive and negative consequences of continued use, (3) self-monitoring to identify high-risk situations and to conduct functional analyses of substance use, (4) recognition of conditioned craving and development of strategies to cope with craving, (5) identification of seemingly irrelevant decisions that can culminate in high-risk situations, (6) preparing for emergencies and coping with relapse to substance use, (7) drug refusal skills, and (8) identifying and confronting thoughts about drugs. Several versions or packages of cognitive behavioral therapy-based interventions are available in manual form, including the National Institute on Drug Abuse cognitive behavioral therapy, a 12-session approach [11]. The Matrix Model is a blended treatment approach that incorporates principles of cognitive behavioral therapy in individual and group settings, family education, motivational interviewing, and behavioral therapy; while not a "pure" cognitive behavioral therapy intervention, the Matrix Model employs cognitive behavioral therapy principles. This manualized therapy has been proven effective in reducing methamphetamine use during the 16-week application of the intervention, in comparison with a "treatment as usual" condition in a large Center for Substance Abuse Treatment-funded multisite trial [77, 78]. The Matrix Model also has been evaluated as a stand-alone treatment for subgroups of methamphetamine abusers (e.g., gay and bisexual men and heterosexuals) and as the behavioral treatment platform in pharmacotherapy trials for methamphetamine dependence [20].

Contingency Management

Also known as motivational incentives, contingency management is an intervention for drug abuse that employs immediate reinforcement for demonstration of desired behaviors (e.g., a drug-free urine test). Roll and colleagues [82] recently conducted a multisite clinical trial in which a contingency management protocol was evaluated as an addition to an outpatient methamphetamine treatment program. Participants in the contingency management condition demonstrated a superior clinical performance on multiple outcome measures (number of methamphetamine-negative urine samples, number of consecutive weeks of abstinence, percent that completed the trial with continual abstinence). At present, contingency management appears to produce the most robust reductions in methamphetamine use of any single technique.

Medications for Treatment of Methamphetamine Abuse and Dependence

Recent discoveries about the effects of methamphetamine abuse on the brain and the mechanisms of methamphetamine dependence have offered many opportunities for the discovery and development of novel medications to treat methamphetamine dependence [64].

Although multiple medications have been investigated for treating methamphetamine dependence, only a handful have shown promise, including bupropion [19, 69]; however, the research literature still lacks substantiation of the efficacy or clinical utility of any medication as a treatment for methamphetamine dependence. Under consideration or in current trials are several compounds, including disulfiram, modafinil, vigabatrin, baclofen, lobeline, varenicline, mirtazapine, topirimate, and aripiprazole. Past work has failed to demonstrate the efficacy of compounds such as selegilene and assorted other medications such as sertraline, gabapentin, rivastigmine, risperidol, and ondansetron [48] as potential treatments for methamphetamine dependence. In a small European study, methylphenidate has shown preliminary efficacy in reducing relapse among newly abstinent individuals who had been amphetamine dependent [99]. Most recently, a Swedish study found naltrexone (the opiate antagonist used as an alcoholism treatment medication) given orally was effective in suppressing relapse to stimulant use among individuals meeting *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for amphetamine dependence [43].

Given that medications for treating stimulant dependence have yet to be proven broadly effective, future pharmacotherapy will probably be integrated with behavioral therapy. Medications in development generally are intended to address some form of deficit caused by methamphetamine use or withdrawal, either neurobiological or syndromal. Medications that may be useful in helping attain abstinence or sustain recovery from methamphetamine dependence are still in development. Briefly, bupropion (Wellbutrin®), modafinil (Provigil®), and, to a lesser extent, baclofen (Lioresal®) have exhibited some utility as adjuncts to behavioral therapy in treating methamphetamine dependence. Other medications (e.g., gabapentin, lobeline, vigabatrin, ondansetron, and varenicline as Chantix®) are under consideration. Also under consideration is agonist therapy (i.e., "replacement/substitution" medication) [28], which is similar to methadone for opioid dependence, although this approach is not designed to produce abstinence from stimulants.

Future Directions in Research and Practice

Research topics on methamphetamine that are garnering increased attention include: (1) cellular mechanisms of action of methamphetamine and their relationship to neurotoxicity; (2) the interplay between the limbic brain circuitry underlying reward and the frontal brain that exercises control over the limbic brain, and (3) the disinhibition of the limbic brain resulting from functional or structural disconnection from the executive brain. As knowledge emerges about these complex interactions, researchers and clinicians face new challenges as well as new opportunities for the development and implementation of pharmacological and behavioral treatment strategies to address methamphetamine dependence.

Regardless of the advances in scientific understanding of the neurobiological phenomena associated with methamphetamine abuse, utilization of such knowledge often occurs with much delay and sometimes never happens. The "real world" in which clinical researchers conduct investigations of new treatments and in which clinicians treat clients is not always receptive to findings from human laboratory studies or even Phase III trials, and implementation of research-proven practices never occur in an optimally timely manner without first overcoming various obstacles.

The first part of any solution to the problem of methamphetamine abuse involves greater awareness by all those involved in pertinent disciplines, from basic scientists to primary care physicians. Clearly, clients must also be educated about what happens to them when they use methamphetamine and when they cease using. To accomplish at least part of that

awareness raising, new curricula need to be developed and refined at all levels, in academic institutions at the undergraduate and postgraduate levels and in community practice settings, where clinicians may seek and find definitive training in the science and practice of addiction medicine.

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Sedative-Hypnotics and Anxiolytics

Bachaar Arnaout and Ismene L. Petrakis

Contents

Introduction

The sedative-hypnotics and anxiolytics are central nervous system depressants that also have muscle relaxant and anticonvulsant effects and are widely used in psychiatry, neurology, anesthesiology, and general medicine. The most common of these are the benzodiazepines and the new-generation non-benzodiazepine hypnotics (i.e., zaleplon, zolpidem, and eszopiclone), which due to their better safety profiles have largely replaced the barbiturates and other older agents, particularly in the treatment of insomnia and anxiety. This group of medications also includes chloral hydrate, meprobamate, carisoprodol, glutethimide, and methaqualone. Gamma-hydroxybutyrate, which has some properties associated with the sedative-hypnotics, is usually classified as a "club drug".

Beyond their use in the treatment of anxiety disorders and insomnia, the benzodiazepines also are often used for the management of agitation, the treatment of seizures, as muscle relaxants, for premedication in anesthesiology, and as the mainstay of treatment for the management of medication detoxification from alcohol. The new-generation non-benzodiazepine hypnotics are used primarily for the treatment of insomnia. The barbiturates nowadays are most commonly prescribed for the treatment of epilepsy and for anesthesia, and can also be used for detoxification from alcohol. The older sedative-hypnotic and anxiolytic agents such as chloral hydrate, meprobamate, carisoprodol, glutethimide, and methaqualone are less commonly used nowadays.

These groups of medications have a similar mechanism of action in that they all enhance the activity of the brain's main inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), leading to the opening of chloride channels and cell membrane hyperpolarization. In a simplified but clinically useful model, the central nervous system maintains a balance between inhibitory signals mediated by gamma-aminobutyric acid and excitatory signals mediated by the brain's primary excitatory neurotransmitter, glutamate

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_23,

[24]. When the balance sways toward glutamate-mediated excitatory transmission, the individual experiences arousal and anxiety; conversely, gamma-aminobutyric acid-mediated inhibitory transmission results in tranquility and sedation. The benzodiazepines bind to gamma-aminobutyric acid-A receptors, where they enhance gamma-aminobutyric acid activity [55]. The new-generation non-benzodiazepine hypnotics have a similar mode of action but appear to have relative selectivity to certain subunits of the gamma-aminobutyric acid-A receptor, resulting in a prominent sedative-hypnotic effect and a relatively weaker anxiolytic effect [18]. The barbiturates also potentiate gamma-aminobutyric acid activity at the gamma-aminobutyric acid-A receptor but may additionally exert a direct effect on opening the chloride channel [42]. Chloral hydrate, meprobamate, carisoprodol, glutethimide, and methaqualone also appear to exert their effects through GABAergic transmission. All of these medications can be used to reduce anxiety at lower doses and to induce sleep at higher doses. Commonly used sedative-hypnotic and anxiolytic drugs along with their approximate dose equivalencies are included in Table 1. Since all of these drugs have wide therapeutic applications and are among the most commonly used, the conceptualization of what constitutes inappropriate use of the sedative-hypnotics and anxiolytics is often difficult to determine. The use of these drugs in a fashion other than as prescribed (i.e., non-medical use) has been defined as "misuse", and the terms "abuse" and "dependence" are based on their *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision definitions [1].

Table 1 List of sedative-hypnotics and anxiolytics with approximate dose equivalencies

Generic name	Trade name	Dose equivalency (mg)
Benzodiazepines		
Alpazolam	Xanax	1
Chlordiazepoxide	Librium	25
Clonazepam	Klonopin	1
Clorazepate	Tranxene	15
Diazepam	Valium	10
Estazolam	ProSom	1
Flurazepam	Dalmane	20
Lorazepam	Ativan	2
Oxazepam	Serax	20
Quazepam	Doral	20
Temazepam	Restoril	20
Triazolam	Halcion	0.25
Non-benzodiazepine hypnotics		
Eszopiclone	Lunesta	3
Zaleplon	Sonata	10
Zolpidem	Ambien	10
Barbiturates		
Amobarbital	Amytal	100
Butabarbital	Butisol	100
Butalbital	Fiorinal	100
Pentobarbital	Nembutal	100
Phenobarbital	Luminal	30
Secobarbital	Seconal	100
Other agents		
Chloral hydrate	Noctec	500
Glutethimide	Doriden	250
Meprobamate	Miltown	800
methaqualone	Quaalude	300

Despite their most common appropriate therapeutic use, non-medical use of the sedative-hypnotics and anxiolytics can be problematic and often occurs in individuals with other substance use disorders as well as those with general psychiatric disorders. In the National Epidemiologic Survey on Alcohol and Related Conditions, conducted in 2001–2002 with a sample of 43,093 respondents representative of the United States, the lifetime prevalence of non-medical use of sedatives and tranquilizers was 4.1 and 3.4%, respectively, and the lifetime prevalence of sedative and tranquilizer abuse and/or dependence was 1.1 and 1.0%, respectively [39]. In the same survey, the 12-month prevalence rates were: 0.09% for sedative abuse, 0.07% for sedative dependence, 0.08% for tranquilizer abuse, and 0.05% for tranquilizer dependence [85]. The survey reported high rates of lifetime comorbidity between sedative and tranquilizer use disorders and alcohol use disorders (odds ratios of 13.4 and 14.2, respectively), mood disorders (odds ratios of 4.9 and 4.8, respectively), anxiety disorders (odds

ratios of 3.7 and 4.2, respectively), and personality disorders (odds ratios of 5.6 and 6.6, respectively) [39]. Comorbidity is likely to be even higher in clinical populations. For example, in a sample of 427 treatment-seeking individuals with alcohol use disorders, the lifetime prevalence of anxiolytic abuse or dependence was 20% [71]. Conversely, in a sample of 30 consecutive patients undergoing inpatient detoxification from benzodiazepines because of severe benzodiazepine dependence, 100% had another lifetime substance use disorder, 33% had lifetime major depression, and 30% had lifetime panic disorder [7].

Intoxication and Overdose

As noted earlier, the benzodiazepines are most commonly used as anxiolytics and sedative-hypnotics. However, there are reports of their consumption for the purpose of intoxication, which is described as similar to alcohol intoxication [73], leading to the saying, "benzodiazepines are the driest of martinis". There are some differences between intoxication from benzodiazepines and alcohol intoxication. For example, benzodiazepine users less commonly report the social disinhibition associated with alcohol use. Disinhibition and aggression related to benzodiazepine use is relatively rare, and is more likely to occur in those with high baseline levels of hostility as well as those with pre-existing brain damage [36]. With dose escalation, pleasurable intoxication may progress to manifestations of more profound toxicity, such as impairment in attention or memory, slurred speech, incoordination, unsteady gait, nystagmus, stupor or coma, and eventually respiratory depression. The benzodiazepines have a fairly wide therapeutic index, and overdose rarely results in death in healthy individuals. However, though safer than the barbiturates [77], the benzodiazepines have been associated with lethal overdoses when used alone [19], and especially when combined with other central nervous system depressants, such as alcohol [43, 77] and opioids including buprenorphine [41, 87, 95].

The mechanism by which benzodiazepines manifest their rewarding potential is not fully understood. While activation of dopamine in the nucleus accumbens of the mesolimbic reward pathway is thought to underlie the rewarding properties of most drugs of abuse, the benzodiazepines appear to decrease rather than increase dopamine activity in the nucleus accumbens [21]. It has been hypothesized that the rewarding effect for the benzodiazepines may be mediated though their actions on the gamma-aminobutyric acid system [17].

Laboratory studies that have tried to evaluate the rewarding properties of the benzodiazepines have found that healthy individuals have no preference for the benzodiazepines over placebo; in fact, healthy subjects have demonstrated a preference for placebo over higher doses of the benzodiazepines [97]. However, individuals with a substance use disorder history, especially to sedatives, may be more likely to experience benzodiazepines as rewarding [97]. There is also evidence that individuals with a history of moderate alcohol consumption, anxiety, and insomnia [31], as well as children of alcoholics [10, 11], may be more likely to experience the reinforcing effects of the benzodiazepines. Interestingly though, research on the use of the benzodiazepines for the treatment of anxiety disorders in former substance abusers has not found evidence of induction of relapse to substance use [56, 61]. There is some evidence that benzodiazepines with a rapid onset of action such as diazepam [30, 32] and those with a short half-life such as alprazolam [3] may have a relatively more reinforcing effect, although these results are controversial [72]. Taking the drug intravenously also has been associated with increased reinforcing effects [78].

When misused, the central nervous system depressants are often taken in combination with other drugs [14, 15], often leading to complex and dangerous interactions. For examples, individuals may use the benzodiazepines to enhance intoxication with opioids or alcohol, or to self-medicate the anxiety associated with stimulant use as well as the discomfort associated with stimulant or opioid withdrawal.

The non-benzodiazepine hypnotics are even less likely to be taken for intoxication; however, they carry a risk of misuse, especially among individuals with other substance use disorders and psychiatric comorbidity [9, 33]. Though they are likely safer than the benzodiazepines, there have been reports of coma, respiratory depression, and fatal overdoses on high doses of zolpidem, especially when combined with other drugs [13]. The barbiturates have a narrower therapeutic window in comparison with the benzodiazepines and carry more risk of dangerous central nervous system depression and death on overdose. Fatal overdose also may occur with other older agents; however, both their medical and recreational use has declined since the introduction of the benzodiazepines.

Benzodiazepine intoxication is managed according to the level of severity. Mild intoxication can be managed with supportive care and medical monitoring, while overdose is managed in an intensive care setting. Flumazenil, a benzodiazepine receptor antagonist, is used intravenously to reverse benzodiazepine overdose [92]. Flumazenil should be used with caution as its use may induce benzodiazepine withdrawal and increase the risk of grand mal seizures [92]. Flumazenil also has been used in overdose related to the new-generation non-benzodiazepine hypnotics [8, 26, 37]. Since the barbiturates exert their activity independently of the benzodiazepine binding site, flumazenil does not block their effects and is not useful in barbiturate overdose.

Tolerance and Withdrawal

Physiological dependence requires the presence of tolerance or withdrawal [1]. Tolerance is marked by the gradual need to use increased doses of the substance to achieve the same effect, or is a diminished effect with the same dose. Tolerance to the sedative-hypnotics and anxiolytics occurs through central nervous system adaptation to the drug at the receptor level [6]. Depending on the agent used, its dose, and the duration of use, tolerance can develop in days to months. Tolerance to the benzodiazepines is more likely to develop to the sedative-hypnotic and motor impairment effects than to the anxiolytic and short-term memory impairment effects [29, 47]. Tolerance can be minimized by using the medication for a short period, taking "drug holidays", and using the lowest effective dose. Cross-tolerance can occur between the benzodiazepines and other depressant drugs, including alcohol [40].

Withdrawal is marked by the presence of a characteristic syndrome on cessation or reduction in the use of the substance, and can be avoided or relieved by taking the same or a closely related substance. Symptoms of withdrawal from the benzodiazepines resemble those of alcohol withdrawal, and are generally the result of central nervous system excitation, which is the opposite of the primary action of the drug. Withdrawal progresses from a syndrome of anxiety, insomnia, and tremor to nausea, vomiting, diaphoresis, tachycardia, hypertension, and rarely to grand mal seizures [51] and delirium in rare, severe cases [46, 99]. Withdrawal usually develops after taking the benzodiazepines for months; however, milder withdrawal may emerge after days to weeks of use. Withdrawal severity correlates with the duration of use [66] and the potency and dose of the drug taken [51], as well as individual susceptibility and general health status.

Syndromes that occur commonly after cessation of use of the benzodiazepines can be divided into:

- Acute withdrawal, characterized by relatively severe symptoms emerging several hours to days following dose reduction or cessation of use. Use of short-acting agents is associated with relatively more intense but shorter duration of acute withdrawal symptoms, peaking 2 days after discontinuation, whereas longer-acting agents result in milder but longer withdrawal, peaking in 4–7 days [58, 67].
- Protracted withdrawal, characterized by ongoing anxiety and depression, as well as mild sensory and motor disturbances

that can linger for months [4]. More severe presentations such as psychotic depression also have been reported [54].

- Symptom recurrence, which is the reemergence of pre-existing symptoms, such as anxiety, that were previously masked by the benzodiazepine [58]. Although often difficult to distinguish, re-emerging symptoms tend to be stable over time, unlike withdrawal symptoms, which tend to subside gradually.
- Symptom rebound, which is the exacerbation of pre-existing symptoms after cessation of use, and is, therefore, a combination of genuine withdrawal and symptom re-emergence [22, 58].

Of note, physiological dependence (i.e., tolerance or withdrawal) may occur even when the medications are adequately used at therapeutic doses, and does not necessarily indicate that substance dependence has developed, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision. Nonetheless, the presence of physiological dependence should alert the clinician that the individual may have *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision–diagnosed substance dependence, in which case the presence of tolerance and withdrawal is associated with greater severity of the disorder [74]. The less ambiguous term "addiction" is not present in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision but is considered to be the equivalent of "substance dependence".

Benzodiazepine withdrawal can be managed by supportive measures in less severe cases. In more severe cases, pharmacologic detoxification is often achieved by substituting the substance with a long-acting benzodiazepine such as clonazepam or chlordiazepoxide and gradually reducing the dose over several days in inpatient detoxification programs. Intermediate-acting benzodiazepines, such as lorazepam, also are effective; however, a simple taper of the original medication also has been used. While inpatient detoxification may be needed when concurrently detoxifying from several drugs such as alcohol and opiates, a more gradual taper also can be achieved over several weeks to months in the outpatient setting [76]. Evidence suggests that gradual detoxification is more effective than abrupt discontinuation, which is associated with a higher dropout rate [16]. It also is recommended that the taper be slower after reaching about 50% of the original dose [69, 76]. An older method, using phenobarbital substitution [81], is less commonly used, but is used when detoxifying individuals from the barbiturates [80]. Since benzodiazepine or barbiturate withdrawal is associated with serious morbidity and the possibility of mortality, the clinician should evaluate individuals carefully and consider pharmacologic management of benzodiazepine withdrawal. Of other, non-sedative-hypnotic/anxiolytic medications studied for benzodiazepine detoxification, the anticonvulsant carbamazepine has the most promising data, suggesting its possible utility when used as an adjunct to the benzodiazepines, and its use also may improve drug-free outcome [16].

The literature on physiological dependence to the new-generation non-benzodiazepine hypnotics has been scarce. Tolerance and withdrawal from these drugs have been reported but appear to be relatively rare, as compared with the benzodiazepines [33], possibly due to their relative selectivity at the gamma-aminobutyric acid-A receptor. Caution, however, is advised, as there have been reported cases of withdrawal seizures [12], as well as withdrawal delirium and psychosis, after discontinuation of the use of the new-generation non-benzodiazepine hypnotics [86, 88, 96]. A detoxification regimen similar to that used with the benzodiazepines and barbiturates has been suggested in managing withdrawal from the new-generation non-benzodiazepine hypnotics [63].

Withdrawal from the barbiturates and other older agents is associated with a clinical picture comparable to that of the benzodiazepines, and may lead to withdrawal seizures as well as delirium. Treatment includes detoxification with phenobarbital, a benzodiazepine, or by a gradual taper of the original substance.

Abuse and Dependence

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision [1] offers clear definitions of substance abuse and dependence that apply to all substances of abuse including the sedative-hypnotics and anxiolytics. Tables 2 and 3 summarize the criteria for substance abuse and dependence, respectively, as adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision [1].

Evaluating for sedative-hypnotic and anxiolytic abuse or dependence when a patient has been prescribed the medication by a physician is potentially difficult. For example, if an individual manifests psychosocial deterioration, it is often difficult to determine whether it is the effect related to benzodiazepine dependence or whether it is the result of an undertreated anxiety disorder. Some potential ways to disentangle this may be to evaluate psychosocial functioning. The trajectory of the patient's level of functioning may be a good clinical barometer; if his or her level of functioning improves with the use of a benzodiazepine, then it is likely that the prescribed substance is beneficial. Conversely, the patient's demand for increasing doses of the medications despite deteriorating psychosocial functioning is one indication that a substance use disorder may have developed. The patient's level of functioning can be evaluated by accessing previous records, as well as collateral information and involvement of significant others, after obtaining the patient's consent.

Other indicators of the presence of a substance use disorder are reports of loss of prescriptions, running out of the medication, obtaining the medication from several prescribers, and other signs of loss of control over use of the substance. Even when these signs are present, the physician should retain an "open mind" to the possibility of what is sometimes called "pseudoaddiction" [48], namely when a behavioral pattern typical of substance dependence occurs but is related to the patient's efforts of obtaining a medication that he or she needs for a genuine disorder. While this term is usually used in pain medicine to refer to patients who seek opioids for undertreated pain, a similar pattern also may occur with benzodiazepine use for anxiety or other disorders. In such instances, with adequate treatment of the underlying psychiatric disorder, this behavioral pattern should resolve. Naturally, there is no simple strategy to managing these complex clinical situations, and in all cases the clinician should clarify the reasons for the patient's use of these agents, evaluate the risk/benefit ratio of prescribing these medications, and subsequently use clinical judgment to develop a reasonable treatment plan in collaboration with the patient.

Table 2 Criteria for substance abuse, adapted from the *Diagnostic and statistical manual of mental disorders*, 4th edition, text revision [1]

Substance abuse is a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by at least one of the following four criteria within a 12-month period:
1. Failure to fulfill major role obligations
2. Recurrent use in physically hazardous situations
3. Recurrent substance-related legal problems
4. Continued use despite persistent or recurrent substance-related social or interpersonal problems

Table 3 Criteria for substance dependence, adapted from the *Diagnostic and statistical manual of mental disorders*, 4th edition, text revision [1]

Substance dependence is a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by at least three of the following seven criteria within the same 12-month period:
1. Tolerance
2. Withdrawal
3. Use in larger amounts or over a longer period than intended
4. A persistent desire or unsuccessful efforts to cut down or control use
5. A great deal of time spent in activities necessary to obtain the substance, use it, or recover from its effects
6. Giving up or reducing important social, occupational, or recreational activities because of use
7. Continued use despite persistent or recurrent substance-related physical or psychological problems

A common clinical dilemma revolves around whether a physician should prescribe benzodiazepines to individuals with a history of other (non-benzodiazepine) substance use disorders. While their use is unquestionably of great value in detoxification from alcohol and other substances, their value as anxiolytics and sedative-hypnotics in this patient population is difficult to determine. The prudent course seems to be that while the benzodiazepines should not be absolutely contraindicated in patients with a history of substance use disorders, since some individuals may in fact benefit from treatment with benzodiazepines without misusing them, special care should be exercised and, if possible, the benzodiazepines should not be the first line of treatment. When absolutely indicated, their use should be monitored and the clinical course followed over time for signs of abuse or dependence.

Treatment of sedative-hypnotic and anxiolytic abuse and dependence usually involves successful detoxification, followed by psychosocial interventions aimed at achieving long-term abstinence. People with sedative-hypnotic and anxiolytic abuse and dependence often have other co-occurring substance use disorders and psychiatric disorders [39], which should be screened, adequately diagnosed, and concurrently treated. There are no agents approved by the Food and Drug Administration for the long-term treatment of benzodiazepine dependence. However, pharmacologic strategies are being investigated to target achieving abstinence from the benzodiazepines; agents that have shown promising potential include the benzodiazepine antagonist flumazenil [27] and the anticonvulsants carbamazepine [16] and valproate [34]. Although controversial, maintenance substitution treatment with a long-acting agent, such as clonazepam, also has been suggested [93]. Long-acting benzodiazepines may provide adequate relief from low-grade anxiety, which may be a trigger to relapse to other benzodiazepine and alcohol use. These strategies, while interesting and promising, are still in their experimental stages, and data supporting their safety and efficacy are limited.

Data on the new-generation non-benzodiazepine hypnotics have been scarce; however, there is emerging evidence that they do carry a risk of abuse and dependence, especially among individuals with other substance use disorders and psychiatric comorbidity [9, 33]. Although abuse and dependence related to these medications seem to be less likely than with the benzodiazepines, caution should nonetheless be exercised with their prolonged use. Since the introduction of the benzodiazepines, use of the barbiturates and other older agents has been declining, and abuse of and dependence on these agents are relatively rare.

Mood and Anxiety Disorders

The benzodiazepines, unlike many other medications used in psychiatry, offer patients substantial and quick relief from anxiety and insomnia, which, whether primary or related to other disorders such as depression or psychosis, are among the most common symptoms in the practice of psychiatry. The benzodiazepines can be taken continuously or as needed and often lack many of the side effects common to psychiatric medications such as weight gain, liver toxicity, and sexual dysfunction. However, while often successfully prescribed for the initial phases of anxiety disorders and depression, the controversy lies in their continued use beyond the acute phase. Some research suggests their continued efficacy for the long-term treatment of panic disorder, without the need for progressive dose escalation [65, 98]. Many long-term benzodiazepine users actually decrease their dose and make attempts to stop use [70]. Other research, however, questions the long-term efficacy of the benzodiazepines for the treatment of anxiety and depression [60], and suggests that their chronic use may be associated with depressive symptomatology [79], although direct causation has not been clearly established. There is also concern that continued use may result in interdose rebound symptoms or simply mask withdrawal rather than treat an underlying anxiety disorder.

Moreover, some research has demonstrated that anxiety levels may actually decrease after successful discontinuation of benzodiazepine use [31]. There also is evidence suggesting that both short-term and long-term use of the benzodiazepines may interfere with other effective treatments such as cognitive behavioral therapy for panic disorder [59, 90]. As noted earlier, depression and psychotic depression have been described in protracted withdrawal from the benzodiazepines [4, 54]. Additional precautions in prescribing these medications should be taken due to the frequent use of the benzodiazepines in suicide attempts [53] and accidental overdose.

It is recommended to use non-benzodiazepine medications such as the selective serotonin reuptake inhibitors, as well as other antidepressants and buspirone, as first-line agents for mood and anxiety disorders, especially in individuals with a history of substance abuse. Other strategies to manage acute anxiety include the use of antihistamines, anticonvulsants, and antipsychotics. Effective psychotherapies, such as cognitive behavioral therapy, also have been developed for specific disorders. The benzodiazepines are safest when reserved either as short-term adjuvants to other medications in the initial stages of treatment or as long-term treatment only in refractory cases. Moreover, they should be avoided generally in individuals with an active substance use disorder and cautiously in those with a remitted substance use disorder.

Many long-term benzodiazepine users can be gradually detoxified from these drugs on an outpatient basis. The difficulty often lies in patients' perceptions that the benzodiazepines are the only effective medications. With a good therapeutic alliance, a detoxification regimen often can be successfully negotiated and achieved. Patients should be reassured that there are numerous non-benzodiazepine medications that are effective in managing insomnia and anxiety disorders. In treating these individuals, clinicians need to distinguish protracted withdrawal from the re-emergence of symptoms of a mood or an anxiety disorder (i.e., symptom relapse).

Cognitive Disorders

Acute use of the benzodiazepines is known to cause cognitive impairment, especially among the elderly and those with pre-existing brain damage, and is likely to resolve after tapering or discontinuing the medication. In more severe cases, this may progress to developing delirium [25]. As noted earlier, delirium also can be a sign of withdrawal from the benzodiazepines.

The extent of the effects of prolonged use of the benzodiazepines on cognition is difficult to determine. Research has demonstrated lack of tolerance to benzodiazepine-associated short-term memory impairment even after years of use [29, 47]. After cessation of use, cognition is likely to gradually improve within weeks [68]; however, some cognitive deficit after prolonged use may linger even months after stopping the medication, and it is unclear whether this reflects permanent residual cognitive deficit [5, 84, 91]. In light of this evidence, caution should be taken with prolonged use of the benzodiazepines, especially in those prone to cognitive impairment.

Use of other GABAergic drugs, including the new-generation non-benzodiazepine hypnotics, can cause cognitive impairment [52]. Delirium also may be associated with the use and withdrawal from the new-generation non-benzodiazepine hypnotics [86, 96], as well as other GABAergic agents.

Psychotic Manifestations

Psychosis related to the use of the benzodiazepines is relatively rare. However, psychosis may be associated with benzodiazepine withdrawal delirium [35] and is an indication for medically supervised detoxification. When part of delirium, psychotic symptoms should be considered as part of the withdrawal picture and treated with appropriate, often very high doses of the benzodiazepines with close medical monitoring. Antipsychotic medications should be used with caution and only as adjuncts to the

benzodiazepines; it is especially unclear to what extent they are beneficial in treating withdrawal delirium beyond their sedative effect. In fact, they may be useful for managing agitation but may also inappropriately cover underlying withdrawal symptoms. Antipsychotic medications also may lower the seizure threshold and potentiate the delirium due to anticholinergic activity. If antipsychotics need to be used in combination with the benzodiazepines to manage agitation in the context of benzodiazepine withdrawal, high-potency antipsychotics such as haloperidol should be considered. As noted earlier, psychotic depression also has been reported as a presentation of protracted benzodiazepine withdrawal [54].

Psychosis, marked by hallucinations and delusions after weeks of benzodiazepine use at a therapeutic level, also has been reported and may be related to underlying brain damage [94]. In this case, psychosis is likely to resolve with dose reduction or cessation of use of the benzodiazepine. Psychosis also may be associated with intoxication or withdrawal from the new-generation non-benzodiazepine hypnotics [50, 86, 88] as well as other GABAergic sedative-hypnotics and anxiolytics.

Sleep Disorders

Short-term use of the benzodiazepines results in a decrease in sleep latency and number of awakenings, an increase in total sleep time, and improvement in sleep quality [38, 57]. Other effects of short-term use include daytime drowsiness [38], as well as disruption of sleep architecture: stage 2 increases, slow-wave sleep decreases, and rapid-eye-movement sleep latency decreases [62]. Continued use of the benzodiazepines can result in tolerance to their sedative action, which may occur after several days [82], and can eventually lead to rebound insomnia when their use is stopped [83]. There also is concern that chronic use may be simply masking rebound insomnia rather than treating an underlying sleep problem [31]. Individuals who demand escalating doses of the benzodiazepines may be misinterpreting tolerance and rebound insomnia as a need for a dose increase.

As noted earlier, the new-generation non-benzodiazepine hypnotics may be less likely to result in tolerance, especially when used at therapeutic doses. Eszopiclone and the extended-release form of zolpidem (Ambien CR®) have been shown to be effective and safe in the long-term management of insomnia in a double-blind, placebo-controlled design [44, 45], and zolpidem and zaleplon have been shown to have long-term efficacy in open-label studies [2, 49]. These data may encourage physicians to prescribe these medications more freely than the benzodiazepines. However, an assessment group from the National Institute for Health and Clinical Excellence, an independent organization providing guidance on health-related issues in the United Kingdom, concluded that randomized controlled trials have not been able to demonstrate substantial consistent differences between zolpidem, zaleplon, zopiclone (of which eszopiclone is an (S)-isomer), and the benzodiazepines in terms of their efficacy or in treatment emergent adverse events [20]. Overall, caution should be exercised with prolonged use of all GABAergic sedative-hypnotics, and other strategies such as sleep hygiene should be incorporated into treatment. Other pharmacologic strategies are also available, such as ramelteon (Rozerem®), a melatonin receptor agonist with no known abuse potential [64].

The barbiturates and other older agents share many characteristics of the benzodiazepines and the new-generation non-benzodiazepine hypnotics but are less likely to be prescribed for the treatment of insomnia.

Sexual Dysfunction

Data on the effect of the benzodiazepines on sexual dysfunction are scarce, at times conflicting, and mostly based on prospective data with certain design limitations as well as on retrospective data and case reports. Benzodiazepine use has been associated with sexual dysfunction in both

men and women, manifested as decreased sexual desire, erectile dysfunction, inhibited orgasm, and inhibited ejaculation [23, 28, 89]. These side effects seem to emerge after weeks of use and are likely to subside after dose reduction or cessation of use. There are few available data on sexual dysfunction related to the new-generation non-benzodiazepine hypnotics, the barbiturates, chloral hydrate, meprobamate, carisoprodol, glutethimide, and methaqualone.

While not a specific side effect of the medication, the dangers of sedative-hypnotic and anxiolytic misuse also include drug-facilitated sexual assaults ("date rape"), especially when potent fast-acting agents are added to alcoholic beverages, inducing passivity and amnesia. Flunitrazepam (Rohypnol), which is not approved by the Food and Drug Administration but is available on the "black market", has been associated with drug-facilitated sexual assaults. Other drugs that have been associated with drug-facilitated sexual assaults include other benzodiazepines, zolpidem, chloral hydrate, meprobamate, and other agents [75].

Summary

The benzodiazepines, the new-generation non-benzodiazepine hypnotics, and the barbiturates, as well as other older agents, share a similar mode of action by enhancing GABAergic transmission in the central nervous system. While all these medications have legitimate medical uses, they also are associated with the risk of misuse, abuse, and dependence, particularly in those with other substance use disorders. They also are associated with psychiatric and medical complications. These medications are safest when they are prescribed for short periods and at the lowest effective dose, their use is monitored, and special precautions are taken when prescribing them for individuals with a substance use disorder history.

Acknowledgements The authors would like to thank the National Institute on Alcohol Abuse and Alcoholism, the Center for the Translational Neuroscience of Alcoholism, and Diana Limoncelli for technical assistance.

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Clinical Aspects of Inhalant Addiction

Yu-Chih Shen and Shih-Fen Chen

Contents

Types of Inhalants Being Abused

Inhalants encompass a wide range of pharmacologically diverse substances that readily vaporize. Unlike most other substances of abuse, which are classified into groups that share a specific central nervous system action or perceived psychoactive effect, inhalants are grouped by their common route of administration. Inhalants are classified into three groups on the basis of their currently known pharmacologic actions (Table 1) [27]. Group I includes volatile solvents, fuels, and anesthetics that contain aliphatic, aromatic, or halogenated hydrocarbons. All of these ingredients are found in thousands of commonly used and readily available consumer products. Group II includes nitrous oxide. Group III includes volatile alkyl nitrites. The most commonly abused inhalants are found in Group I. Virtually any hydrocarbon can have mind-altering effects when inhaled in large enough doses. Nitrous oxide, or "laughing gas", is diverted from medical or dental anesthesia use and sold in balloons for inhalation or is simply inhaled from whipped cream aerosol cans. Alkyl nitrites, or "poppers", are also abused; typically, amyl nitrite ampoules intended to treat angina are "popped" open and inhaled.

Epidemiology

The type, frequency, and method of inhalant abuse vary widely in relation to the age of the abuser, the geographic region, and availability. Overall, the onset of inhalant abuse may occur in children as young as 5 or 6 years of age, and the peak age of abuse is 14–15 years. Inhalant abuse usually declines by 17–19 years of age but can continue into adulthood. Abuse by adults may be related to certain occupations where abusable solvents, propellants, or anesthetics are readily available. Inhaled nitrites have a long history of being abused in combination with male homosexual behaviors [27]. Inhalants are sometimes referred to as "gateway" drugs, which means

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_24,

Table 1 Pharmacologic classification of inhalants and common street names

Group	Common street names
I. Volatile solvents, fuels, and anesthetics	Air blast, discorama, hippie crack, medusa, moon gas, oz, poor man's pot
II. Nitrous oxide	Laughing gas, buzz bomb, shoot the breeze
III. Volatile alkyl nitrites	Poppers, snappers, boppers, pearls, amys, quicksilver

they are among the first drugs people try before moving on to other substances, such as alcohol, marijuana, and cocaine [28].

According to a 2006 survey by the National Institute on Drug Abuse [14], the prevalence of lifetime inhalant use among adolescents in the U.S. has ranged between a low of 10.3% in 1976 (when inhalants were first included in the survey) and a peak of 18.0% in 1990. The 2006 rate was 11.1%; this rate has remained stable since 2002. According to the 2008 National Survey on Drug Use and Health [26], inhalants were the most frequently reported class of illicit drugs among adolescents aged 12 or 13 (3.4 and 4.8%, respectively). Among first-time users of inhalants aged 12–15 years of age, the three most commonly used types of inhalants were glue, spray paints, and gasoline. In comparison, nitrous oxide or nitrites were the most common type of inhalants used among past-year inhalant initiates aged 16 or 17. This survey showed no significant male-female differences in lifetime prevalence of inhalant abuse in the 12- to 17-year-old group but confirmed a greater prevalence of inhalant abuse by men than by women in the 18- to 25-year-old group, suggesting that sustained use of inhalants is more common among males.

In India and South Asia, three of the most widely abused inhalants are the contact adhesives, toluenes in paint thinners, and Iodex®, an anti-infective, muscle-stress-relieving balm. Another very common inhalant in India and Asia is Erase-X™, a correction fluid that contains toluene. It has become very common for grade school, high school, and college students to use it because it is easily available in stationery shops in India. Dung sniffing has also been noted as a problem among poor and homeless people in countries such as Thailand and Malaysia. Animal or human dung is placed into a plastic bag or tin and left out in the sun, where it starts to decompose, releasing methane gas, which has narcotic properties. Local police were unsure of what action could be taken, given that dung is not an illegal substance and it would be nearly impossible to restrict supplies of it [16]. Despite these epidemiologic data, inhalants remain among the least-studied groups of abused substances.

Mechanisms of Action

The immediate effects of groups I and II inhalants are similar to the early classic stages of anesthesia [3]. The abuser is initially stimulated and then disinhibited and prone to impulsive behaviors. Speech becomes slurred and gait is uneven. Euphoria, frequently with hallucinations, is followed by drowsiness and sleep, particularly after repeated inhalations. Coma is unusual because as the user becomes drowsy, exposure to the inhalant is terminated before large enough doses are absorbed. The mechanisms of action of these inhalants have not been well defined. It is likely that inhalants act as a mix of *N*-methyl-*D*-aspartic acid antagonist and gamma-aminobutyric acid agonist to produce central nervous system depressant effects [4].

Nitrites have pharmacologic effects that are significantly different from those of other inhalants. Instead of direct central nervous system effects, they primarily cause vasodilation and smooth muscle relaxation [22]. The sensations of floating and increased skin tactility as well as warmth and throbbing occur within 10 s of inhalation and then diminish within 5 min. Abuse of nitrites may result in tachycardia, flushing, blurred vision, headache, lightheadedness, significant hypotension, syncope,

and high enough levels of methemoglobinemia to cause cyanosis and lethargy. Other inhalants are used to alter mood, but nitrites are inhaled to enhance sexual feelings, penile engorgement, and anal sphincter relaxation to intensify sexual experience.

Morbidity and Mortality

Inhalant abuse causes psychosocial as well as organic morbidity. Ongoing inhalant abuse is associated with failure in school, delinquency, and an inability to adjust to societal norms [7]. The chief organic morbidity is central nervous system damage resulting in dementia and cerebellar dysfunction [9, 11, 23]. Typically, there is a loss of cognitive and other higher functions, gait disturbances, and loss of coordination. Imaging studies demonstrate a loss of brain mass [11] and white matter degeneration [9, 23]. Other organic effects are related to specific chemicals found in some but not all products. The strength of the association ranges from definite to likely to speculative. Definite associations include peripheral neuropathy, deafness, and metabolic acidosis. Likely morbidities include embryopathy, neonatal withdrawal, and lung damage. Speculative morbidities include cardiomyopathy, toxic hepatitis, decreased visual acuity, aplastic anemia, and leukemia [27].

Death due to inhalant abuse can occur by several mechanisms, including asphyxia, suffocation, risky behaviors, aspiration, and sudden sniffing death syndrome [21]. Asphyxia is probably of only theoretical concern because it requires the partial pressure of the inhalant to be so high that oxygen is displaced. Suffocation occurs when the mode of use involves inhalation through the nose and mouth from a plastic bag, which may occlude the airway if the user loses consciousness. Disinhibition while under the influence of inhalants may cause dangerous behaviors such as drowning, jumps or falls from heights, hypothermia, and fire-associated deaths (due to the flammability of most inhalants). The risk of death from aspiration is similar to that for alcohol or other depressants and is related to the combination of decreased level of consciousness and loss of protective airway reflexes.

Chronic nitrous oxide abuse causes short-term memory loss and peripheral neuropathy [5]. The peripheral neuropathy results when nitrous oxide inactivates vitamin B12 and mediates a pernicious-anemia-type syndrome, which includes anemia, leukopenia, sensorimotor neuropathy, and posterior/lateral column spinal cord disease. Nitrites are abused mainly for their sensory and sexual effects, and use may promote higher-risk sexual practices, facilitate transmission of sexually transmitted infections, and result in pharmacologic interactions, such as with sildenafil (Viagra®) [22]. Chronic abuse of volatile alkyl nitrites has documented hematologic and immune system effects without associated cognitive deficits [22].

Psychiatric Disorders in Inhalant Users

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, provides two categories of inhalant-related disorders (Table 2) [1]. The first category is inhalant use disorders (inhalant abuse and dependence), which are characterized by a maladaptive pattern of inhalant use. The second category,

Table 2 *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision, inhalant-related disorders

Inhalant use disorders
Inhalant abuse
Inhalant dependence
Inhalant-induced disorders
Inhalant intoxication
Inhalant intoxication delirium
Inhalant-induced persisting dementia
Inhalant-induced psychotic disorder[a]
Inhalant-induced anxiety disorder[a]
Inhalant-induced mood disorder[a]
Inhalant-related disorder not otherwise specified

Modified from American Psychiatric Association [1]
[a]Specify if: with onset during intoxication

inhalant-induced disorders (intoxication delirium, persisting dementia, psychotic disorder, anxiety disorder, and mood disorder), results from the toxic effects of inhalants. Conditions related to abuse of either anesthetic gases or nitrites are not listed under the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision, categories for inhalant use disorders. Instead, these are classified as other (or unknown) substance-related disorders. Some effects and disorders associated with those compounds are briefly discussed elsewhere in this chapter.

Inhalant Abuse and Dependence

The cardinal feature of inhalant abuse is repeated use of inhalants that produces adverse social consequences or physical hazards. Inhalant dependence is characterized by repeated use of inhalants, resulting in combinations of social or physical consequences, loss of control, or development of tolerance or withdrawal symptoms. Despite the absence of an inhalant withdrawal diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision, some people still complain about withdrawal symptoms, including sleep disturbances, irritability, sweating, tachycardia, nausea, shakiness, illusions, delusions, and hallucinations [15].

Two differential diagnoses should be considered [24]. First, polysubstance dependence is common in adolescents. Abuse of or dependence upon other drugs can be traced through an individual's history, physical findings, and drug screens. Second, impulsive behaviors during chronic inhalant use might mimic or be comorbid with conduct disorder or antisocial personality disorder. Conduct or antisocial behaviors that appear before the onset of inhalant abuse or in periods of abstinence suggest the presence of these disorders.

No controlled studies guide the treatment of inhalant use disorder. Treatment usually takes a long time and involves enlisting the support of the person's family; changing the friendship network if the individual "uses" with others; teaching coping skills, and helping the individual increase his or her self-esteem.

In research with animal models of inhalant abuse, *N*-methyl-*D*-aspartic acid, gamma-aminobutyric acid, glycine, nicotine, and serotonin-3 receptors appear to be important targets of action for several abused solvents. Emerging evidence suggests that other receptor subtypes and nerve membrane ion channels are also involved [4]. Evidence postulates that lamotrigine (Lamictal®), a phenyltriazine anticonvulsant, might be effective for inhalant dependence because it modulates release of the excitatory amino acid, glutamic acid, blocks serotonin-3 receptors, and inhibits dopamine uptake [25]. Buspirone (BuSpar®) and risperidone (Risperdal®) also have been reported to be effective for treating inhalant use disorder [19, 20]. The efficacy of these agents in inhalant use disorder requires more investigation.

In addition to inhalant use disorder, most inhalant users have comorbid conduct disorder, attention-deficit hyperactivity disorder, major depressive disorder, dysthymic disorder, alcohol dependence, and psychosis [17, 24]. Psychiatrists often prescribe bupropion (Wellbutrin®) or atomoxetine (Strattera®) for attention-deficit hyperactivity disorder, antidepressants for depression, naltrexone or acamprosate (Campral®) for comorbid alcohol dependence, and antipsychotics for psychotic symptoms [24]. In addition to psychiatric management, appropriate medical care is also required for the disorder's medical sequelae [18].

Inhalant Intoxication and Inhalant Intoxication Delirium

When too much of an inhalant is taken, the user becomes intoxicated. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision, the signs

of inhalant intoxication include: dizziness, nystagmus, incoordination, slurred speech, unsteady gait, lethargy, depressed reflexes, psychomotor retardation, tremor, generalized muscle weakness, blurred vision, diplopia, euphoria, stupor, or coma. Inhalant intoxication delirium is a state in which a person gets extremely intoxicated, with a disturbance of consciousness and a change in cognition.

Differentiation of the diagnosis of inhalant intoxication from that of other types of substance intoxication depends on an individual's history and the evidence of inhalant use such as perioral rash and the presence of inhalant odor and residue. Polysubstance dependence is common among inhalant users. Concomitant intoxication with other substances may be assessed by history and toxicologic examinations [24]. Intravenous injection of dextrose and naloxone (Narcan®) will help rule out coma due to diabetes and coma of narcotic origin, respectively [18]. If the mood disturbance, anxiety, or psychosis appears prominently during inhalant intoxication and is severe enough to warrant clinical attention, the diagnosis should be inhalant-induced mood, anxiety, or psychotic disorder, respectively. If delirium develops in the course of inhalant intoxication, the diagnosis is inhalant intoxication delirium rather than inhalant intoxication [8].

Inhalants are rapidly metabolized and excreted. Inhalant intoxication usually lasts a few hours or less unless there are medical complications. Inhalant intoxication usually resolves spontaneously and requires no medical attention [10]. However, medical complications such as cardiac arrhythmias, trauma, bronchospasm, or laryngospasm need treatment, and clinicians should note the client's vital signs and level of consciousness [18]. The treatment of inhalant intoxication delirium is similar to that used for inhalant intoxication, but the variations of levels of consciousness require special attention to the individual's safety. If the delirium results in severe behavioral disturbances or cognition changes, short-term treatment with a dopamine receptor antagonist may be helpful [13]. Sedative medications, including benzodiazepines, are contraindicated because they may enhance the inhalant's depression of the central nervous system [4].

Inhalant-Induced Persisting Dementia

Inhalants are commonly used both in industry and by consumers as fat solvents. Thus, because the brain is a lipid-rich organ, chronic solvent abuse is neurotoxic and can cause dementia [9, 11, 23]. Inhalant-induced dementia is typically associated with memory impairment and at least one of the following: aphasia, apraxia, agnosia, and executive function disturbance. These symptoms can be associated with delirium, which can persist beyond the usual duration of inhalant intoxication or withdrawal [1].

There are, typically, two other differential diagnoses that should be considered among individuals suspected of having inhalant-induced persisting dementia. First, many inhalant-dependent individuals are concomitantly dependent on alcohol or other sedatives that can also produce dementia. Second, histories of head injury are common among those who are dependent on inhalants [18, 24]. Thus, even among individuals with a documented course of inhalant-induced persisting dementia, other causes of dementia also need to be considered in the differential diagnosis.

Few inhalant-dependent individuals have been studied prospectively. Despite some reports of improvement after abstention from inhalants, most neurocognitive deficits persist and worsen [29]. Additionally, as neurocognitive deficits progress to dementia, inhalant-dependent individuals gradually lose the cognitive capacity to avoid relapses, and each relapse may accelerate brain degeneration.

No controlled studies have been performed to guide the treatment of individuals with inhalant-induced persisting dementia. Correcting the reversible—and slowing the progression of irreversible—factors of inhalant-induced dementia are the primary approach to treatment. Individuals may require extensive support within their families or in foster or domiciliary care.

Inhalant-Induced Psychotic Disorder

Clinical evidence suggests that tetraethyl lead can provoke psychotic symptoms [6]. The cardinal features of inhalant-induced psychotic disorder are prominent delusions or hallucinations (mostly visual) developing during or within 1 month of inhalant intoxication or withdrawal. These psychotic symptoms can occur during intoxication, delirium, and even some time after the inhalant has been withdrawn, and can complicate a pre-existing psychotic disorder [1].

The course of inhalant-induced psychotic disorder is typically brief, lasting a few hours to days beyond the intoxication. Treatment of medical complications, together with conservative management of inhalant intoxication, is appropriate [18]. Agitation, confusion, and psychosis may respond to the administration of antipsychotics such as haloperidol (Haldol®) [13].

A thorough search of the literature revealed only one controlled study that investigated therapy among people with inhalant-induced psychotic disorder [13]. In this study, 40 males admitted to an acute psychiatric unit for treatment of inhalant-induced psychotic disorder were assigned to receive 5 weeks of treatment with carbamazepine (Tegretol®) or haloperidol, supplied in identical-appearing capsules. Individuals in both treatment groups improved significantly over time, but adverse effects were significantly more common and more severe in the haloperidol group. Carbamazepine appears to have comparable efficacy but fewer adverse effects than haloperidol for the treatment of inhalant-induced psychotic disorder. Nevertheless, because there was no placebo group in this study, these data cannot establish that medication was better than no medication.

Inhalant-Induced Anxiety Disorder

The essential features of inhalant-induced anxiety disorder are prominent anxiety, panic attacks, obsession, or compulsion developing during or within 1 month of inhalant intoxication or withdrawal. Inhalant use that is etiologically related to the disturbance causes clinically significant distress or impairment in social or occupational life, or disruptions in other important areas of functioning. The anxiety symptoms are not better accounted for by an anxiety disorder that is not inhalant induced, and the anxiety does not occur exclusively during the course of a delirium [1].

The course and treatment of inhalant-induced anxiety disorders are like those of inhalant intoxication. Sedative medications, including benzodiazepines, are contraindicated because they may enhance the inhalant's depressant effects on the central nervous system, thereby precipitating inhalant-induced anxiety disorder [4].

Inhalant-Induced Mood Disorder

The essential features of inhalant-induced mood disorder include prominent and persistent disturbance in mood with: (1) depressed mood or markedly diminished interest or pleasure in daily life and activities, and (2) elevated, expansive, or irritable mood developing during or within 1 month of substance intoxication or withdrawal. The depressed mood is not better accounted for by a mood disorder that is not inhalant induced, and the mood disturbance does not occur exclusively during the course of an episode of delirium [1].

The course and treatment of inhalant-induced mood disorders are like those of inhalant intoxication. The course is brief, lasting a few hours to days beyond the intoxication. Although antidepressants or antimanic medications are seldom appropriate for these relatively brief disorders, the risk of suicide requires a carefully monitored psychosocial intervention. Suicidality has a very strong relationship with inhalant use disorder [12]. Inhalant use disorders in incarcerated youth, as well as inhalant use without abuse or dependence (particularly in girls), may signal elevated suicide risk. Suicide risk assessments, therefore, should include questions about inhalant use.

Prevention and Management Considerations

As with other types of substance abuse, the most effective way to curtail use is through prevention [2]. There are many potentially preventive strategies; however, most of these have proved to be impractical. Restricting the availability of some of these products merely results in a shift to the use of other products. Limiting the availability of inhalants is impractical because they comprise a large group of products that are universally available and have legitimate uses. Reformulating a product by replacing the hydrocarbons with other chemicals is not practical because this usually results in a less effective product. Adding a noxious chemical to the product to prevent misuse also is ineffective because there are multiple products that would require such adulterants. Warning labels on packages may be counterproductive because they allow children to identify sniffable substances more easily. Criminalization of the user is not a meaningful deterrent for the prevention of inhalant abuse, either for the experienced user or for the person who is experimenting for the first time. Criminalization of the vendor is ineffective, again because of the issue of dealing with multiple products that have legitimate uses.

Education is considered to be the most effective preventive strategy [2]. Progressive, school-based inhalant abuse prevention courses, taught beginning in kindergarten, with developmentally appropriate modules taught throughout elementary school, are seen as the most efficient strategy and should be implemented—particularly in areas where inhalant abuse is prevalent. Offering alternative activities in recreational facilities, for example, and promoting traditional cultural values encourage positive lifestyles, thereby reducing the risk for inhalant abuse and other destructive behaviors. Prevention workers are especially effective when they are from the local community. However, they must be appropriately trained and have access to ongoing support.

Psychiatrists are encouraged to be aware that inhalant abuse can occur in all client populations, including their own. They need to be knowledgeable about the epidemiology of inhalant abuse, particularly regarding local and regional trends, and about the serious health consequences of inhalant abuse. In particular, they need to know about unique clinical features such as central nervous system damage and sudden sniffing death syndrome. Finally, they need to help educate children, adolescents, parents, teachers, media representatives, and vendors of volatile substances about inhalant abuse prevention and the health risks of inhalant use. Psychiatrists can serve as a valuable community resource regarding inhalant use awareness, prevention, detection, and management [27].

Treating inhalant users is difficult because of the many pharmacologic, clinical, and demographic factors that make this type of substance abuse unique. Treatment strategies are still being developed, and additional research is needed to identify effective strategies to help these individuals.

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Anabolic-Androgenic Steroids

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Contents

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Introduction

Anabolic-androgenic steroids refer to the male hormone, testosterone, and many of its natural and synthetic derivatives. All anabolic-androgenic steroids have androgenic (masculizing) and body-building (anabolic) effects, despite efforts to develop compounds with only anabolic effects; but some are relatively more anabolic or androgenic than others. Oxandrolone, for example, has greater anabolic activity and less androgenic activity than testosterone [67]. All anabolic-androgenic steroids also share a cholesterol-like and -derived chemical structure in common with other classes of steroid compounds, such as corticosteroids, mineralocorticoids, and estrogens. The current development of synthetic non-steroidal selective androgen receptor modulators has recently produced anabolic-androgenic drugs that are not steroids [30, 84], but little is known about the abuse potential of these pre-marketed substances.

United States Food and Drug Administration-approved medical uses of anabolic-androgenic steroids include male hypogonadism (androgen deficiency [6]) hereditary angioedema (a dermatological disorder), treatment of weight loss associated with AIDS, burns, and other catabolic states [67], and relatively rare types of anemias including Fanconi's and those related to bone marrow suppression (aplastic anemia) or kidney failure. Other uses of anabolic-androgenic steroids, including experimental ones, have included male contraception

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_25,

[60], post-menopausal hormonal therapy and treatment of depression [43], sexual disorders [87], osteoporosis [96], and metastatic breast cancer. For many of these indications, except male hypogonadism and hereditary angioedema, anabolic-androgenic steroids are second or third-line choices. For example, erythropoietin has largely replaced anabolic-androgenic steroids to treat specific types of anemia.

Anabolic-androgenic steroids are used illicitly to facilitate muscle growth and strength, which many consider to improve athletic performance or aesthetic appearance. Thus, anabolic-androgenic steroids are sometimes referred to as performance-enhancing drugs (also known as ergogenic drugs), which include human growth hormone, erythropoietin, stimulants, clenbuterol, and various nutritional supplements, the latter of which are popular in adolescents [15, 37]. Within the international sports community, ergogenic aids are commonly referred to as "doping agents" and subject to detection by the World Anti-Doping Agency [5, 86]. It is now accepted that anabolic-androgenic steroids can increase muscle size and strength when combined with proper exercise and nutrition [50], but that does not necessarily translate into enhanced performance for any given sport.

Anabolic-androgenic steroids have both similarities to and differences from so-called "classical" addictive drugs, such as alcohol, cocaine, nicotine, and opioids. A major difference is that anabolic-androgenic steroids are not initially taken for their psychoactive or euphorigenic effects. Anabolic-androgenic steroids users are much more generally focused on their bodies than their minds. Subgroups of anabolic-androgenic steroids users may even avoid "classical" addictive drugs [90], because of their damaging effects to the body (e.g., cigarettes). Unfortunately, an emphasis on the myoactive (muscle-active) effects of anabolic-androgenic steroids has in part contributed to an underestimation of their psychoactive effects. Nevertheless, from the time that testosterone was first synthesized in 1935, the medical world quickly became interested in its potential to improve mood [101], and the interest continues to the present day [43]. Recent advances in the neurobiology of anabolic-androgenic steroids and the discovery of neurosteroids have further increased overall attention to the psychoactive properties of anabolic-androgenic steroids. There is now general consensus that anabolic-androgenic steroids have important psychiatric effects [50, 86], including the potential for addiction [103]. As Wood [102] wrote, "it is time to cease pretending that the effects of anabolic-androgenic steroids stop at the neck".

Epidemiology

The use of anabolic-androgenic steroids to enhance athletic performance dates back at least to the early 1950s. At the 1956 World Games, Americans discovered that Soviet athletes were using testosterone, and soon began adopting the practice for their own athletes. Up until the late 1970s, use of these drugs was largely confined to, and endemic in, elite athletes, including competitive college-level and professional athletes. By the early 1980s, the drugs had clearly filtered down to high school athletes. As the decade progressed, use had spread to all classes of athletes as well as to non-athletes who simply wanted to enhance their physical appearance. A now classic epidemiological study published in 1988, revealed that 6.6% of male high school seniors in the United States reported using anabolic-androgenic steroids, and over two-thirds had started prior to age 16 years [13]. By 1991, over 1 million Americans had tried anabolic-androgenic steroids [105].

The annual University of Michigan Monitoring the Future study has tracked anabolic-androgenic steroid use in 8th, 10th, and 12th graders since 1989 [42]. In 2006, lifetime use among 8th and 12th graders, respectively, was 1.6 and 2.7% (2.2 and 4.3% for males and 1.1 and 1.2% for females, respectively). Among college students, lifetime non-medical use of anabolic-androgenic steroids was generally stable from 1993 to 2001 at <1%, although past-year use by men increased from 0.4 to 0.9%

[62]. Thus, use appears to decline from high school to college, perhaps due to a selection effect.

Overall, young men who train extensively by lifting weights for athletic or aesthetic purposes are at highest risk to use anabolic-androgenic steroids [3]. Most studies also support a correlation with alcohol and other drug abuse, with some exceptions (e.g., Striegel et al. [90]). Other studies have found that dissatisfaction with body image is associated with anabolic-androgenic steroid use [11, 47]. When severe, dissatisfaction with one's physique may meet diagnostic criteria for body dysmorphic disorder [76]. Among anabolic-androgenic steroid users, a subtype of body dysmorphic disorder has been labeled muscle dysmorphia [14]. Men who view their size and muscularity as inadequate no matter how big or muscular will usually fit *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria. This syndrome has been compared to eating disorders—especially among women who believe they are too fat no matter how much weight they lose—thus acquiring the name *reverse anorexia nervosa* or *bigorexia* [19, 44, 65]. Muscle dysmorphia also has features of obsessive-compulsive disorder [17].

Pharmacology

Chemical Structure

Derived from cholesterol, anabolic-androgenic steroids have a four-ring structure with 19 carbon atoms. Modifications at the C-17 and other carbon atoms are responsible for much of the variety among synthetic anabolic-androgenic steroids [50]. Alkylation at the C-17 atom in its alpha position results in most of the oral forms of anabolic-androgenic steroids, because this structural modification confers resistance to first-pass liver metabolism. The C-17-alkyl-anabolic-androgenic steroids may also be more likely to cause liver toxicity and cholesterol abnormalities. Esterification at the C-17 atom in its beta position results in the commonly injected testosterone esters (testosterone cypionate, testosterone enanthate, and testosterone propionate). Because testosterone is rapidly metabolized by the liver, the testosterone esters were designed as depot medications, and are released slowly from the muscles into which they are injected.

Pharmacokinetics

Most oral forms of anabolic-androgenic steroids are relatively short-acting with half-lives of approximately 24 h, whereas injected anabolic-androgenic steroids are relatively long-acting with half-lives of several days to weeks. Thus, testosterone esters when injected for medically-indicated replacement therapy are usually administered every 2–4 weeks; whereas oral forms are typically administered daily. Gel forms and transdermal forms of testosterone are applied topically to, and absorbed by, the skin for replacement therapy. Their pharmacokinetics also requires daily administration. A buccal form of testosterone is available that is applied to the upper gingiva and requires dosing every 12 h. The topical forms of testosterone are not typically used illicitly, however, because they are difficult to administer in the supraphysiological doses preferred by illicit users.

Testosterone can be viewed as a "prohormone" for both dihydrotestosterone [23] and estradiol. When testosterone is aromatized by the enzyme, aromatase, estradiol is formed and acts on estrogen receptors. When reduced by the enzyme 5α-reductase, dihydrotestosterone is formed and acts on androgen receptors. Testosterone also acts directly on androgen receptors, but dihydrotestosterone is about 10 times more potent. Different organs are genetically programmed to express one enzyme or the other preferentially depending on its function. Thus, 5α-reductase predominates in the testes where spermatogenesis occurs, and aromatase predominates in the female breast causing enlargement. Similarly, preferential gene expression may drive the synthesis of either

estrogen or androgen receptors depending on the tissue site and function of the organ.

Urine Testing

Testing for anabolic-androgenic steroids in the urine, although critical for athletic competitions at the elite level, is rarely performed in routine clinical practice, including addiction treatment settings. One reason is that anabolic-androgenic steroid users are not frequently seen in addiction treatment settings. Another reason is that testing is expensive and requires specialized laboratories that can perform mass spectrometry/gas chromatography across a large number of different anabolic-androgenic steroids (Table 1). The detection of anabolic-androgenic steroids in urine has recently been reviewed [81].

Patterns of Illicit Use

Illicit use of anabolic-androgenic steroids is typically characterized by: (1) combining several anabolic-androgenic steroids, including injection and oral preparations together ("stacking"); (2) increasing doses of anabolic-androgenic steroids to a peak regimen and then tapering doses over time ("stacking the pyramid"); (3) alternating periods of use with periods of non-use ("cycling"); (4) using a combination of human and veterinary preparations, and (5) adhering to a regulated training schedule and dietary regimen. Other drugs are commonly taken together with anabolic-androgenic steroids to enhance physical performance [5], to treat or prevent unwanted side effects of anabolic-androgenic steroids (e.g., estrogen blockers), and to mask detection of anabolic-androgenic steroids in the urine (e.g., probenicid). Many surveys suggest that anabolic-androgenic steroid users are more likely than non-users to abuse other addictive drugs. In this regard, it is of interest that anabolic-androgenic steroids can increase sensitivity to alcohol [40], amphetamine [7, 88], and opioids [16]. Arvary and Pope [1] reported that anabolic-androgenic steroids may serve as gateway drugs to opioid dependence. On the other hand, abuse of illicit drugs may be less likely among by elite athletes and some bodybuilders, because they do not want to harm their bodies with drugs that could degrade their performance or appearance [90].

Anabolic-androgenic steroids are readily available through social networks associated with weightlifting gyms [61]. While classified as Schedule III controlled substances in the Unites States, anabolic-androgenic steroids have recently been available without a prescription in some other countries. Among such countries has been Mexico, which has resulted in smuggling anabolic-androgenic steroids across the border.

Table 1 Representative anabolic-androgenic steroids used by weightlifters and bodybuilders

Injected testosterone esters
Testosterone cypionate
Testosterone propionate (Testoviron)
Testosterone enanthate (Delatestryl)
Testoseterone ester mixture (Sustanon)
Injected veterinary forms
Boldenone undecylenate (Equipoise)
Stanozolol (Winstrol-V)
Trenbolone acetate (Finajet, Finaplex)
Other injected forms
Nandrolone decanoate (Deca-Durabolin)
Nandrolone phenpropionate (Durabolin)
Oral forms
Methandostenolone (Dianabol), also known as methandienone
Methyltestosterone (Android, Testred)
Oxandrolone (Anavar)
Oxymethalone (Anadrol)
Stanozolol (Winstrol)

Adverse Medical Effects

Adverse medical effects of anabolic-androgenic steroids have been well reviewed [46, 59]. Adverse medical effects may be short-term, relatively reversible, and limited to periods of use and acute withdrawal; or long-term, relatively irreversible, and persistent during periods of sustained abstinence. The short-term effects generate less disagreement among experts than do the

long-term effects, because good epidemiological studies of the latter are lacking. The major organ systems that are adversely affected by anabolic-androgenic steroids are endocrine, hepatic, and cardiovascular. Endocrine side effects result from having too high or too low concentrations of gonadotropins and sex steroids. In men, these effects include testicular atrophy, abnormal and reduced spermatogenesis, gynecomastia (due to metabolism via aromatization of some anabolic-androgenic steroids into estrogens), and premature male pattern baldness. Gynecomastia, particularly when painful, may require surgical correction. In women, these effects include clitoral hypertrophy, decreased breast size, hirsutism including abnormal facial hair (such as mustache and beard growth), menstrual irregularities, and deepened voice. Clitoral hypertrophy and deepened voice may be irreversible. If taken during pregnancy, anabolic-androgenic steroids can masculinize a female fetus. Hepatic effects include benign and malignant tumors, cholestatic jaundice, liver failure, and peliosis hepatis. Peliosis hepatic describes a condition characterized by blood-filled sacs or cysts in the liver that can be fatal upon rupture. Cardiovascular effects include hypertension, abnormal cholesterol levels, and cardiomyopathy as well as numerous case reports of myocardial infarction or stroke. Orally active C-17-alkylated anabolic-androgenic steroids are more toxic to the liver and cholesterol metabolism than injected anabolic-androgenic steroids including testosterone. Other adverse effects include acne, peripheral edema due to water retention, polycythemia, exacerbation of tic disorders, sleep disorders [100], and infections due to non-sterile injection practices. Taken by children, anabolic-androgenic steroids can cause premature closure of epiphyseal growth plates in long bones resulting in small stature.

Psychiatric Aspects and Effects

There is general consensus that anabolic-androgenic steroids are psychoactive drugs that can contribute to and cause psychiatric effects [4, 74, 80, 95, 97]. Many factors can influence the development of adverse psychiatric effects to drugs. Such factors include genetic vulnerability, social context, stress, personality characteristics, a past history of psychiatric problems, use of other substances, and expectancies. Case reports, retrospective studies, and psychiatric diagnostic studies of anabolic-androgenic steroids users provide some clues regarding the range of adverse psychiatric effects observed, however, it can be difficult to prove that anabolic-androgenic steroids, rather than co-existing factors (e.g., other drug use, predisposition, or environment) were responsible. Therefore, double-blind placebo-controlled trials that measure psychiatric effects of anabolic-androgenic steroids are more conclusive (see below).

The most frequently described adverse psychiatric effects of anabolic-androgenic steroids are extreme mood swings ranging from mania to depression, suicidal thoughts and behaviors, marked aggression including homicidal thoughts and behavior (“roid rage”), grandiose and paranoid delusions, and addiction [56, 74]. Mania or hypomania, violent aggression, and delusions typically begin during a course of anabolic-androgenic steroid use, whereas depressive episodes and suicide attempts are most likely to occur within three months of stopping anabolic-androgenic steroid use, i.e., during anabolic-androgenic steroid withdrawal [57]. Fortunately, most psychiatric effects such as mood swings are reversible with medically monitored cessation of anabolic-androgenic steroid use, but suicides and homicides are obviously irreversible.

The true rate of adverse psychiatric effects among anabolic-androgenic steroid users is unknown. Studies of illicit anabolic-androgenic steroid users typically include small numbers of subjects who may not be representative of all anabolic-androgenic steroid users; and the studies rely on self-report of past events which may not always be accurate [66, 70, 77]. One controlled study of 160 athletes reported that 23% of 88 anabolic-androgenic steroid users were diagnosed with major mood disorders (i.e., mania, hypomania, or depression) in association with

their anabolic-androgenic steroid use, including 11% diagnosed with major depression [77]. That study also suggested that psychiatric effects are dose-related: none of the anabolic-androgenic steroid users taking low doses had major depression whereas medium-dose and high-dose users had rates of 6 and 28%, respectively. Another study [57] found that rates of depression were higher during anabolic-androgenic steroid withdrawal than when actively taking anabolic-androgenic steroids (6.5% vs. 1.3%). That study also found that 3.9% of 77 illicit anabolic-androgenic steroid users had made suicide attempts during the withdrawal period [57]. Rates of completed suicides, however, are especially hard to estimate. In a series of 34 forensically evaluated deaths among male anabolic-androgenic steroid users, 11 users committed suicide, 9 were victims of homicide, 12 deaths were judged as accidental, and 2 were indeterminate [94].

Adverse psychiatric effects appear to be dose-related [68]. There are at least four double-blind, randomized placebo-controlled trials that employed relatively high doses of anabolic-androgenic steroids [78, 91, 98, 104]. Three of these studies indicate that some individuals will experience severe, adverse psychiatric effects after high doses of anabolic-androgenic steroids are administered [78, 91, 104], although one study found no evidence of psychiatric effects [98]. Averaging across studies, recent reviews have concluded that the incidence of prominent irritability or hypomania attributable to steroids during controlled trials is 5% [78, 82]. These gold standard studies, however, are likely to underestimate the incidence and severity of psychiatric effects, because ethical considerations limit the maximum doses of anabolic-androgenic steroids that can be administered to human subjects [78]. Illicit anabolic-androgenic steroid users typically consume 10–100 times the therapeutic doses prescribed legitimately by physicians to restore testosterone levels in patients who cannot make their own. By contrast, the maximum doses administered in the cited controlled trials were 5–6 times the therapeutic dose [78, 91, 98, 104].

Neurobiology

The following structures have been implicated in the psychoactive properties of anabolic-androgenic steroids: the midbrain [28, 41], nucleus accumbens [27], amygdala [20], hippocampus [29, 38, 54], and prefrontal cortex [28, 38]. Androgen receptors are prominent in the hippocampus, amygdala, and prefrontal cortex [39], structures involved in learning and/or aggression. Synaptic density in the hippocampus is androgen-dependent [54]. The size of the medial amygdala is also anabolic-androgenic steroid dependent [20].

Neurotransmitter systems altered by anabolic-androgenic steroids include gamma-aminobutyric acid [27, 33, 34], glutamate which correlated with aggressive behavior [25], dopamine [27, 51, 52, 83], opioids [41, 55, 71], norepinephrine [92], and serotonin [22, 53, 79, 92].

The mechanism of action of anabolic-androgenic steroids can vary depending on the availability (in different brain regions) of specific enzymes such as 5α-reductase or aromatase, and receptors such as androgen or estrogen. This is because many of the metabolites of testosterone are active [27, 29]. Thus, the actions of anabolic-androgenic steroids on the brain can be exceedingly complex.

Addiction

The term, addiction, is used here synonymously with substance dependence as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria. Abuse, which is conceptually defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition as either repeated use of a substance despite recurring adverse psychosocial consequences or as repeated use in hazardous situations, caused little debate among scientists when applied to anabolic-androgenic steroids. Accordingly, most articles on the topic include

the word *abuse* in their titles rather than *addiction* or *dependence*. Furthermore, the generally accepted abuse potential of anabolic-androgenic steroids led to their classification in 1991 by the Drug Enforcement Agency as Schedule III Controlled Substances. By contrast, addiction to anabolic-androgenic steroids has been historically controversial since it was originally proposed in a peer-reviewed journal [48], especially when anabolic-androgenic steroids are compared with traditional addictive drugs such as cocaine and opioids [24]. Some experts have been slow or reluctant to accept that the addiction-like aspects of long-term, heavy anabolic-androgenic steroid use could be dissociated from co-occurring compulsive behaviors such as repetitive, rigorous weight training activity [2]. Such activity might be reinforcing in itself, similar to "exercise dependence," or psychosocially (if not monetarily) rewarding in terms of winning competitions, or having athletic prowess or a fit-appearing body.

Animal studies have the advantage of eliminating the sociocultural influences of competitive athletics and bodybuilding. Although earlier animal studies failed to find self-administration of anabolic-androgenic steroids [26], it has now been shown that some animals will self-administer anabolic-androgenic steroids, particularly the anabolic-androgenic steroids that have relatively stronger androgenic than anabolic effects [102]. The evidence of addiction to anabolic-androgenic steroids from animal studies was a subject of comprehensive review [103]. One can hypothesize, therefore, that the anabolic effects of anabolic-androgenic steroids fuel their initial abuse by bodybuilders and athletes, whereas the androgenic properties endow anabolic-androgenic steroids with their psychoactive and reinforcing effects, including their potential for addiction.

When case reports and survey studies were reviewed in 2002, a total of at least 165 instances of anabolic-androgenic steroid dependence had been reported in the scientific literature among weightlifters and bodybuilders [10]. In 2005, 68 more instances were added [69] for a total of 233. Because all published reports of anabolic-androgenic steroid dependence involved convenience samples, the prevalence of anabolic-androgenic steroid dependence is not known. Across five studies involving a total of 426 anabolic-androgenic steroid users, rates of individual diagnostic criteria are listed in Table 2 [12, 21, 32, 64, 69]. Frequencies of withdrawal symptoms are shown in Table 3.

All reported instances of anabolic-androgenic steroid dependence have occurred in non-medical or illicit users who took anabolic-androgenic steroids for weightlifting and bodybuilding. Importantly, no cases of anabolic-androgenic steroid dependence have been reported in patients legitimately taking medically prescribed anabolic-androgenic steroids for clinical indications, which is primarily an issue of dose. Medical indications only require doses to restore normal physiologic function, whereas use for athletic performance or aesthetic appearance require supraphysiological doses of anabolic-androgenic steroids. In contrast to prescription opioid dependence, therefore, the development of addiction to anabolic-androgenic steroids does not appear to start with therapeutic doses that escalate over time as addiction emerges. Rather, dependence on anabolic-androgenic steroids seems to require deliberate self-administration of supratherapeutic doses from the beginning. The lack of anabolic-androgenic steroid dependence in individuals taking them for legitimate medical purposes has led to the erroneous conclusion that dependence does not develop without compulsive weightlifting activity, but this conclusion is confounded by the correlation between weightlifting and supratherapeutic doses.

Screening and Assessment

History

There is no one best way to screen or assess individuals for the use and consequences of consuming anabolic-androgenic steroids for

Table 2 Numbers of individuals meeting *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria for substance dependence

Study	Brower et al. [12]		Gridley and Hanrahan [32]		Midgley et al. [64]		Copeland et al. [21]		Perry et al. [69]		Total	
N[a]	49		21		50		100		206		426	
DSM-IV criteria	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
1 Tolerance	9	18.4	4	19.0	7	14.0	12	12.0	56	27.2	88	20.7
2 Withdrawal	41	83.7	12	57.1	17	34.0	64	64.0	56	27.2	190	44.6
3 Substance taken in larger amounts than intended	25	51.0	8	38.1	16	32.0	12	12.0	58	28.2	119	27.9
4 Desire yet unable to cut down or control use	8	16.3	8	38.1	10	20.0	17	17.0	8	3.9	51	12.0
5 Much time spent on substance-related activity	19	38.8	14	66.7	2	4.0	9	9.0	78	37.9	122	28.6
6 Other activities replaced by substance use	14	28.6	10	47.6	2	4.0	29	29.0	21	10.2	76	17.8
7 Continued use despite knowledge of problems	18	36.7	10	47.6	12	24.0	35	35.0	31	15.0	106	24.9
Individuals meeting 3 or more DSM-IV criteria	28	57.1	12	57.1	13	26.0	23	23.0	68	33.0	144	33.8
DSM-III-R criteria											*N*=120	
8 Intoxication or withdrawal symptoms when expected to function or when physically hazardous	4	8.2	0	0.0	2	4.0	–	–	–	–	6	5.0
9 Substance used to relieve or avoid withdrawal	2	4.1	4	19.0	14	28.0	–	–	–	–	20	16.7

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[a]All samples were 100% male except that of Copeland et al. [21], which included 6 females, of whom 2 were reported to meet DSM-IV criteria for anabolic-androgenic steroid dependence

Table 3 Endorsed anabolic-androgenic steroid withdrawal symptoms

	Brower et al. [12] *N*=49	Midgley et al. [64] *N*=50	Copeland et al. [21] *N*=100
Anorexia	24%	–	33%
Anxiety	–	–	12%
Body image dissatisfaction	42%	–	38%
Decreased libido	20%	10%	1%
Decreased size or weight	–	52%	–
Decreased strength	–	38%	–
Depressed mood	41%	–	31%
Depressed (due to size loss)	–	30%	–
Depression (unexplained)	–	6%	–
Desire to take more steroids	52%	–	28%
Fatigue	43%	4%	24%
General loss of interest	–	–	23%
Headaches	20%	–	6%
Increased aggression	–	10%	–
Insomnia	20%	–	–
Nausea	–	–	2%
Nosebleeds	–	–	1%
Restlessness	29%	–	10%
Suicidal thoughts	4%	–	2%
Sweating	–	–	1%

non-medical purposes. What follows are sample questions that illustrate important areas to be covered.

Screening: Do you train or work out? How many times weekly? How many hours do you train on the days you do? How long have you been working out seriously? Do you train at a gym? Do you spend time there when not working out? Have you ever used substances such as nutritional supplements to increase your strength, body size, or athletic performance? Do you have any friends who use anabolic-androgenic steroids? Have you ever considered using them? Have you ever used anabolic steroids? If yes, what were you hoping to accomplish by taking them? If no, do you think you will take them in the future?

Assessment: Give me a list of all of the anabolic-androgenic steroids you have taken, which ones you take now, how much, how often, and for how long. Please indicate which anabolic-androgenic steroids you take by mouth and by injection. Do you cycle on and off? How long are your cycles? How much recovery time do you give yourself between cycles? What do you consider the benefits of using anabolic-androgenic steroids? Is there anything about using them that you do not like? Have they ever made you sick? "Messed" with your moods? Scared your friends or family? (If used by injection), have you ever shared needles with other users? What other drugs, if any, do you take to increase the effects of anabolic-androgenic steroids? To treat or prevent side effects, such as enlarged breast tissue? For fun or to get high? Do you use drugs to prevent detection by drug tests for anabolic-androgenic steroids? Where do you get your anabolic-androgenic steroids? Someone you know who sells them? (You don't need to tell me who it is.) A physician? The Internet? Travel to other countries?

Physical

Vital signs—hypertension. *Appearance*—muscle hypertrophy that is disproportionately larger in the upper torso than lower torso. *Skin*—acne, needle marks in large muscle

groups, especially the gluteals, male pattern baldness or alopecia in men and abnormal facial hair in women, jaundice if severe liver disease. *Eyes*—jaundice if severe liver disease. *Chest*—gynecomastia and tender breasts in men or decreased breast size in women. *Abdomen*—right upper quadrant tenderness, enlarged liver if diseased. *Urogenital system*—prostatic hypertrophy and testicular atrophy in men and clitoral hypertrophy in women. *Extremities*—edema/water retention.

Mental Status

Large clothes may be worn to hide physical build if there is a body image disorder. Deepened voice and other masculine features may be observed in women. In terms of psychomotor behavior, speech, mood and affect, thought content, thought processes, and perception, the mental status exam can be consistent with depression, hypomania, or mania, with or without psychotic features. Suicidal and/or homicidal ideation must be assessed due to well-documented increases in aggression and impulsivity. Paranoid ideation or delusions with or without hallucinations are also important to assess.

Labs

The most common laboratory test to detect the use of anabolic-androgenic steroids is an analysis of urine [81]. Although most clinical laboratories do not do these tests because they are specialized and expensive (most will eventually involve mass spectrometry/gas chromatography), clinicians should not hesitate to ask their local labs to send samples to where they can be analyzed. While waiting for the results, some common blood tests can be ordered as reviewed below.

Muscle enzymes can be elevated because of intensive weight training and intramuscular injections. Because alanine transaminase and aspartate transaminase overlap with liver enzymes, creatinine phosphokinase should also be ordered. Cases of rhabdomyolysis have been reported.

Liver enzymes can be elevated because many of the oral anabolic-androgenic steroids, especially the 17-alpha-alkylated ones, are metabolized there and can be toxic to the liver. Because alanine transaminase and aspartate transaminase overlap with muscle enzymes, bilirubin should also be ordered. Needle sharing, while not as common as among heroin addicts, can also infect the liver with hepatitis B or C.

A complete blood count may reveal elevations in hemoglobin, hematocrit, or red blood cell count, because anabolic-androgenic steroids can stimulate erythropoesis.

The hormones, luteinizing hormone and follicle-stimulating hormone, can be expected to be decreased, due to negative feedback of anabolic-androgenic steroids on the hypothalamus and pituitary gland. Testosterone and estradiol will be elevated with use of testosterone esters, but endogenous output of these hormones will be minimal.

A cholesterol profile will likely show elevated low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol. Because this profile is generally associated with cardiac disease, it is important to bring it to the attention of the user. An electrocardiogram and echocardiogram may reveal cardiac disease more directly if present. Left ventricular hypertrophy is typical in anabolic-androgenic steroid users and sometimes other weightlifters, but diastolic dysfunction is more likely in anabolic-androgenic steroid users, and may also extend to the right ventricle [49].

A sperm analysis is not required but it will likely reveal either a decreased or zero sperm count, abnormal morphology, and reduced motility.

Treatment

Anabolic-androgenic steroid users are not commonly seen in addiction treatment settings, unless they are also dependent or abusing other substances like alcohol, opioids, or stimulants

[18]. They may present for psychiatric symptoms, but are most likely to be seen in primary care clinics or sports medicine clinics. It must be emphasized that no controlled studies of treating anabolic-androgenic steroid-related disorders exist [9, 74]. In the absence of a higher-level evidence base, the best we can do is borrow strategies shown to be effective for treating other substance-related disorders, while at the same time both respecting and targeting some unique features found among anabolic-androgenic steroid users. As with dependence on other substances, the goals of treatment are abstinence from all addictive drugs, restoration of physical and mental health, and improved coping and psychosocial functioning. Whether maintenance with testosterone agonist therapy is a reasonable goal will be discussed below. The remaining part of this section will be organized by specific anabolic-androgenic steroid-related disorders.

Anabolic-Androgenic Steroid Abuse

Anabolic-androgenic steroid abuse is defined as recurrent use that either causes adverse consequences or occurs in situations that are physically hazardous. It could be argued that elite athletes frequently compete in physically hazardous situations, making it rather easy to fulfill the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for abuse. Usually treatment is aimed first at motivating anabolic-androgenic steroid users to stop their use via motivational interviewing and involvement of their social support network. The nature and severity of the adverse consequences require discussion in the context of the potential benefits of anabolic-androgenic steroids that users perceive for themselves.

Anabolic-Androgenic Steroid Withdrawal

Anabolic-androgenic steroid withdrawal does not ordinarily require medical detoxification. Anabolic-androgenic steroid users whose pattern of use included cycling and pyramid dosing, already know how to taper themselves from anabolic-androgenic steroids and should be encouraged to do so. Those who are motivated to stop using but have difficulty doing it will likely have the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition-defined dependence in addition to physiological withdrawal; and such users may benefit from medical detoxification. There are neither controlled studies nor agreement about how to do it. Suggested techniques include testosterone substitution therapy followed by a taper at a rate that is tolerable and safe [8]. Prior to such treatment, blood work for follicle-stimulating hormone, luteinizing hormone, testosterone, and estrogen should be obtained. There are several cases described of persisting human pituitary gonadotropin abnormalities weeks to months after tapering. Persisting human pituitary gonadotropin abnormalities may manifest clinically as sterility or depression, the latter of which should be treated as an anabolic-androgenic steroid-induced mood disorder (see below). Whether these cases may possibly benefit from long-term testosterone supplementation, analogous to agonist therapy for opioid dependence, is unknown and regarded as experimental. In addition, testosterone supplementation would not correct sterility. Instead, medications that stimulate the human pituitary gonadotropin axis such as human chorionic gonadotropin [63], luteinizing hormone, gonadotropin-releasing hormone [99], and estrogen blockers [85, 93] may be required. These latter hormones are also used illicitly [89]. Anabolic-androgenic steroid withdrawal shares characteristics with other endocrine withdrawal syndromes [36].

Anabolic-Androgenic Steroid Dependence

Treatment of anabolic-androgenic steroid dependence is subject to the same challenges as addiction therapy in general. Users often fail to appreciate the adverse consequences of their

use and/or overvalue the perceived benefits of their use. Thus, they lack motivation to stop using. Motivational interviewing and motivational enhancement therapy may be indicated for these cases. For individuals whose dependence is associated with intolerable withdrawal symptoms that lead to relapse, agonist therapy with testosterone may be considered with an endocrine consult. Agonist therapy has the advantages of replacing illicit drugs of unknown contents with pharmaceutical-grade medication that is injected by a nurse or doctor every 2–4 weeks during an office visit. Unfortunately, there are no controlled trials of any of these approaches.

In approaching the psychological aspects of treatment, several differences from other drugs of abuse are important to consider. One difference between anabolic-androgenic steroid-dependent individuals and many other addicts is that getting high is not the predominant goal of using anabolic-androgenic steroids (even though anabolic-androgenic steroid users may have used other substances to get high). Instead, the goals of using anabolic-androgenic steroids are very culturally congruent with American values: to be bigger, better, competitive, and a winner. Reaching such goals requires hard work, discipline, and delayed gratification whether or not one uses anabolic-androgenic steroids. Accordingly, anabolic-androgenic steroids are used to align with, not escape from, mainstream societal values.

Another difference is that anabolic-androgenic steroid users are more likely than other individuals with substance use disorders to be preoccupied with their bodies and physical attributes as a source of identity and self-esteem. Their goals, daily activities, and ways of coping with interpersonal conflicts will likely reflect their being a physical presence in the world. This is not to minimize anyone's intellectual abilities. Rather, it is to highlight that a reliance (or over-reliance) on physical attributes, and anything which interferes with that, may be expected to emerge as a therapeutic issue. The livelihood and self-esteem of professional athletes, bodybuilders, male models, etc., depend on it. While this is a crucial difference, it has some similarity to what is expected of other addicted individuals—that they let go of a substance and sometimes a lifestyle on which they have come to depend and value highly.

Physical attributes can refer to appearance or athleticism. For individuals focused on appearance, Pope et al. [76] and others [14, 35] have drawn deserved attention to the underlying body image distortion that can drive anabolic-androgenic steroid use. The struggle to get bigger, no matter how big one already is, has been referred to as "reverse anorexia nervosa". Later, the term, "body dysmorphic disorder", was coined by Pope and colleagues [76] and is a preferred descriptive, because distorted body image, not disordered eating, is at the core of the disorder (even though anabolic-androgenic steroid use has been linked to disordered eating [73]). While using anabolic-androgenic steroids for their myoactive effects is a crucial difference between anabolic-androgenic steroid users and other substance users, it bears a resemblance to addicted individuals who use substances to overcome and self-medicate social anxiety, depression, and chronic pain as a step toward functioning better, not worse, in our society. As with other individuals, the original goals are important to understand and manage in other ways, but this only works well when the addiction itself is treated.

Anabolic-Androgenic Steroid-Induced Mood Disorder

Anabolic-androgenic steroid-induced mood disorder may resemble mania during episodes of use and depression during episodes of withdrawal. The cycling of mood states can resemble bipolar disorder, and parallel the cycling on and off the anabolic-androgenic steroids. Acute mania is best treated with antipsychotic medication, but mood stabilizers are not necessary when individuals are willing to stop using anabolic-androgenic steroids unless an

independent mood disorder with bipolar features co-occurs. Whether a mood stabilizer would normalize bipolar-like symptoms for those who resist stopping anabolic-androgenic steroids is not known.

For individuals diagnosed with major depression who have no history of manic or hypomanic episodes (whether or not anabolic-androgenic steroid induced), antidepressant medication is indicated. For depressed individuals with a history of manic or hypomanic episodes that were only anabolic-androgenic steroid induced, then antidepressant therapy should be initiated cautiously and monitored closely. Whether anabolic-androgenic steroid-induced mania or hypomania predicts antidepressant-induced mania or hypomania is unknown. There is anecdotal case-report data that anabolic-androgenic steroid-induced depression can be treated successfully with selective serotonin reuptake inhibitors [58]. For individuals who do not respond to an adequate trial with selective serotonin reuptake inhibitors and who also have below-normal testosterone levels in the morning, consideration may be given to augmentation with testosterone gel [75]. Another approach involves short-term use of human growth hormone [31]. Suicides have been reported in anabolic-androgenic steroid users especially during withdrawal [72], and safety must be prioritized, including hospitalization when needed.

While medication can address the biological aspects of depression, anabolic-androgenic steroid users may also feel depressed in response to losing momentum with their training activities. Individuals cannot be expected to achieve or maintain the peak physical progress they made on anabolic-androgenic steroids with training and diet alone. Thus, they may feel smaller and weaker from losing muscle size and strength, which can contribute to depression. Individuals may need guidance in setting realistic expectations for themselves and in balancing their lives with other enjoyable activities that do not depend on muscle size and strength. This may entail a similar kind of lifestyle change that other individuals with addiction need to make in order to stay clean and sober. Alternative social supports and sources of gratification is a common theme in addiction treatment. In addition to selective serotonin reuptake inhibitors, cognitive behavioral therapy that challenges body image distortions may also help to alleviate depression in individuals with muscle dysphoria.

Anabolic-Androgenic Steroid-Induced Psychotic Disorders

Anabolic-androgenic steroid-induced psychotic disorder may require hospitalization for safety reasons and to insure abstinence. Treatment includes cessation of anabolic-androgenic steroid use and the temporary use of antipsychotic medication. With proper treatment, psychosis can be expected to remit within a few weeks.

Conclusions

Anabolic-androgenic steroids, which consist of testosterone, selected metabolites, and synthetic derivatives with cholesterol-like chemical structures, have both anabolic (muscle-building) and androgenic (masculizing) properties and legitimate medical uses. Their use is endemic among some groups of bodybuilders and male athletes, who take supratherapeutic doses (10–100 times therapeutic doses) primarily for their anabolic effects. By 1990, an estimated 1 million Americans had tried anabolic-androgenic steroids. Non-medical or illicit use is characterized by combining (“stacking”) multiple forms, including oral and intramuscularly injected preparations, as well as taking various other substances to augment their effects, ameliorate side effects, or escape detections. Use may occur in cycles, with drug-free intervals between cycles. A variety of adverse medical consequences are known, involving the endocrine, cardiovascular, hepatic, and central nervous systems. Psychiatric

effects result from the neurobiological actions of anabolic-androgenic steroids and include mood disorders, psychotic disorders, aggressive and impulsive behaviors with suicide and homicide as extreme outcomes, and addiction. Addiction treatment should account for both similarities and differences in taking anabolic-androgenic steroids when compared with classical addictive drugs such as stimulants, opioids, and alcohol, but controlled trials are lacking to guide clinical practice.

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Caffeine

Jack E. James

Contents

Introduction

Of the numerous psychoactive compounds that humans ingest, none is more popular than caffeine. Indeed, caffeine is unusual amongst psychoactive compounds in being part of the daily diet of most people. With more than 80% of people worldwide consuming caffeine daily [95], current usage transcends almost every social barrier, including age, gender, geography, and culture. The popularity of caffeine exceeds that of any other psychoactive substance, whether it is nicotine, alcohol, or illicit drugs. Caffeine occurs naturally in a number of plant species, where it serves as a toxin to defend against herbivores. A common but erroneous belief, sometimes implied in advertisements for caffeine products, is that caffeine has always been widely present in the human diet. In fact, it was not until after European colonization in the seventeenth and eighteenth centuries that caffeine

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_26,

products, previously unavailable to most people, became widely accessible. That is, the ubiquitous presence of caffeine in the human diet is a phenomenon of fairly recent origin.

The aim of this chapter is to provide an overview of caffeine and its use, with particular attention being given to consequences for health and well-being. In that context, the emphasis throughout is on dietary use, taking account of both acute and chronic effects. Following relevant background, including mention of the main sources of caffeine and prevailing patterns of usage, attention is given to the pharmacology of caffeine, including the main mechanism of action and the key processes of physical dependence and tolerance. This is followed by a discussion of the psychopharmacology of caffeine, with particular attention being given to effects on psychomotor performance and mood, and the processes of withdrawal and withdrawal reversal. The remainder of the chapter deals mostly with the health consequences of dietary caffeine, beginning with mental health and well-being. That section is followed by two separate sections dealing with physical health, the first of which is concerned with cardiovascular disease, and the second with cancer, maternal use, and potential adverse interactions between caffeine and other drugs. Questions as to whether caffeine is addictive and whether there is a level of consumption that may be considered safe are examined, and processes for reducing and quitting caffeine consumption are reviewed. In the section thereafter, attention is given to emerging interests in potential health benefits of caffeine products, especially in relation to Type 2 diabetes mellitus and Parkinson's disease, and the growing interest in compounds other than caffeine in caffeine beverages. The section preceding the conclusions considers processes that threaten the integrity of caffeine science, a topic that to date has received far too little attention.

Main Sources of Caffeine and Patterns of Consumption

The main dietary sources of caffeine are tea and coffee beverages, and increasingly, soft drinks (e.g., colas) and energy drinks. The tea plant is indigenous to regions of China, South Asia, and India. Written accounts in China of tea leaves being used to brew a beverage date to as early as 350 A.D., and by about 600 A.D. tea had been introduced to Japan from China. It is unclear, however, to what extent tea was consumed by the general population of either country during these early periods. In the seventeenth century, the Dutch introduced tea to Europe and America, and today tea is cultivated commercially in about 30 countries. Coffee is indigenous to Ethiopia from where it was transported for cultivation to Arabia in the fifteenth century. By the early sixteenth century, the practice had been established in the Islamic world of extracting caffeine by infusing ground roasted beans. The Dutch brought coffee plants to Europe in the early seventeenth century, and established plantations in the Dutch East Indies. Subsequent colonization by other European powers led to new and extensive plantations being established in the West Indies, Latin America, Africa, and India.

By the late-eighteenth century, coffee replaced tea in popularity in the United States, and today coffee is the main source of caffeine globally. Tea continues to be consumed more widely, but qualifies as the second main source because its caffeine content is generally lower than that of coffee. Other common sources of caffeine include cocoa and chocolate (in both solid and beverage form), but the caffeine content of these is generally low and represents a negligible fraction of the total amount of caffeine consumed. In addition, although the daily intake of caffeine from sources specific to particular regions (e.g., maté in parts of South America) may be substantial for individual consumers, the overall intake from such sources is small relative to total global consumption of the drug. Similarly, some medications, both prescribed and over-the-counter, contain as much as 200 mg (approximately 2–4 cups of coffee or tea) per tablet or capsule, and could be an important (even the main) source of caffeine for some individuals. For the general population, however, caffeine-containing medications are typically taken intermittently, or not at all,

thereby contributing little to total population caffeine intake. Notwithstanding variations in per capita consumption between geographic regions, intake for the majority of consumers ranges from about 200 to 400 mg of caffeine per day (the approximate equivalent of 2–6 cups of coffee or tea per day).

Caffeine soft drinks are an increasingly important source of the drug, and often the main source for children. The more recently developed so-called "energy" drinks are also increasing in importance as a source of caffeine for young people. Whereas the caffeine in sodas and energy drinks sometimes partly derives from plant products involved in manufacture (e.g., cacao, cola nut, guarana), most of the caffeine content of such drinks is added in refined form. That is, these products, which are targeted primarily at children and adolescents, are explicitly designed to be psychoactive. The seeming inexorable growth in the consumption of caffeine by children has become a cause for concern in its own right (e.g., [72]) as well as giving rise to concerns that caffeine in the form of sodas and energy drinks may serve as a gateway to increased use of other drugs.

Although consumption patterns relating to the various main sources of caffeine may change during the lifespan (e.g., an individual may switch from drinking sodas during childhood to coffee in adulthood), exposure to caffeine is essentially lifelong for the majority of people. Indeed, the first exposure for most people precedes birth. Caffeine crosses the placenta [17, 236], and because most women consume caffeine while pregnant, the majority of newborns show pharmacologically active levels of plasma caffeine [36]. Exposure typically continues during childhood, with patterns of use tending to consolidate during adolescence and early adulthood. Thereafter, usage tends to stabilize, generally undergoing little change for the remainder of life [95]. The unparalleled prevalence of caffeine use introduces multipliers in relation to the possible impact of the drug. At the individual level, lifelong use could lead to effects accumulating over the lifespan. Furthermore, considering the near-universal use of caffeine, individual effects, even if small, could have a substantial cumulative impact when assessed across entire populations.

Pharmacology of Caffeine

Caffeine belongs to a family of purine derivative methylated xanthines often referred to as methylxanthines or merely xanthines. At room temperature, caffeine is a white odorless powder with a bitter taste [238]. Caffeine was first isolated from green coffee beans in 1820 by Ferdinand Runge in Germany, and later was found to be present in a variety of other species (e.g., tea, mate, cacao). Figure 1 shows the structure of caffeine (1, 3, 7-trimethylxanthine) and the three dimethylxanthine primary metabolic products of caffeine in humans. Following oral ingestion, caffeine is rapidly absorbed into the bloodstream from the gastrointestinal tract [7]. Approximately 90% of the caffeine contained in a cup of coffee is cleared from the stomach within 20 min [25], and peak plasma concentration is typically reached within about 40–60 min [177].

Once ingested, caffeine is readily distributed throughout the body, and the concentrations attained in blood are highly correlated with those found in the brain, saliva, breast milk, semen, amniotic fluid, and fetal tissue [95]. The drug has an elimination half-life of about 5 h in adults [171], and typical consumption patterns of 3–4 doses (e.g., cups) per day, result in plasma concentrations that remain at pharmacologically active levels for most of the waking hours. In adults, caffeine is virtually completely transformed by the liver, with less than 2% of the ingested compound being recoverable in urine [214]. Although the beverages and foods that contain caffeine may have other constituents (e.g., sugar, milk) that possess nutritional value, it should be noted that caffeine itself has no nutritional value.

Main Mechanism of Action

Caffeine exerts a variety of pharmacological actions at diverse sites, both centrally and

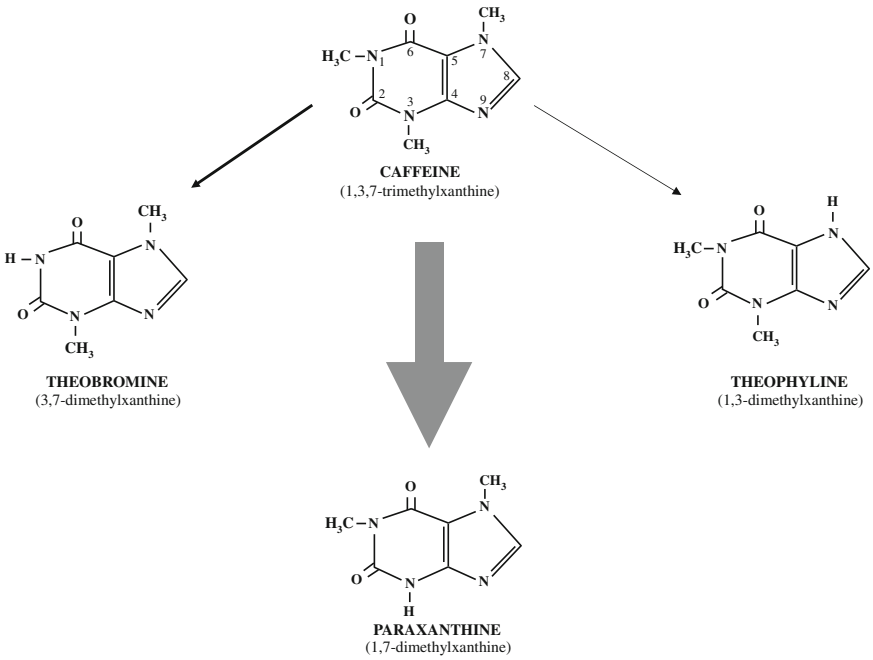

Fig. 1 Caffeine and its dimethylated metabolites in humans (*arrow widths* indicate approximate relative proportions of the metabolites in plasma)

peripherally, which are generally believed to be due mostly to competitive blockade of adenosine receptors [37]. Adenosine is a neuromodulator that acts on specific cell-surface receptors distributed throughout the body [19, 151, 197, 244]. Due to similarities in the molecular structure of caffeine and adenosine, caffeine occupies adenosine receptor sites, with A_1 and A_{2A} receptors appearing to be the primary targets. Table 1 summarizes some of adenosine's main actions, which are generally to inhibit physiological activity. At typical dietary levels of intake, caffeine blocks adenosine receptors, producing effects broadly opposite to those summarized in Table 1 [14, 20, 53, 135]. It appears, also, that A_1 and A_{2A} receptors may interact in functionally important ways with dopamine receptors [44, 59]. In particular, A_{2A} receptors may be involved in the control of the dopaminergic signaling system essential to motor control [31]. In addition, caffeine has been reported to stimulate neuroendocrine activity, especially the catecholamine stress hormones of epinephrine and norepinephrine (e.g., [129]). Increases in serum cortisol and/or urinary cortisol metabolites have also been reported [123, 142, 143, 173, 174]. However, findings have not been entirely consistent in that some investigators have found cortisol levels to be unresponsive to caffeine [121, 165]. It may be that the inconsistencies indicate that the typical challenge of about 250 mg (2–3 cups of coffee) represents a "borderline dose" to which some people may be unresponsive. For example, in one study, 250 mg of caffeine had no effect, whereas 500 mg increased plasma cortisol levels [216].

Table 1 Some acute biological effects of adenosine[a]

Biological system	Effect
Central nervous system	Decreased transmitter release, sedation
Cardiovascular	Dilated cerebral and coronary blood vessels
Renal	Antidiuresis
Respiratory	Bronchoconstriction
Gastrointestinal	Inhibition of acid secretion
Metabolic	Inhibition of lipolysis

[a]By blocking adenosine receptors, caffeine has effects broadly opposite to those summarized above

Physical Dependence

Repeated use of caffeine, such as occurs in the context of dietary use, generally leads to the development of physical dependence, evidenced by the appearance of behavioral, physiological, and subjective "withdrawal" effects provoked by abrupt cessation of use [111]. Although incompletely understood, the mechanism responsible for caffeine physical dependence is believed to involve adenosine. Repeated exposure to caffeine, including dietary use, is thought to result in an increased number of adenosine receptors and/or enhanced affinity, resulting in hypersensitivity during abstinence [14, 168, 242]. Sleepiness, lethargy, and headache are common symptoms of caffeine withdrawal in humans [40, 58, 80, 97, 122, 127, 172, 218, 220, 234], and cessation of as little as 100 mg (1 cup of coffee) per day, and possibly considerably less can produce symptoms (e.g., [140, 207]). These may be felt within about 12–16 h, with a peak at around 24–48 h, generally abating within 3–5 days, and only infrequently extending for up to 1 week [67, 81, 82]. Notably, studies show that decreases in psychomotor performance (not necessarily discernible to the individual) are detectable after as little as 6–8 h since caffeine was last ingested [73].

Tolerance

Drug tolerance refers to the progressive reduction in responsiveness which sometimes accompanies repeated exposure to a drug. It is evidenced by a decline in efficacy, whereby the same drug dose has less effect following repeated use or an increased dose is required to produce effects previously experienced. Although caffeine tolerance has been shown in relation to the locomotor stimulant effects of the drug in rats [46, 79], there have been relatively few empirical demonstrations of caffeine tolerance in humans. One focus of attention in relation to caffeine tolerance in humans has been the drug's cardiovascular effects [34, 90, 91], which it is widely believed undergo tolerance. The most often (and frequently, only) cited source for the claim of hemodynamic tolerance is a study by Robertson and colleagues [181], which is widely misquoted as having demonstrated complete hemodynamic tolerance to dietary caffeine. James [89] (pp. 111–113) has shown that the Robertson et al. [181] study did not demonstrate complete tolerance to caffeine, and that due to its many methodological shortcomings the study could not have demonstrated complete tolerance. On the contrary, as discussed in more detail below, empirical evidence from diverse sources converges to show that blood pressure remains reactive to the pressor effects of caffeine despite repeated exposure such as that which occurs when caffeine is part of the daily diet (e.g., James [90, 91, 99]).

Overall, it appears unlikely that complete tolerance occurs in relation to most effects arising from typical patterns of caffeine consumption. Importantly, the response magnitude to successive doses of the drug is generally inversely proportional to plasma caffeine level [211, 212]. Also, it is notable that overnight abstinence, which characterizes usual patterns of consumption, results in almost complete depletion of systemic caffeine by early morning [138, 171, 201]. Several lines of inquiry suggest that the pattern of diurnal depletion of systemic caffeine experienced by most consumers contributes to tolerance, if it occurs at all, typically being partial rather than complete. Indeed, the very fact that many hundreds of published experiments have reported significant caffeine-induced behavioral, physiological, and subjective effects provides strong evidence that usual patterns of consumption do *not* produce complete tolerance. Most participants in such experiments have been typical caffeine consumers who arrive at the experimental laboratory following a brief period of abstinence. Notwithstanding the brevity of the typical period of abstinence (e.g., overnight) employed in experimental studies of the acute effects of caffeine, participants are generally observed to be caffeine responsive. As is discussed in the following section, some

caffeine-induced responses (especially enhanced performance and mood) are attributable to withdrawal reversal. However, other responses, particularly increased blood pressure, are not attributable to withdrawal reversal. By definition, any observed caffeine-induced effects not attributable to withdrawal reversal provide proof positive that tolerance, if it has developed at all, cannot have been complete.

Psychopharmacology of Caffeine: The Critical Processes of Caffeine Withdrawal and Withdrawal Reversal

The earliest systematic examinations of the psychopharmacology of caffeine were conducted about a century ago [77, 78]. The strong consensus for most of the intervening period has been that caffeine is a stimulant capable of enhancing aspects of human psychomotor performance and mood. In recent years, however, that traditional view has been essentially disproved. Recent advances in knowledge about the dynamics of caffeine withdrawal and withdrawal reversal have radically transformed our understanding of caffeine psychopharmacology. In a typical study, behavioral and psychological outcomes are measured in healthy volunteers before and after double-blind administration of caffeine and placebo, and (compared with baseline and placebo) changes have often been reported in post-caffeine outcomes. This has been particularly evident in studies of performance and mood, wherein it has often been concluded that caffeine has enhancing properties. However, a critical appraisal of the typical study design shows that the findings yielded by such studies are, at best, ambiguous [92, 94, 105].

Paralleling the time-honored practice of placebo-controlled studies of medications, caffeine is typically withheld for a period prior to testing for effects, with the aim of ensuring all participants are equivalent in systemic drug levels at time of testing. Such efforts to achieve experimental control appear especially relevant to the assessment of caffeine effects, because the drug is used daily by most people. Typically, caffeine is consumed in separate portions throughout the day, with fewer portions consumed later in the day, followed by overnight abstinence [95]. With the half-life of caffeine in healthy adults being approximately 5 h [171], overnight abstinence usually leads to complete or near-complete elimination of systemic caffeine by early morning [138, 139]. Consequently, when employing the placebo-controlled paradigm, caffeine researchers have frequently made use of naturally occurring overnight abstinence by asking participants to forgo their usual morning caffeine beverage prior to laboratory testing.

What has not been fully appreciated until recently is that, having avoided caffeine since the evening before, study participants are generally entering the early stages of caffeine withdrawal by the time they are tested in the laboratory (typically, at least 12–14 h since caffeine was last ingested) (see [92] and [105]). As mentioned above, habitual use of caffeine produces physical dependence, evidenced by the appearance of readily measurable withdrawal symptoms following periods of abstinence (e.g., Juliano and Griffiths [111]). Thus, the crucial question is: To what extent do effects (e.g., enhanced performance and mood) generally attributed to caffeine represent genuine net effects of the drug or reversal of withdrawal effects induced by short periods of abstinence? [92]

Performance and Mood

The fact that caffeine is consumed daily by most people as part of a "normal" diet presents formidable methodological obstacles when trying to accurately isolate the net effects of the drug. Although the problem was largely ignored for decades, systematic attempts have begun to tackle key methodological challenges posed by caffeine withdrawal and withdrawal reversal. Approaches have varied, but generally fall into three broad categories, consisting of studies that compare consumers and low/non-consumers, pre-treatment and ad lib

consumption studies, and long-term withdrawal studies [95, 105]. The first two approaches (studies comparing consumers with low/non-consumers and pre-treatment/ad lib consumption studies) have been shown to involve substantial limitations (for a discussion see James [95] and James and Rogers [105]). In contrast, the third approach (long-term withdrawal) has proven successful. This has entailed taking the core features of the traditional drug-challenge paradigm, with its attendant strengths of double blinding and placebo control, and extending them to include alternating periods of daily caffeine use and non-use (abstinence).

Table 2 summarizes the core design features of an experimental paradigm employed successfully by James and colleagues (e.g., James [88, 90, 91, 97] and Keane et al. [117]) to elucidate caffeine's net effects using "long-term" withdrawal. During caffeine phases of that paradigm, participants ingest the approximate equivalent of 1 cup of coffee three times daily, thereby simulating the typical population pattern of caffeine consumption. The protocol employs six consecutive days of placebo/caffeine intake to achieve stability of responding before "challenging" participants on the 7th day of each alternating 1-week period. The 1-week time frame was chosen on the grounds that studies of caffeine tolerance in humans have generally found that effects plateau within 3–5 days of continuous use [34, 90, 91, 181]. In addition, there is a strong body of evidence showing that withdrawal effects generally abate within a similar time frame of 3–5 days (e.g., [66, 81]). The full research design, as shown in Table 2, offers the substantial benefit of being able to examine and compare the separate acute and chronic effects of caffeine in the one experiment. An abridged version of the design has also been used, consisting of the "PP" and "CC" conditions outlined in Table 2 without the "PC" and "CP" conditions (e.g., James and Gregg [100, 101] and James et al. [102]). While not elucidating the more detailed processes of withdrawal and tolerance, the abridged design allows key questions concerning caffeine's net effects to be addressed.

Long-term caffeine withdrawal studies have provided strong support for the withdrawal reversal hypothesis in relation to performance and mood [105]. That is, overnight caffeine abstinence has been found to be detrimental to performance and mood, with these adverse effects being removed when caffeine is re-ingested (restoration due to reversal of withdrawal effects). Importantly, recent studies have yielded consistent evidence of caffeine having little or no net beneficial effect on performance and mood under conditions of sustained caffeine use versus sustained abstinence [97, 101, 102]. Several other studies, which may not all strictly

Table 2 Summary of a double-blind placebo-controlled crossover protocol incorporating alternating periods of "long-term" caffeine exposure and abstinence[a]

Week	Run-in days (days 1–6)	"Challenge" (day 7)	Condition (abbreviation)	Effects revealed by challenge
1	Placebo	Placebo	PP	Sustained abstinence (i.e., caffeine "wash out"). Serves as a caffeine-free baseline.
2	Placebo	Caffeine	PC	Acute challenge. When compared with PP and CC, reveals the presence of tolerance.
3	Caffeine	Placebo	CP	Acute abstinence. When compared with PP and CC, reveals the presence of withdrawal.
4	Caffeine	Caffeine	CC	Habitual use. When compared with PP, reveals the net effects of habitual consumption.

PP Placebo ingested for 6 consecutive days followed by 1 day of placebo challenge, *PC* 6 days of placebo followed by 1 day of caffeine challenge, *CP* 6 days of caffeine followed by 1 day of placebo challenge, *CC* 6 days of caffeine followed by 1 day of caffeine challenge.

[a]Design originally described by James [90, 91, 97], versions of which have been employed in subsequent studies (e.g., James and Gregg [100, 101], James et al. [102], and Keane et al. [117])

qualify as "long-term" studies, have reported similar results in relation to performance and mood in adults [98, 110, 180, 184, 185] and children [72].

Sleep and Wakefulness

Former strong beliefs about caffeine being capable of enhancing psychomotor performance and mood are matched by equally strong beliefs that caffeine is effective in reversing negative effects of sleep loss [103]. Until very recently, however, studies of caffeine and sleep failed to take account of the processes of withdrawal and withdrawal reversal. Employing the abbreviated version of the experimental paradigm summarized in Table 2 (i.e., "PP" versus "CC" as defined in the table), James et al. [102] examined the effects of dietary caffeine in healthy volunteers who alternated weekly between placebo and caffeine and who were either rested or deprived of more than 50% of their usual nighttime sleep on the evening before testing. Confirming previous studies, caffeine was found to have no significant net enhancing effects for either performance or mood when participants were rested, while also having no net restorative effects when performance and mood were negatively affected by sleep restriction. Indeed, James and Gregg [101] found that caffeine exacerbated the marked adverse effects of sleep restriction on mood.

Similarly, after controlling for caffeine withdrawal effects, Rogers et al. [185] found that cognitive performance was unimproved by caffeine in participants who were sleep restricted. Acute (overnight) caffeine withdrawal was found to impair performance on tasks requiring sustained attention, and subsequent caffeine intake merely prevented further deterioration in performance (withdrawal reversal). In contrast, the significantly better levels of performance on the same tasks shown by long-term (3 weeks) withdrawn participants were not improved by caffeine. Additionally, acute caffeine withdrawal had a variety of negative effects on mood. More recently, Keane et al. [117] examined the effects of caffeine on patterns of electroencephalographic activity in a rare example of a study of electroencephalography in which caffeine withdrawal and withdrawal reversal were controlled. While again finding little evidence of positive stimulant effects, Keane et al. [117] found some similarities in effects on brain activity following caffeine ingestion (challenge) and acute caffeine withdrawal. As such, these findings are consistent with results from studies of performance and mood in which caffeine withdrawal and withdrawal reversal had been controlled. That is, rather than having positive stimulant effects, a change in drug state, whether in the form of acute caffeine challenge or acute caffeine withdrawal, may disrupt normal electrophysiological activity in the brain, which may in turn be the substrate for the observed negative effects on performance and mood.

The terms "sleep" and "wakeful" lack precise definition, and are sometimes used as if they were exact antonyms of one another. Possibly everyone, however, has had the experience of being both sleepy and wakeful (i.e., tired but unable to sleep, for example, during periods of acute worry). This should not be surprising, since it is unlikely that a single mechanism controls the processes of sleepiness and wakefulness. As such, caffeine may directly interfere with an aspect of sleep (e.g., block receptors in the adenosine mechanism) and thereby forestall sleep without necessarily or appreciably benefiting wakefulness. At the same time, sleepiness is a reliable effect of even brief periods of caffeine abstinence.

One source of confusion concerning caffeine's putative anti-soporific effects is the fact that withdrawal-induced sleepiness is reversible by ingesting caffeine, thereby creating the illusion that caffeine is effective in "stimulating" wakefulness and overcoming sleepiness. In reality, the overall effect of caffeine on the sleep cycle is likely to be disruptive, involving an increased risk of caffeine-induced sleep delay and withdrawal-induced periods of sleepiness. The former, caffeine-induced sleep delay, is possibly largely avoided by the majority of consumers who typically do not ingest caffeine after early evening. In contrast, although

sleepiness induced by caffeine withdrawal is possibly widely experienced, most people are probably unaware of it (i.e., unaware of caffeine withdrawal as a cause of daytime sleepiness). Indeed, there is a strong possibility, yet to be verified, that sleepiness induced by caffeine withdrawal is a common, though largely unrecognized, cause of fatigue-related traffic and industrial accidents.

Mental Health and Well-Being

Major systems of medical and psychiatric diagnosis give formal recognition to "disorders" of psychological function arising from caffeine misuse, noting that "misuse" in this context includes levels of use falling within the range seen in the general caffeine-consuming population. Since formal diagnoses can only be made after affected persons come to the attention of relevant professionals, it follows that a sizable proportion of the general public may be engaging in caffeine "misuse" even if a formal diagnosis has not been made. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems [252] has a specific diagnostic classification of mental and behavioral disorders due to use of "other stimulants", including caffeine, which includes subcategories of acute intoxication, dependence syndrome, and withdrawal state. Similarly, under the label of caffeine-related disorders, under the broader rubric of substance-related disorders, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision [5] has classifications for caffeine intoxication, caffeine-induced anxiety disorder, and caffeine-induced sleep disorder.

Diagnostic and Statistical Manual of Mental Disorders, *4th Edition, Text Revision*

Considering the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision more specifically, the essential features of caffeine intoxication are shown in Table 3, which cites recent consumption of caffeine and five or more symptoms that develop during, or shortly after, caffeine use. As the name implies, the classification of caffeine-induced anxiety disorder refers to the occurrence of symptoms of anxiety (e.g., nervousness, worry, apprehension) associated with, and believed to be precipitated by, the consumption of caffeine. Caffeine-induced sleep disorder typically refers to insomnia (e.g., increased sleep latency, decreased sleep time, fragmented sleep) provoked by caffeine consumption. However, as explained above, periods of reduced caffeine intake or abstinence can also lead to bouts of sleepiness (hypersomnia). Thus, on the one hand, caffeine-induced sleep disorder refers to nighttime wakefulness, which many people may recognize as having experienced. On the other hand, caffeine-induced sleep disorder also refers to the occurrence of withdrawal-induced daytime sleepiness due to caffeine abstinence or reduced caffeine intake. Again, as suggested above, given that caffeine-induced nighttime insomnia is easily avoided by not consuming caffeine latter in

Table 3 Diagnostic criteria for caffeine intoxication

A. Recent consumption of caffeine, usually in excess of 250 mg (e.g., more than 2–3 cups of brewed coffee).
B. Five (or more) of the following signs, developing during, or shortly after, caffeine use:
(1) Restlessness
(2) Nervousness
(3) Excitement
(4) Insomnia
(5) Flushed face
(6) Diuresis
(7) Gastrointestinal disturbance
(8) Muscle twitching
(9) Rambling flow of thought and speech
(10) Tachycardia or cardiac arrhythmia
(11) Periods of inexhaustibility
(12) Psychomotor agitation
C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder (e.g., an Anxiety Disorder).

Adapted from the American Psychiatric Association [5]

the day or evening, withdrawal-induced daytime sleepiness is possibly a more common occurrence, even if (or possibly because) it is less often recognized by consumers as a symptom of their caffeine use.

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision [5] also makes reference to a more general category of caffeine withdrawal, but refers to it as a syndrome under consideration and not yet a formal diagnosis. As pointed out by James (1997), this is an ironic position, because there is substantially more empirical evidence for the existence of caffeine withdrawal as a specific syndrome, than for any of the accepted caffeine diagnoses. Furthermore, the proposed diagnosis of caffeine withdrawal includes headache as a defining symptom. In reality, headache is a common, though not universal, symptom of caffeine withdrawal (e.g., [101]). By excluding cases of caffeine withdrawal headache not accompanied by other symptoms, and cases in which other withdrawal symptoms (e.g., lethargy, tiredness, irritability) are experienced without headache, the proposed diagnosis of caffeine withdrawal seems bound to lead to under-diagnosis.

The symptoms listed in Table 3 fall into two broad categories considered to be of lesser or greater seriousness. Less serious symptoms include restlessness, nervousness, excitement, insomnia, flushed face, diuresis, and gastrointestinal complaints, and may occur following daily use of as little as 100 mg of caffeine (about 1 cup of coffee). More serious symptoms include muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, and psychomotor agitation, said to occur at levels of intake of 1 gram or more per day. Although substantially above average dietary levels, consumption at this higher level of intake is not rare, possibly involving about 10% of the population. Indeed, Hughes et al. [83] interviewed 162 randomly selected caffeine users and concluded that 7% met the criteria for caffeine intoxication. Among those who had tried to stop caffeine permanently, 24% satisfied the criteria for caffeine withdrawal. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision [5] stipulates that reported symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. These stipulations, however, remain open to interpretation. Thus, of the many caffeine-induced dysphoric effects that are experienced in the population, the relative proportions that fall above and below the threshold of clinical significance remain unknown.

The Epidemiology of Caffeine Disorders

Given what appears to be a relatively low level of awareness of caffeine-induced dysfunction in the general as well as professional communities, there is a strong suspicion that caffeine "disorders" remain substantially undiagnosed despite the existence of formal diagnostic protocols. Moreover, in addition to clinical diagnosis, caffeine ingestion and withdrawal appear to have a variety of other commonplace psychological and behavioral outcomes that can be serious. For example, as well as the possibility that withdrawal-induced sleepiness contributes to fatigue-related accidents, caffeine-induced hand tremor has been found to undermine surgical precision. In a double-blind placebo-controlled crossover study, Urso-Baiarda et al. [229] found that moderate amounts of caffeine had a detrimental effect on microsurgical ability due to the adverse effect of the drug on hand steadiness. Also within a general surgical context, evidence indicates that patients commonly experience perioperative caffeine-withdrawal headache due to the requirement that they fast (and therefore do not receive their usual caffeine intake) prior to anesthesia [41, 57, 162]. Prophylactic administration of caffeine appears to provide a simple and effective remedy [69, 245]. Indeed, the reversal of headache under such circumstances is further evidence of the role of caffeine withdrawal in the development of headache. Findings such as these contribute to the impression that the population prevalence of

caffeine-induced disorders far exceeds that which would be implied by the frequency with which such problems are diagnosed in clinical settings.

Dietary Caffeine and Physical Health: Cardiovascular Disease

When considered in totality, the large and diverse body of relevant scientific literature is conclusive in pointing to adverse acute effects of caffeine on cardiovascular function, especially blood pressure. Though evidence of chronic effects is less conclusive (for reasons outlined below), the available evidence nevertheless provides strong grounds for concluding that dietary caffeine is a significant factor in the development of cardiovascular disease. The extent of the evidence is such as to suggest the need for primary prevention at a population-wide level, including appeals to consumers to avoid caffeine in the interests of cardiovascular health. Such action, however, has been largely absent and it is important to examine possible reasons. Accordingly, this section provides an overview of relevant experimental and epidemiologic findings, and considers reasons why the evidence may not have caught the attention of health authorities to the extent that it should. Two main reasons for this neglect, considered below, appear to be: confusion regarding the epidemiology of caffeine and cardiovascular disease due to exposure misclassification, confounders, and possible misunderstanding of putative threshold effects; and the belief that habitual caffeine use leads to the development of tolerance to the cardiovascular effects of the drug.

Concerns for cardiovascular health in the context of dietary caffeine have a firm foundation in demographics. Cardiovascular disease is the major cause of mortality and morbidity in the developed countries of the world accounting for approximately half of all deaths [233, 250, 251]. It is expected also that within the near future cardiovascular disease will be the major cause of death and disease throughout much of the developing world [169, 182, 183]. As well as being of high prevalence, cardiovascular diseases are generally of long latency, and have complex multifactorial causation involving lifestyle variables including diet. As mentioned above, the prevalence of dietary caffeine is extremely high and essentially lifelong. In that context, it is especially noteworthy that adenosine has an important role in the regulation of cardiovascular function as well as being the main mechanism of action for caffeine, thereby providing strong biological plausibility for a possible link between the two. Blood pressure level is of particular concern, because it is the single most important predictor of cardiovascular disease [156, 182], and compared with several other key indices of cardiovascular function blood pressure is particularly responsive to dietary caffeine.

Acute Effects of Caffeine on Blood Pressure

It has been shown conclusively that caffeine increases blood pressure acutely, with reports generally indicating increases in the range of 5–15 mg Hg systolic and 5–10 mg Hg diastolic. This acute pressor effect occurs across a wide age range, with effects lasting for up to several hours in healthy men and women (see James [95, 99] for a discussion). In addition, the pressor effect of caffeine is additive to that of cigarette smoking [54, 104, 210], is at least additive (e.g., France and Ditto [52], Greenberg and Shapiro [64], James [88, 90], and Lane and Williams [129]) and may be synergistic (e.g., [3, 128]) to the pressor effect of psychosocial stress, and is evident in persons with hypertension as well as normotensives (e.g., [71, 200]). Furthermore, studies show that caffeine produces acute increases in aortic stiffness and enhances wave reflection, both of which contribute to increased blood pressure as well as being independent risk factors for cardiovascular disease [116, 149, 239, 240]. Again, these effects have been observed in persons who are

normotensive as well as those being treated for hypertension, and appear to be synergistic to similar effects of smoking [241].

Epidemiology of Caffeine and Cardiovascular Disease

More than 100 large epidemiologic studies in more than a dozen countries have reported data on the relationship between dietary caffeine and cardiovascular function, morbidity and/or mortality. Taken as a whole, epidemiologic findings suggest that dietary caffeine is detrimental to cardiovascular health [99]. However, one feature of this large literature is the many inconsistencies in the reported findings. The response of some commentators and reviewers to this inconsistency has been to dismiss concerns about caffeine, a response that is neither logical nor consistent with overall findings. Dismissing concerns is particularly unjustified in light of the large and consistent body of evidence from experimental studies. By their nature, experimental studies afford a greater level of control than epidemiologic approaches. Indeed, by integrating experimental and epidemiologic findings, the former help to clarify inconsistencies in the latter.

Considered comprehensively, the experimental and epidemiologic findings raise concerns over the implications of dietary caffeine for population cardiovascular health. The assumption that clear consistency should have emerged in the epidemiologic findings, if caffeine were having substantive effects on blood pressure and other indices of cardiovascular function, fails to take account of the many methodological shortcomings in the epidemiologic studies published to date. In particular, there are grounds for concluding that the many "null" reports (i.e., non-significant associations) in the epidemiologic literature on caffeine and cardiovascular disease reflect a high rate of Type II error (i.e., failure to observe a real effect when one exists).

Misclassification

A major shortcoming of many studies is poor measurement of the key "exposure" variable, namely, caffeine consumption. Although this shortcoming has long been the subject of criticism (e.g., [61, 89, 198]), relatively little improvement or innovation has been undertaken by epidemiologists over the past three decades to try to overcome the problem. Although at least half of the relevant epidemiologic studies conducted to date collected blood samples (mostly for the purpose of measuring serum lipid levels), none took the obvious next step of measuring systemic levels of caffeine or its metabolites [99]. As such, use has not been made of the fact that good estimates of dietary caffeine levels can be obtained by analyzing plasma and saliva caffeine (or paraxanthine, the major metabolite in humans) using high-performance liquid chromatography (e.g., [1]) or enzymeimmunoassay techniques [100].

Furthermore, although dietary caffeine levels can be measured reliably using detailed self-report inventories [107], many studies have employed poor self-report protocols and have shown little regard for the reliability of the measurements employed. Since the inadequate methods frequently used are likely to have produced largely undifferentiated (i.e., random) measurement error, the effect in many epidemiologic studies will have been to underestimate the true association between caffeine and cardiovascular disease or to report "no association". Thus, while overall epidemiologic findings suggest that dietary caffeine has a modest detrimental effect on cardiovascular health, actual effects may be larger considering the often imprecise methods that have been employed [95, 96, 99].

Confounding in Epidemiologic Research

A frequent erroneous observation about the epidemiology of caffeine and cardiovascular health is that much of the research has ignored the influence of confounders. This "confounder myth" [95] asserts that reports of significant positive

correlations between caffeine consumption and cardiovascular disease are the result of failure to control confounders, especially cigarette smoking. As well as being a cardiovascular risk factor, smoking has been found to be positively correlated with caffeine use (e.g., [119, 167, 226]). The myth, however, arises from the fact that, for the past three decades, epidemiologic studies of caffeine have routinely controlled for cigarette smoking. Excepting one or two early studies, virtually all of the literature reporting a positive correlation between caffeine consumption and cardiovascular disease controlled for the influence of cigarette smoking.

In the context of population studies there is always a risk of unanticipated influence of an as yet unidentified confounder. The level of such risk is probably lower in epidemiologic studies of dietary caffeine and health than in many other areas, because the list of potential confounders controlled for in caffeine studies (including those that reported positive findings) is very long, including: age, gender, cigarette smoking, alcohol consumption, body mass index, dietary factors, serum cholesterol, blood pressure, medical history, use of oral contraceptives, family history of heart disease, physical activity, personality, region of residence, education level, and religion [89]. Indeed, rather than being inadequately controlled for confounder effects, there has probably been a tendency toward overadjustment for confounders in epidemiologic studies of caffeine (e.g., [120, 190]). In particular, findings have frequently been adjusted for blood pressure and cholesterol, which may be caffeine-related and coffee-related causal pathways in their own right. Thus, as with measurement error, the likely effect of overadjustment for confounder effects would be to increase the risk of Type II error; that is, to underestimate the actual strength of the association between caffeine consumption and cardiovascular disease.

Threshold Effects

It is common in epidemiologic studies of caffeine to stratify according to level of reported caffeine use. A proportion of studies adopting that approach have reported the existence of a "threshold", whereby a positive association is observed in consumers reporting higher levels of intake (e.g., "6 or more cups of coffee" per day) but not in consumers reporting lower levels of intake. Although such reports may be reassuring for "average" consumers, the notion of an actual threshold in this context is not persuasive. Experimental studies of caffeine have consistently found the acute hemodynamic effects of caffeine to be proportional to systemic caffeine level (e.g., [211, 212]). In the absence of other intervening variables, this dose-response effect would be expected to result in a relatively continuous relationship between caffeine and cardiovascular health outcomes rather than one marked by a threshold. Unreliability in the data, especially due to imprecise measurement of dietary exposure (as outlined above), is a more likely explanation of the threshold effects sometimes reported in epidemiologic studies of caffeine and population cardiovascular disease.

Epidemiology of Caffeine and Blood Pressure

As part of the much larger body of epidemiologic research on caffeine and cardiovascular disease, James [99] identified 18 population studies that were specifically concerned with caffeine and blood pressure. Of these, 5 reported no association between dietary caffeine and blood pressure, 6 reported a significant positive association for systolic and/or diastolic pressure, and 7 reported an inverse association for either systolic or diastolic pressure. The diverse findings are not explained by differences in the study populations, as these were similar in demographics and socioeconomics. Indeed, the level of inconsistency highlights the extent of the shortcomings that exist in the epidemiologic findings, which contrast the largely consistent pattern of pressor effects reported in experimental studies (discussed below). Of particular concern is

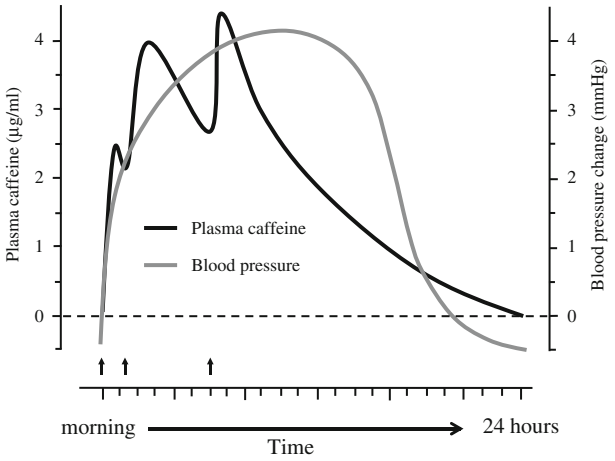

Fig. 2 Schematic representation of estimated 24-h plasma dietary caffeine concentration time course and associated change in blood pressure. Estimated plasma caffeine concentration assumes an elimination half-life of 5 h and ingestion of 1 cup of coffee after awakening and at two further time points (arrows) during the earlier part of the day (with evening and overnight abstinence). Associated blood pressure changes are relative to caffeine-free levels

the fact that epidemiologic studies have generally ignored issues related to the plasma caffeine concentration time course and associated pressor effects. The general pattern is shown in Fig. 2, which is a schematic representation of the estimated 24-h plasma caffeine concentration time course, assuming an elimination half-life of 5 h and ingestion of the approximate equivalent of 1 cup of coffee in the morning, mid-morning, and mid-afternoon.

Figure 2 helps to show that the strength, and even the sign, of the correlation between dietary caffeine and blood pressure level depends on the timing of blood pressure measurement relative to when caffeine was last ingested [99]. Using 24-h ambulatory monitoring, James [91] found that overnight abstinence produced transient modest decreases in blood pressure. Thus, taking a cross-section of the population, recent caffeine consumption is likely to have a pressor effect (positive association), whereas brief caffeine abstinence (10–12 h) may have no effect, and longer periods of abstinence (12–24 h) may decrease blood pressure modestly (inverse association due to withdrawal). In view of this analysis, a noteworthy feature of several of the studies in which dietary caffeine was said to have been protective (i.e., inverse association between intake and blood pressure) is that participants were asked to fast before being examined [99]. Specifically, participants in 5 of the 7 relevant studies were reported to have fasted, while one reported non-fasting and one omitted to report whether participants fasted or not. Thus, in the majority of the studies involved, caffeine consumers' blood pressure readings were likely to have been transiently lower (due to withdrawal) than "normal" for themselves and potentially lower also than their non-consuming counterparts.

Although interpretation of the findings of epidemiologic studies of caffeine and blood pressure depends crucially on knowing when blood pressure was measured relative to when participants ingested caffeine, with one exception [203], none of the relevant studies provides that level of detail. In the one exception, an overall analysis revealed no association between caffeine consumption and blood pressure level after adjustment for age, body mass, cigarette smoking, alcohol consumption, serum cholesterol, and family history of hypertension [203]. On closer examination, however, the authors reported that participants who had consumed

caffeine during the 3 h prior to measurement had significantly elevated blood pressure compared with participants consuming no caffeine for the same period. Importantly, because the increases in blood pressure associated with recent ingestion of caffeine were independent of average daily intake (a measure of habitual use), the results also confirm experimental findings that habitual caffeine consumption does not lead to complete tolerance to the pressor action of the drug.

Chronic Effects of Dietary Caffeine on Blood Pressure

Before the last decade, there had been little direct (experimental) examination of the chronic hemodynamic effects of dietary caffeine. Among the first studies to undertake such an examination, modest sustained decreases in blood pressure were reported when caffeine beverages were either removed from the diet [10] or replaced by decaffeinated alternatives [235]. Similar results were reported in a number of subsequent studies in which ambulatory monitoring was used to measure blood pressure level for extended time periods [63, 91, 109, 176, 221].

Moreover, it is known that blood pressure responses of similar magnitude may be accompanied by different patterns of change in cardiac output and total peripheral resistance, and these differences in hemodynamic profile may be implicated in cardiovascular pathology [65]. Speculation has existed as to whether caffeine-induced pressor effects are due to cardiac stimulation of contractility leading to increased cardiac output, or vasoconstriction leading to increased total peripheral resistance. Findings generally suggest that the blood pressure-elevating effect of caffeine is due primarily to increased vascular resistance [30, 56, 70, 100, 209]. Because greater risk has been attached to hemodynamic reactivity in which vascular, rather than myocardial, responses predominate [112], findings of caffeine-induced vascular resistance add to concerns regarding the possible implications of dietary caffeine for cardiovascular health.

Dietary Caffeine and Population Blood Pressure Levels

If, as this review indicates, dietary caffeine contributes to statistically significant elevations in blood pressure, it should be noted that such increases are modest in absolute terms, amounting to possibly 2–4 mm Hg for most waking hours of the day. The question, therefore, that needs to be considered is whether such increases are likely to have an appreciable effect on population cardiovascular mortality and morbidity. It is sometimes presumed that increases of such magnitude are not meaningful, on the grounds that blood pressure level is inherently variable. However, it should be remembered that the effects of caffeine are at least additive, and possibly synergistic, to blood pressure increases due to a variety of other factors (e.g., smoking, hypertension, stress). In this sense, caffeine represents a preventable additional burden on the cardiovascular system.

The clearest insight into the contribution of blood pressure increases to cardiovascular disease is provided by population statistics describing the relationship between blood pressure level and cardiovascular mortality and morbidity. Since the association between the population distribution of blood pressure and cardiovascular disease is primarily linear, any contribution by caffeine to population blood pressure level may be expected to contribute to the overall incidence of cardiovascular mortality and morbidity [147, 148, 175, 183, 233]. It is important to remember that exposure to caffeine is generally long (essentially lifelong for most consumers), the prevalence of exposure is high (more than 80% in most countries), and the incidence of cardiovascular disease is high throughout the world. While reduced blood pressure associated with reductions in dietary caffeine may be expected to be modest in absolute terms, even modest absolute changes in population levels of blood

pressure translate to significant changes in the population burden of cardiovascular death and disease.

For example, it has been estimated that a downward shift of 2–3 mm Hg in the population distribution of blood pressure would produce life-saving benefits equal to the cumulative benefits achieved by antihypertensive treatment [183, 188]. It has also been estimated that population-wide reductions of 2 mm Hg could avert 5% of deaths from coronary heart disease and 15% of stroke deaths [182, 183]. More specifically, James [87] estimated that if caffeine consumption had the effect of elevating average population blood pressure by 2–4 mm Hg (a reasonable inference considering the relevant experimental data (e.g., [96, 99, 109, 221]), extrapolation based on epidemiologic blood pressure data [147, 148] suggests that population-wide cessation of caffeine use could lead to a reduction of 9–14% of premature deaths from coronary heart disease and 17–24% of premature deaths from stroke. If caffeine were removed from the diet in populations where coffee specifically is widely consumed, additional benefits would be achieved due to the adverse impact of that beverage on serum cholesterol and homocysteine [99].

Dietary Caffeine and Physical Health: Non-Cardiovascular Disease

Cancer

Although numerous studies of cultured cells in vitro have demonstrated the mutagenic potential of caffeine, in vivo studies of intact nonhuman animals have suggested variously that caffeine: is not a carcinogen, is carcinogenic under some conditions, and is antitumoric under other conditions [95]. Moreover, the relevance of the in vitro and in vivo findings to lifelong dietary use of caffeine in humans remains unclear. Overall, there is a strong consensus that the experimental evidence as a whole suggests that the drug is not a significant carcinogen in humans. In addition, there has been extensive epidemiologic study of caffeine beverage consumption and cancer. Most of this research has been primarily concerned with coffee consumption, although over the past decade tea has also been a focus of attention. Because comparatively few studies have examined caffeine specifically, it is necessary to treat the findings for coffee and tea consumption as being only indirectly suggestive of the carcinogenic potential of caffeine.

All Cancers

Cancer is not a single disease, and therefore it is not surprising that most studies have been concerned with cancers located at one or a small number of specific sites rather than overall cancer rates. However, regarding overall rates, studies have tended to suggest no adverse impact of caffeine on cancer mortality (e.g., [137, 152]). On the other hand, studies of specific sites indicate more complex associations than that suggested by examination of the relationship between caffeine consumption and overall cancer incidence.

Lower Urinary Tract

Following an early report by Cole [29] of a significant association between coffee consumption and cancer of the lower urinary tract (renal pelvis, bladder, and urethra), there has been considerable epidemiologic interest in coffee as a possible cause of bladder cancer. The substantial body of literature that has accumulated tends to suggest a positive but weak association [84, 89]. However, although the association has been reported intermittently in different populations during the past two decades [26, 33, 158], widespread doubt exists as to whether the association is causal.

Pancreas

Early studies reported a relationship between caffeine beverages and pancreatic cancer [146,

219], one of the most rapidly fatal of human malignancies. Subsequent epidemiologic studies, however, yielded mixed results. In a review of relevant research conducted prior to 1990, the International Agency for Research on Cancer [84] concluded that the evidence was suggestive of a weak relationship between high levels of coffee consumption and the occurrence of pancreatic cancer, but cautioned that even this association could be due to bias or confounding. More recent studies have tended not to support the existence of even a modest positive correlation [55, 114, 202, 253, 255], although in one meta-analysis it was concluded that small amounts of coffee may be protective while high intake increases disease risk [163].

Breast

The epidemiology of caffeine and breast disease is somewhat mixed, especially among older studies, with some reporting a modest increased risk associated with caffeine consumption [131, 134, 150, 187] and others reporting no association [144, 189, 196]. More recent studies, however, have tended increasingly to report no association [47, 155, 208] and, more recently still, reports have appeared of an inverse association (i.e., "protective" effect) between caffeine consumption and breast cancer. Unfortunately, however, the pattern of findings has been inconsistent, with one study reporting an inverse association in premenopausal women and no association post-menopause [11], and another study reporting a weak inverse association in postmenopausal women but no association for the cohort overall [155].

Colon

Results of studies of caffeine consumption and cancer of the colon and/or rectum have also been highly varied. Some reported no association between coffee consumption and increased risk of disease [136, 164, 166], whereas others reported an increased risk [205, 213]. Still others, however, have reported a reduced risk [1, 12, 23, 86, 132, 133, 206, 223]. The frequency of reports of reduced risk (i.e., potential protective effect) has led to speculation about possible mechanisms of action, including rates of bile acid secretion and colonic motility [86, 223].

Other Sites

Results for other sites also tend to be mixed, with a pattern seeming to emerge of more recent studies reporting no association, or even a protective effect in some instances, thereby negating earlier findings of adverse effects. For example, Armstrong and Doll [6] reported a positive correlation between coffee consumption and cancer of the kidney, whereas later studies, with the exception of Asal et al. [8], have mostly failed to observe any relationship between coffee and/or tea consumption and kidney cancer. Similarly, whereas several earlier studies reported significantly increased risk of ovarian cancer in coffee consumers [130, 225, 249], more recent studies have tended to report no association [76, 215, 222].

Maternal Use of Caffeine

As mentioned above, caffeine readily crosses the placenta during pregnancy. Thus, throughout pregnancy, the developing fetus is exposed to concentrations of the drug equal to systemic levels in the mother. Naturally, questions arise regarding the implications of this exposure, especially considering the known pharmacological actions of caffeine. In 1980, responding to reasonable suspicions and early empirical findings, the United States Food and Drug Administration issued a warning advising pregnant women to restrict, or eliminate, coffee consumption. The focus of this warning was in relation to gross morphological (i.e., physical) abnormalities that had been observed in animal studies. However, animal studies usually

involved dosing levels higher than those typical of human dietary use, and the consensus today is that dietary levels are unlikely to result in morphological abnormalities [95].

Notwithstanding reassurance regarding gross defects, the question arises as to what represents an appropriate margin of safety for intrauterine exposure to caffeine in the human fetus. The usual safety standard employed by the Food and Drug Administration in relation to the human consumption of food additives is one-hundredth the maximum safe level of exposure in animals [227]. By that standard, virtually any pattern of regular caffeine consumption by a woman who is pregnant would put her unborn child at risk. That is, applying the Food and Drug Administration's usual standards, pregnant women should abstain from caffeine completely. Moreover, teratology (the scientific study of conditions caused by the interruption or alteration of normal development) includes not only the study of physical defects, but also the study of more subtle behavioral and emotional anomalies. Although a wide range of caffeine-induced developmental effects on behavior and neurochemistry have been demonstrated in animals, there have been very few reported studies in humans. The results that have been reported point to the need for further studies to examine caffeine as a potential behavioral teratogen [95].

Pregnancy Outcome

In addition to concerns about possible teratogenicity, there are concerns that maternal caffeine use could have adverse effects on pregnancy outcomes. Several studies have reported a positive association between maternal caffeine use and spontaneous abortion [28, 35, 60, 178, 247], whereas some others have found no association [43, 157]. It has been suggested that positive findings could be due to confounding from pregnancy-induced nausea, which is less frequent in pregnancies that miscarry than those that go to term. It is plausible that women who experience nausea might respond by reducing their caffeine intake. Consequently, it could be this "loss of taste" for caffeine rather than reduced caffeine per se that might be the basis for the observed positive correlation between higher caffeine use and spontaneous abortion. However, the nausea hypothesis has not been supported by studies that took account of nausea experienced during pregnancy [42, 60].

The mixed, sometimes contradictory nature of the findings for fetal loss is also characteristic of the findings for other major pregnancy outcomes. In particular, several studies have reported an inverse association between maternal caffeine use and fetal growth [159, 217, 237], while others have found no association [27, 68, 204]. Although the findings are far from consistent, it appears that the current weight of evidence is suggestive of an adverse effect of caffeine in that at least two meta-analyses have concluded that caffeine consumption is associated with a significant decrease in birth weight [45, 195]. Even then, it remains a possibility that the seemingly adverse effects of caffeine on particular pregnancy outcomes could have been due to the influence of confounders (e.g., recall bias). Overall, however, the available evidence points to maternal caffeine use being associated with increased risk of adverse pregnancy outcome, especially increased spontaneous abortion and lower birth weight.

Notwithstanding evidence of an association between caffeine consumption and adverse pregnancy outcomes, advice as to the need for caution regarding caffeine intake during pregnancy has tended to be heavily qualified. This appears to be partly due to the fact that several of the relevant studies have observed significant associations only for higher levels of intake, which has contributed to the belief that any causal involvement of caffeine is subject to a threshold. For example, in its most recent position statement on "nutrition and lifestyle for a healthy pregnancy outcome", the American Dietetic Association has specified a threshold of 300 mg/day, advising that pregnant women should avoid only higher levels of intake [113]. However, although there appears to be good agreement that caffeine can be harmful at higher levels of intake, there is no clear evidence-based reason that explains why immunity from harm is conferred at lower dietary levels. Moreover, as discussed above in

relation to cardiovascular disease, unreliability in the data due to imprecise measurement of dietary exposure to caffeine would appear to be a more likely explanation of any threshold of harm pertaining to maternal caffeine use. Indeed, with regard to the particular threshold advised in this context, 300 mg/day cannot reasonably be regarded as "high", since that level of intake can be readily reached and exceed by consuming as little as 2 cups of brewed coffee. All things considered, abstinence, as frequently recommended in relation to tobacco and alcohol, would appear also to be the most appropriate recommendation regarding caffeine use during pregnancy.

Adverse Interactions Between Caffeine and Other Drugs

Considering the near-universal use of caffeine, it is inevitable that the taking of other drugs will often coincide with that of caffeine. Regarding recreational drugs, it is commonplace to see smokers light up when drinking a caffeine beverage, and indeed cigarette smokers consume more caffeine on average than non-smokers. Similarly, alcohol is sometimes consumed in conjunction with caffeine, either as separate beverages or, as appears to be increasingly popular among younger-age groups, in a single beverage containing both alcohol and caffeine. Caffeine is also sometimes used to "cut" illicit drugs such as heroin, cocaine, and amphetamine, with the users of those drugs sometimes consuming substantial amounts of caffeine even when not intending to do so. Particular concerns, however, arise in relation to pharmaceuticals with which caffeine may interact adversely or whose therapeutic efficacy may be undermined by caffeine (e.g., benzodiazepines and some antibiotics) [89, 95].

Is Caffeine Addictive, and Is There a Safe Level of Consumption?

The evidence reviewed above indicates that dietary caffeine is a probable risk to cardiovascular health, poses a threat to fetal growth, interacts adversely with common therapeutic drugs, and produces dysphoric effects after brief abstinence. Therefore, taking account of its widespread and persistent use, should caffeine be considered a drug of addiction? Physical dependence is a common feature of drugs widely regarded as addictive. On this point, the evidence is conclusive; the occurrence of a characteristic syndrome of abstinence effects shows that repeated caffeine use leads to the development of physical dependence. Accordingly, it may reasonably be said that caffeine is a drug of addiction. On the other hand, the term "addiction" has wide currency, and carries a variety of emotive connotations (e.g., illegal importation, criminal syndicates, and violent crime) that have little relevance to dietary caffeine. Accordingly, it might be prudent not to be too strident in labeling caffeine an "addictive" substance. This stance, however, should not distract us from the evidence that dietary caffeine is harmful.

Considering the evidence of harm, it is appropriate to ask: Is there a safe level of consumption? As previously stated by this author, a balanced (if unpopular) answer to this question is that there is no daily level of intake that can be regarded safe [95]. The equivalent of as little as 1 cup of coffee produces modest increases in blood pressure lasting 2–3 h, which over the course of a lifetime is likely to contribute to increased cardiovascular disease; any exposure to caffeine during pregnancy exposes the fetus to a dose equivalent to that received by the mother; caffeine interacts negatively with therapeutic medications, and dietary use produces physical dependence.

Reducing and Quitting Caffeine Consumption

Despite strengthening evidence that dietary caffeine is harmful, few reports exist of systematic efforts for assisting habitual consumers to reduce or cease their use of the drug. Indeed, following a brief rise in interest about 2 decades ago, reports of systematic attempts to manage caffeine intake

appear to have all but disappeared from the literature. One early commentary on the subject more than a century ago advised that negative withdrawal effects could be avoided by a gradual reduction of caffeine [18]. That advice has stood well the test of time. Using a single-subject experimental design, Foxx and Rubinoff [51] reported favorable results for three participants who received a program of behavioral intervention based on nicotine and cigarette "fading" methods that the same research group had developed for smokers (e.g., [49, 50]. Treatment consisted of a combination of self-monitoring and a series of predetermined step-wise reductions in daily caffeine consumption in the direction of a specified terminal goal of reduced daily intake. Subsequently, Foxx [48] obtained follow-up data from the three original participants, reporting that the reduced intake of all three was substantially maintained 40 months following the termination of treatment. Bernard et al. [13] employed similar procedures with a single subject, and again reported favorable results.

These generally promising initial findings were confirmed in a larger study by James et al. [107] in which 27 chronic heavy caffeine consumers were monitored before and during a 4-week treatment program and at 6- and 18-week follow-up. However, because the results of this and previous caffeine-reduction studies were expressed solely in terms of participant self-reports, the reliability of the findings could be open to question. Accordingly, James et al. [107] reported plasma concentrations of caffeine and its primary demethylated metabolites (paraxanthine, theophylline, and theobromine) as well as self-reported caffeine intake during the course of a caffeine-fading regimen similar to that employed in the previous study by the same authors [106]. Overall, the 12 subjects, each with a history of heavy caffeine use, provided highly reliable self-reports of caffeine intake during the course of the 18-week program. However, unlike the earlier studies in which follow-up data had been obtained, participants in the James et al. [107] study showed signs of relapse at 12 weeks follow-up.

It has long been known that the accuracy of self-reports is enhanced when subjects are aware that their behavior may be independently checked (e.g., [141, 161]. Hence, the independent measurement of plasma caffeine levels in the James et al. [107] study may have encouraged subjects to be more accurate than participants in previous studies in reporting follow-up caffeine intake. If accurate and generalizable, the relapse reported by James et al. [107] is broadly consistent with reports of treatment outcomes for other dependence-producing substances. Although the reasons for the relapse observed by James et al. [107] remain unclear, relapse would not appear to have been due to the direct influence of withdrawal effects, since the resumption of higher levels of consumption did not occur until many weeks after the original treatment goal had been achieved. As such, firm statements cannot be made at this time regarding the long-term level of success of attempts to reduce caffeine intake. Nevertheless, it is clear from the available evidence that motivated individuals wishing to reduce or quit their use of caffeine can do so without experiencing pronounced (if any) negative withdrawal effects, provided that intake is reduced in a graduated (step-wise) fashion rather than abruptly (as when "going cold turkey").

Does Caffeine Have Health Benefits?

There has long been interest in caffeine beverages as possible sources of benefit, and much of that interest has centered on the putative benefits of caffeine for psychomotor performance and mood. However, as discussed above, there is now a firm body of evidence showing that caffeine has little or no net benefits for performance or mood. At the same time, at least partly fostered by industry-sponsored research, there has been substantial growth in interest in caffeine beverages as possible sources of benefit for physical health, especially in relation to diabetes and Parkinson's disease.

Type 2 Diabetes Mellitus

Several epidemiologic studies in the United States and Europe have reported significant dose-dependent reductions in the risk of developing Type 2 diabetes mellitus in association with caffeine and coffee consumption (e.g., [2, 191, 193, 231, 232]). While findings have prompted some authors to claim that caffeine and coffee protect against Type 2 diabetes, it is important to note that the studies in question were non-experimental and shared many of the same potential confounder effects that have generally undermined interpretation of epidemiologic studies of caffeine and health. More importantly, experimental studies have found the opposite pattern of results than would be expected from the population studies.

Double-blind placebo-controlled trials have consistently found that caffeine impairs glucose tolerance and decreases insulin sensitivity, and the findings have been reported for a wide range of participant groups including persons with diabetes and those without (e.g., [62, 118, 124–126, 140, 170, 232]). As such, it is difficult to reconcile how caffeine could offer protection against Type 2 diabetes when experimental studies have shown that it compromises glucose metabolism both before and after development of the disease. Thus, although caffeine appears distinctly unlikely to confer any protection against the development of diabetes, one issue is whether there may be a compound other than caffeine in coffee that offers such benefit. If such a compound exists, to be of benefit, it would need to be sufficiently potent not only to negate, but to exceed, the negative effects of caffeine.

Parkinson's Disease

There is a substantial body of recent epidemiologic evidence of an inverse association between caffeine consumption and the development of Parkinson's disease (e.g., [9, 74, 192]). This finding has been widely assumed to be causal, and has contributed to speculation about the "neuroprotective" action of caffeine. In particular, attention has focused on interactions between the dopaminergic and adenosinergic systems and caffeine's putative ability to forestall dopaminergic neuron degeneration through its action on the A_{2A} adenosine receptor (e.g., [21, 24, 115, 154, 199, 224]). An earlier population study by Jarvis [108] is sometimes cited as supportive of the idea that caffeine has neuroprotective properties. In a cross-section of the population, Jarvis reported that higher caffeine intake was positively related to better performance on certain psychomotor and cognitive tasks, and the effect was reported to have been larger in older participants. However, a more recent prospective study involving a larger population sample found little evidence of improved performance associated with caffeine consumption or of reduced age-related cognitive decline [230].

Moreover, Evans et al. [39] recently suggested that the inverse association between caffeine consumption and Parkinson's disease, as well as the similar relationship that exists with cigarette smoking (which has fostered the belief that nicotine is neuroprotective), may be "epiphenomena" rather than causal. Broadly, Evans et al. [39] argued that confounding due to individual differences in the personality disposition of impulsive sensation seeking may have led to misunderstanding of the findings. The authors cited evidence that sensation seeking is inversely associated with Parkinson's disease, with higher sensation seeking also being associated with higher caffeine consumption and smoking. Evans et al. [39] hypothesized that there are biological features characteristic of low-sensation-seeking individuals that also predispose to Parkinson's disease. Thus, rather than indicating any neuroprotective capability, higher caffeine and nicotine intake may simply be two behavioral manifestations of a generalized personality disposition, namely, impulsive sensation seeking, which itself is the expression of a biological substrate that confers a level of protection against the development of Parkinson's disease.

"Other" Active Compounds in Caffeine Beverages

Notwithstanding the strength of the evidence that dietary caffeine poses a number of significant risks to health, an important caveat arises when other compounds in caffeine beverages are considered. Whereas caffeine is generally accepted as being the main biologically active ingredient of those beverages, the presence of other compounds also having biological effects has become a focus of interest. Of course, the "other" active compounds could have either positive or negative implications for health. An example of the latter is the presence of a cholesterol-raising factor in unfiltered brewed coffee [194, 228, 243, 248]. However, influenced by industry-sponsored research over the past decade, interest has been strengthening in the search for beneficial effects from non-caffeine active compounds in coffee and tea (e.g., the relation between coffee and Type 2 diabetes mentioned above).

Accordingly, any assessment of the overall health implications of caffeine beverages must take account of the benefits, if any, of these other compounds. For example, it is claimed that polyphenols, especially chlorogenic acid, in coffee have potential cardiovascular benefits due to antioxidant properties (e.g., Bonita et al. [16]). Similarly, theanine, a non-proteinic amino acid, has been posited as having a blood pressure-lowering effect (e.g., [186]). At the same time, it must be emphasized that a notable feature of research into the benefits of caffeine beverages is the involvement of the caffeine industry at all levels of research, including basic and applied animal and human studies, and the production of published scientific articles including empirical studies and literature reviews. By any measure, industry involvement is extensive, even pervasive, and the conflicts of interest inherent in industry-sponsored research (including the dissemination of research findings) raise serious questions regarding the increasing frequency of "scientific" claims for the benefits of caffeine-containing beverages. In short, for some time, the integrity of caffeine science has been under threat.

Threats to the Integrity of Caffeine Science

Industry Influences on Research

The available experimental evidence, and to a lesser extent the epidemiologic evidence, supports the conclusion that caffeine use is a likely risk factor for health. Notwithstanding the importance of the implications of this conclusion for population health, there is little organized effort to inform and to advise the public on ways consistent with the magnitude of that threat. Indeed, it is evident from a close examination of the caffeine literature that this is a field of enquiry marred by a considerable amount of misinformation and misrepresentation. In particular, it is necessary to confront the reality that the academic pursuit of research on caffeine is extensively linked to the trade in caffeine products. Each of the main sources of caffeine, namely, coffee, tea, soft drinks, and energy drinks, is a multinational, multibillion dollar enterprise. By their own account, these industries have sought to lessen the impact of scientific findings that could threaten their commercial interests (see James [93, 98]).

Over the past quarter-century, various methods have been employed by industry to influence public opinion about caffeine and caffeine products. Such attempts include dissemination of selective information and funding for selected caffeine research [93]. During the 20 years from 1962 to 1982, the average number of cups of coffee consumed per day in the United States declined 39% [153], and it is evident from caffeine-industry publications that manufacturers attributed much of that decline to increased public awareness of scientific concern about possible caffeine-induced harmful effects [93]. Around 1990, there was an arrest in the downward trend, and thereafter a reversal evidenced by substantially increased sales of all categories

of caffeine beverages. Manufacturers of caffeine products appear to have been in no doubt about the reason for the improved commercial outlook for caffeine products. Industry representatives congratulated themselves on the success of their campaign to counter scientific findings that threatened their interests [75, 179]. In this regard, there appear to be parallels between actions by the caffeine industry to protect its commercial interests and similar activities by the tobacco and alcohol industries.

One influential industry body is the International Life Sciences Institute, which lists its Committee Members as including Coca-Cola, Kraft Foods, Mars, Nestlé, Procter & Gamble, Unilever, and others having commercial interests in caffeine products [85]. The International Life Sciences Institute actively pursues affiliations with the United Nations Food and Agriculture Organization and the World Health Organization, and is directly and extensively involved in publicly funded European Union research in areas of interest to its members [98]. The International Life Sciences Institute and the companies it represents commission scientific research into caffeine, and take an active role in sponsoring the production of scientific literature on caffeine [85]. Although affiliation with industry and material assistance from industry do not themselves constitute evidence of wrongdoing, such collaboration is worryingly commonplace in caffeine research (e.g., [15, 22, 85, 186]).

Despite being reported to have been extensively involved in assisting the tobacco industry to counter the World Health Organization's efforts to promote tobacco controls, especially in developing countries, the International Life Sciences Institute describes itself as having ongoing close involvement with the World Health Organization's activities [76]. A World Health Organization Committee of Experts on Tobacco Industry Documents reported that for many years tobacco companies operated with the "purpose of subverting the efforts of the World Health Organization to address tobacco issues [and that the] attempted subversion has been elaborate, well financed, sophisticated and usually invisible" [254] (p. 18). Subsequently, the Tobacco Free Initiative, a World Health Organization project, identified the International Life Sciences Institute as one such group [145, 160]. Moreover, the International Life Sciences Institute has been the subject of editorial criticism for its reticence in declaring a possible conflict of interest regarding its involvement in a publication concerned with health issues related to alcohol consumption [38]. The picture that has emerged is of an "institute" presenting itself as dispassionate and independent, while actually serving as a "third party" representative of commercial interests [98].

The research community needs to heed the dangers of industry influence on research. It is important that ways are found for ensuring exposure of possible conflicts of interest where they are not freely declared. Where possible conflicts do exist, ways must be found to safeguard against resulting threats to scientific integrity [98]. The importance and urgency of steps by the scientific community to counter such threats is highlighted by empirical evidence of bias attributable to pharmaceutical industry involvement in biomedical research. For example, in a study of the association between funding source and conclusions in randomized medication trials, Als-Nielsen et al. [4] found that after adjustment for study characteristics, industry-sponsored trials were 5 times more likely to yield conclusions favorable to industry's commercial interests than trials funded by nonprofit organizations.

Conflict of Interest and the Self-Serving Bias

A conflict of interest exists when an ethical or professional interest clashes with a pecuniary self-interest. Although a necessary prerequisite for openness, the mere declaration of a conflict of interest is unlikely to foil outcome bias in industry-sponsored research. For one thing, a simple declaration provides no basis for consumers of scientific research, including

scientists, policy makers, and the public, to judge the nature and extent of any consequential bias. Indeed, drawing on relevant experimental findings from social psychology, Dana and Loewenstein [32] have argued that declaring a conflict of interest can actually be counterproductive by exacerbating the declarer's bias. Dana and Loewenstein [32] explained that part of the difficulty in dealing with the problem is that it is usually assumed that bias founded on a conflict of interest is a matter of deliberate choice. This perspective contributes to the indignation that is sometimes expressed when the subject is raised. Unfortunately, however, the "deliberate choice" view of bias arising from conflicts of interest is inconsistent with empirical findings, which show that even when individuals try to be objective their judgments are subject to an unintentional self-serving bias [32]. In other words, self-serving bias is part of human nature. It is the role of the scientist to safeguard the integrity of research in the face of human limitations.

Indeed, unintentional self-serving bias might help to explain some apparent contradictions alluded to above. Weinstein [246] has shown that "behavioral performance tends to produce perceptions supportive of the behavior" (p. 2). If so, it is likely that caffeine consumers will be more readily accepting of conclusions consistent with their own extant caffeine-consuming behavior than findings that conflict with such behavior. Thus, it is possible that a subtle inherent self-serving bias inclines consumers of caffeine products to be more influenced by neutral or positive findings concerning caffeine than is engendered by more objective assessments. Furthermore, since most people consume caffeine daily, it is likely that the large majority of researchers, reviewers, and editors of scientific literature are caffeine consumers. As such, the resulting impact of an inherent self-serving bias on the way scientific findings are promulgated could be pervasive. For example, experimental findings are ordinarily accepted as providing stronger evidence of causal relationships than epidemiologic findings. Yet, the opposite view could be said to have been in operation in a number of important areas of caffeine research. In relation to cardiovascular disease and Type 2 diabetes mellitus, in particular, there appears to have been a tendency to ignore experimental findings of likely harm in favor of accepting epidemiologic findings of no harm. Unfortunately, however, there is relatively little published literature addressing the topic of self-serving bias in science, and as such little systematic knowledge has accumulated as to the extent of industry-based threats to scientific integrity.

Conclusions

Claims that dietary caffeine is of little importance to health are ill founded. Short-term withdrawal of caffeine has negative effects on psychomotor performance and mood, and these effects may reoccur chronically in habitual consumers. Caffeine produces modest increases in blood pressure that have long-term implications for cardiovascular health, caffeine interacts adversely with some medicines, and there is suggestive evidence of increased risk of spontaneous abortion and lower birth weight associated with caffeine use in pregnancy. Conversely, there is little or no satisfactory evidence of net benefits of dietary caffeine. Although further evidence is needed, it is unlikely that adverse effects are necessarily limited to groups characterized as "heavy" consumers. Notwithstanding the need for further research, the extensive involvement of industry bodies in that research effort raises questions concerning the integrity of caffeine science.

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Serotonergic Hallucinogens

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Contents

Introduction

This chapter focuses on hallucinogens with psychoactive properties mediated through the serotonin system. Although commonly referred to as "hallucinogens", a lexigraphic disclaimer is warranted as the psychological experience elicited by these drugs centers on distortion of perception, not true hallucinations. The historical term "psychotomimetic" is also inaccurate as the state they produce has proven to be a poor model for schizophrenia. The most apt term is probably "psychedelic" from the Greek *psukhē*, meaning "mind" and *dēloun,* meaning "reveal" or "make visible". While the enlightenment sought by recreational users may be an artifact of the psychoactive experience, researchers study these compounds hoping to gain insight into how the brain produces the mind. Nonetheless, in conforming to common usage, in this chapter these drugs will be referred to as "hallucinogens".

History

Perceptions provide reassurance into our existence and the existence of the world around us. Thus it is not surprising that compounds capable of producing altered states of perception are regarded with mystical fascination and trepidation. The ritualistic consumption of plants, many of which derive there psychoactive properties through the serotonin system, has been an important part of religious and social ceremonies throughout human history.

Conceivably the oldest known ritualistic use of hallucinogens was in the Indus Valley during the second millennium B.C. A group of people known as Aryans worshiped a deity they named "Soma", which recent evidence suggests is the mushroom Amanita muscaria or Fly agaric [140]. This red and white spotted mushroom incidentally bears resemblance to the mushroom featured in the Mario Brothers video game worshipped by many adolescents in the second millennium A.D.

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_27,

Spiritual use of hallucinogens has been a part of various cultures throughout the world. In the fourteenth century A.D., Aztecs and other Indians of Central America took psilocybin containing mushrooms to bestow powers of clairvoyance during religious ceremonies. Contemporary South American and Caribbean peoples snorted a narcotic powder (Cohoba) which, reminiscent of modern club drugs was used to promote friendliness during convulsive dance ceremonies. In Western cultures, hallucinogens may underlie mythos of witchcraft and sorcery. In his book *Hallucinogens and Shamanism* (1973), Michael Harner relates the symbol of a witch riding on a broomstick to the practice of medieval women achieving magical powers by anointing their mucous membranes with hallucinogenic substances. In a similarly clever fashion, Linnda Caporael hypothesized that that the affliction of the girls sparking the Salem witch trials resulted from ergot (the natural substance from which lysergic acid diethylamide is derived) poisoning caused by ingestion of rye grains contaminated with the fungus Claviceps purpurea [21]. More recently a study conducted by Griffiths et al. at the Johns Hopkins University found that when administered under supportive conditions psilocybin occasioned experiences similar to spontaneously occurring mystical experiences [50].

The modern synthetic drug era began in the late 1960s with the legendary synthesis of lysergic acid diethylamide by the Swiss chemist, Albert Hoffman. While working at Sandoz Laboratories, Hoffman synthesized lysergic acid diethylamide as part of an effort to develop ergot derivatives capable of reducing post-partum bleeding. Not useful in this regard, the compound was shelved. Five years later, according to psychedelic lore, Hoffman was haunted by a "peculiar presentment" and repeated its synthesis. After accidentally absorbing a small amount he experienced its psychoactive effects while bicycling home. Psychedelic enthusiasts refer to this fateful day, April 16th 1943, as "Bicycle Day".

In the 1960s and 1970s, Timothy Leary brought lysergic acid diethylamide and other psychedelics to the forefront of pop culture. His introduction of psychedelic drugs to academic and therapeutic settings led to the research responsible for most of what is currently known about these drugs. However, his temerarious promotion of these drugs for individual enlightenment and the ensuing underground abuse precipitated strict government regulation, which for several decades halted any legitimate research.

Prior to the Drug Abuse Control Amendments to the Harrison Narcotics Act in 1965 lysergic acid diethylamide was used as tool, albeit with debatable efficacy, in analytic therapy to uncover repressed memories and to elicit therapeutic abreactions [19, 115]. Attempts were also made to treat obsessive compulsive disorder, childhood schizophrenia, sociopathy, and alcoholism [4]. Perhaps thwarted by government restrictions, there have been no well designed studies confirming a clear therapeutic use for these drugs in treating somatic or mental illnesses. Today, restrictions on research have loosened and an organization known as the Multidisciplinary Association for Psychedelic Studies assists scientists in designing, obtaining approval and carrying out research on psychedelic drugs.

In the 1980s, attention to hallucinogen use reemerged with the trend of all night dance parties known to as raves. These large gatherings feature electronic dance music and laser light shows. Attendees often use psychedelic drugs to promote sociality and heighten the sensory stimuli of the music and lights. While 3,4-methylenedioxymethamphetamine (also known as Ecstacy) is the most notorious club drug, lysergic acid diethylamide and the traditional psychedelics make more than cameo appearances.

Epidemiology

Hallucinogen use has declined since the 1970s with the annual prevalence remaining below ten percent [66, 96, 99, 102]. The types of hallucinogens used have also changed. Lysergic acid diethylamide which was the most widely used

hallucinogen has been surpassed by psilocybin and newer synthetic club drugs. The National Survey on Drug Use and Health released a report describing patterns of hallucinogen use between 2004 and 2005 in persons over 12 years of age. Just over 1.5% of persons reported having used hallucinogens in the preceding year with use among males being twice that of females. On average, 943,000 persons tried hallucinogens for the first time each year and of these first time users 52.3% tried psilocybin mushrooms and 42.9% tried ecstasy. First time female users were more likely to have tried ecstasy (49.5% vs. 37.7%) while first time males were more likely to have tried psilocybin (61.1% vs. 41.1%). Highest rates of use are in persons between the ages of 18–25 [131], and there is a positive correlation between hallucinogen use and years of education [5].

Classification

Serotonergic hallucinogens can be divided by chemical structure (Fig. 1). Indolealkylamines, which have more than one carbon ring and are structurally similar to serotonin, include lysergic acid diethylamide, ibogaine, psilocin, psilocybin, and *N,N*-dimethyltryptamine. The phenethylamines because they have only one carbon ring more closely resemble amphetamine and the catecholamine neurotransmitters (dopamine, epinephrine, and norepinephrine). This class is comprised of mescaline, 3,4-methylenedioxymethamphetamine (or ecstasy), 3,4-methylenedioxyamphetamine, and dimethoxymethylamphetamine. The psychopharmacology of all of the serotonergic hallucinogens (except for Ecstacy) is similar.

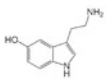
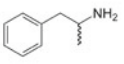
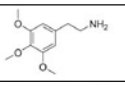
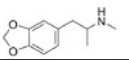
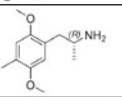
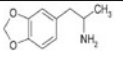
Indolealkylamine			
Serotonin 	LSD (d–lysergic acid diethylamide)		Average dose: 30–300 µg Onset: 5 minutes Duration: 12 hours
	DMT (N,N–dimethyltryptamine)		Average dose: 60–100 mg smoked or intramuscular Onset: 3 minutes Duration: 30 minutes
	Ibogaine (12–methoxy–ibogamine)		Average dose: 2 to 5 grams Onset: 45 minutes Duration: up to 24 hours
	Psilocybin (O–phosphoryl–4–hydroxy–N,N–dimethyltryptamine)		Average dose 10–30 mg Onset: 10–40 minutes Duration: 2–6 hours
	Psilocin (4–hydroxy–N, N–dimethyltryptamine)		(The active metabolite of psilocybin)
Amphetamine 	Phenethylamine		
	Mescaline (3,4,5–trimethoxyphenethylamine)		Average dose: 300–500 mg Onset: 30 minutes Duration: 10–12 hours
	Ecstasy (MDMA; 3,4–methylenedioxymethamphetamine)		Average dose: 80 to 160 milligrams Onset: 30–45 minutes Duration: 6 hours
	DOM (2,5–dimethoxy–4–methylamphetamine)		Average dose: 3–10 mg Onset: 30 minutes to 1 hour Duration: 14–20 hours
	MDA (3,4–methylene-dioxyamphetamine)		Average dose: 80 to 160 mg Onset: 1 to 1.5 hours Duration 6 to 10 hours

Fig. 1 Chemical structures of indolealkylamine and phenethylamine hallucinogens

In order to avoid redundancy, this chapter begins with a general discussion of mechanism of action and then concentrates on representative idolealkylamines (lysergic acid diethylamide and psilocybin) and phenethylamines (mescaline and 3,4-methylenedioxymethamphetamine) with lysergic acid diethylamide serving as a prototype for comparison. Of note, although 3,4-methylenedioxymethamphetamine is technically a phenethylamine its pharmacology and psychoactive properties are different enough to warrant a separate discussion.

Mechanism of Action

After nearly a half a century of research, it is currently understood that the psychoactive effects of both indolealkylamine and phenethylamine hallucinogens are mediated primarily through agonist activity at the 2A subtype of serotonergic receptors (serotonin-2A receptors). The structural resemblance of indolealkylamines to the serotonin neurotransmitter led researchers to suspect their psychoactive effects were serotonergically mediated. Furthermore, the reported similarity of psychic experiences elicited by the phenethylamines and the indolealkylamines [57] as well as cross-tolerance between the two classes [13, 143, 145] suggested a shared mechanism of action. With advancements in molecular biology, 14 distinct serotonergic receptors comprising seven families (serotonin-1–7) [15] were discovered. Determining which receptors mediate the psychoactive effects, however, presented a challenge. Ethical and legal restrictions precluded the use of human subjects leaving researchers to rely on animal models. Recognizing that perceptions, being subjective experiences, are impossible to unequivocally assess without verbal communication the astute reader may wonder how one could to tell if a rat is hallucinating. The reader should refer to a review article by Winter outlining the role of drug-induced stimulus control in uncovering the mechanism of action of serotonergic hallucinogens [144].

Serotonin Receptor

The monoamine family of neurotransmitters is comprised of serotonin, epinephrine, norepinephrine and dopamine. The serotonin receptor system is the most complicated. Fourteen distinct receptors belonging to seven families have been discovered so far. The system is made more complex by posttranslational receptor modifications, multiple G-proteins, phenotypic switching and crosstalk within and probably between receptor families [61]. All but one of the serotonin receptors are coupled to G-proteins. The serotonin-2A and serotonin-2C receptors are similar and often referred to as the serotonin-2A/2C receptor. There is a paucity of ligands with selectivity between these two subtypes making it difficult to rule out an ancillary role of serotonin-2C receptors in the psychoactive effects of hallucinogens [39].

The serotonin-2A receptor is located on chromosome 13q14-q21 and is comprised of 471 amino acids. It is coupled to $G_{q/11}$ and agonist activity stimulates hydrolysis of inositol phosphates which increases levels of cytosolic $[Ca^{2+}]$. Serotonin-2A receptors are widely distributed. Peripherally, they mediate vascular smooth muscle contraction, platelet aggregation, capillary permeability and they regulate hormone secretion. Centrally, they are located in the cortex, claustrum and basal ganglia.

Indolealkylamine Hallucinogens

Lysergic Acid Diethylamide

Street Information

Today, the majority of lysergic acid diethylamide is synthetic. However, it can be derived from two naturally occurring substances; the embryo of morning glory seeds (Rivea corymbosa) and Claviceps purpurea (the parasitic fungus mentioned above). Sunlight and chlorine—even at tap water concentrations—will inactivate

Fig. 2 Photographs of lysergic acid diethylamide taken from the United States Drug Enforcement Administration Website

lysergic acid diethylamide but it can be stored as a solid salt or dissolved in pure water as long as it is kept at low temperatures and protected from light and air [123]. Synthetic lysergic acid diethylamide is crystalline. It is crushed into a white odorless, tasteless powder that is dissolved and administered orally, sublingually, intramuscular or intravenous. Sublingual mediums include postage stamps, chewing gum or sugar cubes often decorated with new age symbols (Fig. 2).

Street names for lysergic acid diethylamide, as for all of the serotonergic hallucinogens, are creative and include, but are not limited to, "Acid", "Loony Tunes", "Elvis", "Window pane", "Dots", and "Mellow yellow". Lysergic acid diethylamide is extremely potent and can even be absorbed subcutaneously. Doses of 20–30 μg produce psychoactive effects in humans [49], and Hoffman estimated it to be five to ten thousand times more potent than mescaline [58]. Surprisingly, lysergic acid diethylamide has a large safety window with no reported human deaths. The only mortality associated with lysergic acid diethylamide has been an elephant that received 300 mg via dart rifle as part of an unusual experiment. He was also administered chlorpromazine and barbiturates; therefore, it is unclear whether lysergic acid diethylamide was in fact the cause of death [142].

Lysergic acid diethylamide is easily produced in great quantity. For example, 25 kg of ergotamine tartrate (a substrate for lysergic acid diethylamide) yields 5 kg of lysergic acid diethylamide or 100 million doses. The returns are lucrative as one dose of lysergic acid diethylamide costs less than one cent to make and sells for about 10 dollars [94]. Today, an average dose ranges from 100 to 300 μg, considerably lower than in the 1970s [24].

Physiological and Psychological Effects

Lysergic acid diethylamide is hepatically metabolized and has no active metabolites. It has a half-life of 3–5 h [8, 105, 112]. Psychoactive effects peak at 2–4 h and can last for up to 12 h depending on dose, tolerance, body weight, and age [123, 135]. Users of lysergic acid diethylamide typically experience autonomic symptoms within several minutes and psychoactive effects approximately 10 min later. The autonomic symptoms are mainly sympathomimetic, e.g., elevated blood pressure and pulse, diaphoresis, piloerection, nausea, uterine contractions, hyperreflexia, and tremor. Anisocoria (unequal pupils) and hippus (rhythmically dilating pupils) are not uncommon [117].

Not only does mood become amplified, but it can shift rapidly and some users have reported experiencing multiple moods simultaneously. Sensory perceptions become enhanced and distorted [68, 78, 97]. Typical descriptions include vivid colorful geometric shapes, trails of actual objects and seeing body parts separate from themselves. Dramatic complex disturbances may occur such as animation of inanimate objects or Satan's face appearing on someone's body [121]. Auditory distortions are less common. At higher doses, synesthesia may occur (perceiving a sensation in different modality such as hearing colors). Distortions in the sense of time include time halting, stretching, repeating, and ceasing to exist.

When the overall experience is perceived as enlightening or emotionally stimulating, it is referred to as a "good trip". Other times the experience might be nightmarish, with fears of insanity or losing control. Such negative experiences are referred to "bad trips". The cause of good

trips versus bad trips is not known. A "guide" is often enlisted to assist the user through the experience. Having a good trip does not predict subsequent good trips, and the reverse appears to be true as well. The psychic experience generally lasts 8–12 h and is often followed by a pleasant "psychic numbness".

Abuse and Dependence Potential

Tolerance to the psychological effects of lysergic acid diethylamide, but not the physiological effects, develops quickly [17]. In contrast to highly addictive drugs such as cocaine and heroin there does not appear to be a withdrawal syndrome and users usually do not develop cravings or seek higher and higher doses. Although humans self-administer lysergic acid diethylamide, it does not serve as reinforcement in animal models. In concordance with these observations, the United States Drug Enforcement Administration does not consider it to be an addictive drug [95].

Adverse Effects

Although lysergic acid diethylamide is considered relatively safe when compared with other drugs of abuse, there are case reports of respiratory failure, hyperthermia, and coagulopathies associated with massive doses [70]. Early on a relationship between lysergic acid diethylamide and chromosomal damage was suspected but this has been consistently refuted and lysergic acid diethylamide does not appear to be teratogenic [23]. Lysergic acid diethylamide, however, does induce uterine contractions which could disrupt pregnancy. In general, there are three main reasons why people who use lysergic acid diethylamide come to clinical attention: "the bad trip", "flashbacks", and persistent psychosis.

The Bad Trip

Bad trips occur in about one in ten lysergic acid diethylamide uses [33] and may lead to an emergency room visit. It is usually easy to figure out that the patient has taken lysergic acid diethylamide. In addition to the psychological and physiological symptoms described earlier, patients usually have a clear sensorium without memory impairment and are able to provide a complete history. Furthermore, they often are accompanied by someone who was with them when they took the drug and who can confirm the suspected diagnosis.

In some cases a "bad trip" from lysergic acid diethylamide may be suspected but a confirmative history cannot be attained. For example, the individual may have unintentionally been exposed, may have been poisoned or may simply be too agitated to provide a coherent history. Toxicology panels in most acute care settings do not routinely screen for lysergic acid diethylamide. In these cases, several additional etiologies should be considered such as intoxication with another hallucinogen, psychiatric illness, and delirium.

Differentiating lysergic acid diethylamide from other phenethylamine and indolealkylamine hallucinogens, for the most part, is academic as they are treated similarly. It is, however, important to differentiate lysergic acid diethylamide from phencyclidine intoxication as the pharmacological management differs. Lysergic acid diethylamide is never smoked; therefore, if an individual reports having smoked the hallucinogen, phencyclidine should be considered. In addition, individuals intoxicated on phencyclidine are often brought in by authorities because of extremely disorganized, inappropriate, or combative behavior.

Acute lysergic acid diethylamide intoxication and the "bad trip" may superficially resemble psychiatric illnesses such as panic disorder, schizophrenia, or the mania of bipolar disorder. Sympathomimetic symptoms, ocular abnormalities (hippos and anisocoria) and visual perceptual disturbances suggest lysergic acid diethylamide intoxication but are not pathognomonic. Time is the best way to differentiate lysergic acid diethylamide psychosis from schizophrenia or mania. After several hours without pharmacologic treatment, lysergic acid diethylamide

intoxication wears off. Mania and schizophrenia do not. While feeling overwhelmed, scared and afraid of losing control occurs in panic attacks, lysergic acid diethylamide intoxication is further characterized by dramatic and persistent perceptual distortions. As with any altered mental state, the clinician should have a low threshold for suspecting delirium. Unlike delirium, there is generally no fluctuation level consciousness with lysergic acid diethylamide intoxication.

The "bad trip" generally does not require inpatient hospitalization because of its time limited course and quick recovery. The patient should be placed in a quiet, non-stimulating environment and provided continuous reassurance that his or her state of mind is drug induced and will not result in permanent brain damage [129]. Given that most emergency rooms are chaotic and understaffed, this may not be a realistic option. Furthermore, the patient may be too disorganized or combative to be "talked down". When medications are needed, benzodiazepines are probably the best choice, as long as delirium has been ruled out. The use of neuroleptics should be reserved for instances where none of the aforementioned efforts have succeeded. High-potency (less anticholinergic) neuroleptics should be used because anticholinergic neuroleptics have been associated with paradoxical reactions [119], hypotension, and anticholinergic crises [79, 125, 126].

Flashbacks

Flashbacks are referred to as hallucinogen persisting perception disorder by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition when they cause significant distress. They are defined as "the transient recurrence of disturbances in perception that are reminiscent of those experienced during one or more earlier Hallucinogen Intoxications" [32]. The most common phenomena are visual distortions such as color confusion, geometric hallucinations and trailing, but the content of the flashback may involve any of the senses [60, 116]. It is not known what causes flashbacks. Theories include persisting damage to visual processing systems [1, 7], death of inhibitory cortical interneurons [3, 42], reverse tolerance [127], and that they are an atypical dissociative state [86].

Flashbacks may occur several days to several years after the antecedent use of lysergic acid diethylamide and have been reported with mescaline, phencyclidine and marijuana [69, 86]. Some users find these episodes pleasant and even refer to them as "free trips". For others, they are terrifying and recur frequently (hallucinogen persisting perception disorder). Obviously, they can be dangerous if they occur at an importune time such as while swimming or driving. An antecedent good trip does not predict a good flashback.

It is unclear what determines who will experience flashbacks and whether or not the experience will be pleasant. Flashbacks have reportedly been induced by a myriad of situations including stress, exercise, pregnancy, sexual intercourse, dark environments, flashing lights, monotony, and use of other psychoactive drugs [2, 9, 24, 74, 121]. It is estimated that anywhere from 15 to 60% of lysergic acid diethylamide users experience flashbacks [121, 141].

People experiencing flashbacks may seek treatment with their general physician, ophthalmologists, neurologists or psychiatrists with concerns about their vision, that they have a neurological disorder, or that they are loosing their mind. The best treatment, as with "the bad trip," seems to be reassurance [134]. There is no established pharmacological treatment, but case reports suggest that such individuals may respond to typical antipsychotics [11, 75, 87, 93], clonidine [73], benzodiazepines [4, 24, 134], naltrexone [76], or phenytoin [133]. The atypical antipsychotic risperidone may exacerbate hallucinogen persisting perception disorder [6, 10, 90]. In addition, there have been reports of both exacerbation [82] and reduction [147] of hallucinogen persisting perception disorder following treatment with selective serotonin reuptake inhibitors. Despite their efficacy and minimal side effects, benzodiazepines may not be the first-line treatment for many individuals with

flashbacks because of abuse potential. Given that the flashback experience is often precipitated by psychiatric illnesses as well as other illicit drug use, it is possible that the success of the medications listed above is related to treatment of concurrent illness. Regardless of treatment, the frequency of flashbacks tends to decrease with time.

Persistent Psychosis and Relationship to Mental Illness

Occasionally, lysergic acid diethylamide appears to precipitate a "persistent psychosis" characterized by visual hallucinations, mania, grandiosity, and religiosity [4]. It is estimated to occur in 0.08% [81] to 4.6% [38] of people who have used lysergic acid diethylamide. This syndrome has led to innumerable studies attempting to establish a relationship between lysergic acid diethylamide use and psychiatric illness. In general, these studies suffer from a multitude of weaknesses. It is beyond the scope of this chapter and not particularly fruitful to present all of the case reports and studies regarding lysergic acid diethylamide-related psychosis. For a comprehensive overview, the reader is referred to Abraham et al. [4].

Speculation that lysergic acid diethylamide could cause schizophrenia was based on [1] a perceived similarity between lysergic acid diethylamide-associated psychoses and schizophrenia and on [2] the observation that lysergic acid diethylamide is a serotonin-2A agonist and the atypical antipsychotics block serotonin-2A receptors. Although the two states are characterized by perceptual disturbances, they are otherwise dissimilar. Auditory hallucinations, delusions and negative symptoms, core features of schizophrenia, are not typical of lysergic acid diethylamide-related psychoses. The frequently reported symptoms of persistent psychosis (grandiosity, religiosity, visual distortions) are not characteristic of schizophrenia. In regard to the serotonin-2A receptor link, it is now clear that the serotonin-2A antagonistic properties of atypical antipsychotics do not lend superior efficacy in treating schizophrenia.

Psilocybin

Psilocybin, like lysergic acid diethylamide, is an indolealkylamine hallucinogen. Psilocybin can be derived from several genera of mushrooms—thus the street name "magic mushrooms." Psilocybe cubensis is the most common source of psilocybin. This mushroom grows on cow and horse manure in South America, Mexico, and most non-arid areas of the United States [128]. As with lysergic acid diethylamide, it was Albert Hoffman who isolated and then synthesized psilocybin. It was marketed by Sandoz laboratories under the trade name Indocybin® as a potential tool for psychotherapy in the 1960s.

Psilocybin and its active metabolite psilocin are both schedule I drugs. The spore prints, however, remain legal (except in California), presumably to provide mycologists the ability to grow pure psilocybin. Not surprisingly, several drug-oriented magazines advertise home cultivation kits that include live mycelia. The mushrooms can be eaten fresh, dried, or brewed. They are usually ingested orally but there is a case report of intravenous injection [28]. Psilocybin is metabolized into psilocin which responsible for the psychoactive effects [77]. Typical doses of psilocybin range from 4–20 mg (40 μg/kg) corresponding to 1–2 g of dried mushrooms [128]. Sympathomimetic symptoms occur at lower doses (3–5 mg), and psychological effects are elicited by doses above 8 mg [108]. Psychological effects begin within 30 min of ingestion, peak at 2–3 h, and dissipate by 12 h [33].

Physiological changes are less pronounced than with lysergic acid diethylamide and are composed mainly of mydriasis and slight elevation in blood pressure and heart rate [33]. The psychological experience is similar to the other indolealkylamine and phenethylamine hallucinogens and cross-tolerance develops rapidly

[64, 113]. Some users report a more spiritual experience with psilocybin, but this may stem from its well-known use historically in spiritual ceremonies. Griffiths et al. conducted a double-blind controlled study in which hallucinogen naïve subjects were given either psilocybin or amphetamine under conditions that would foster a spiritual experience. In this study, psilocybin occasioned sustained experiences similar to spontaneously occurring mystical experiences [50].

As with lysergic acid diethylamide, use of psilocybin from a physical standpoint, is relatively safe and the adverse reactions, albeit uncommon, are managed similarly. Only one third of "magic mushrooms" bought on the street actually contain psilocybin (many are simply store-bought mushrooms laced with phencyclidine) and there are many wild poisonous mushrooms. Adulteration and misidentification are the most common cause of serious adverse outcomes. As with the other serotonergic hallucinogens, tolerance develops quickly but physical dependence does not occur.

Phenethylamine Hallucinogens

Mescaline

Mescaline (3,4,5-trimethoxyphenylethylamine), commonly referred to as Peyote, is a phenethylamine hallucinogen found in several species of North and South American cacti. These cacti have been dubbed the "Divine Cacti" in reference to their several thousand year history of spiritual use by natives of Northern Mexico and the Southwestern United States. The North American peyote cactus, Lophophora williamsii, is a small, spineless cactus that grows in the Rio Grande and in parts of the Mexican plateau.

Mescaline was first isolated from peyote cacti in 1896 and was synthesized approximately 20 years later. It is extracted from the head (top) of the cactus which must be carefully cut at ground level to allow re-growth. Improper harvesting will kill the plant [80]. Because of improper harvesting in Southern Texas Peyote is now listed as an endangered species. Peyote, like the other serotonergic hallucinogens is a Schedule I compound. However, many states allow "bona fide religious" use by members of the Native American Church.

Natural peyote has a bitter taste. It is dried and chewed, soaked in water and drank or injected. Mescaline is typically sold as disk shaped "buttons" composed of either crushed peyote or synthetic mescaline. Genuine peyote is rare outside of the southwestern United States with less than 17% of street samples actually containing mescaline [120]. The hallucinogenic dose is approximately 5 mg/kg (0.3–0.5 g). Each button contains about 50–100 mg of mescaline [120], and users typically ingest 3–8 buttons [71].

Mescaline is markedly less tolerable than the other serotonergic hallucinogens. Within the first 30 min, before the onset of psychological symptoms, users experience nausea, vomiting, restlessness, and headaches [33, 59]. By 1–2 h, however, these unpleasant physiologic symptoms dissipate and the psychic phase characterized by euphoria, sensory distortions, and feelings of confidence begins. The entire experience lasts up to 14 h [33, 59]. As is the case with lysergic acid diethylamide and the other serotonergic hallucinogens, tolerance develops rapidly and physical dependence does not occur [67, 80]. Treatment of acute intoxication and adverse consequences as with lysergic acid diethylamide and psilocybin involves reassurance and use of benzodiazepines if necessary.

3,4-Methylenedioxymethamphetamine, also Known as "Ecstasy"

3,4-Methylenedioxymethamphetamine (ecstasy) is a synthetic drug, primarily smuggled into the United States from clandestine laboratories in Canada, Belgium, and the Netherlands

[34]. It differs from traditional indolealkylamine and phenethylamine serotonergic hallucinogens in structure, pharmacology and psychoactive properties, falling somewhere between amphetamine and mescaline. 3,4-Methylenedioxymethamphetamine was first synthesized in 1912. It was patented as a precursor for a psychotherapeutic agent in 1914, as a cough suppressant in 1956, as a tranquilizer in 1960, and as an appetite suppressant in 1961, but it was never marketed [22]. Rumors abound that the military tested its use as an interrogation tool hoping to capitalize on its ability to instill feelings of openness and intimacy [92]. In the early 1980s, 3,4-methylenedioxymethamphetamine was used in psychotherapy and was purported to improve self-esteem and therapeutic communications [47]. As with lysergic acid diethylamide, there are no data to support its efficacy, and in 1985 the United States Drug Enforcement Administration classified 3,4-methylenedioxymethamphetamine as a schedule I drug.

Pharmacology

While 3,4-methylenedioxymethamphetamine promotes the release and inhibits the breakdown of all monoamine neurotransmitters (serotonin, dopamine and norepinephrine), its most potent and probably most psychologically important interactions are with the serotonin system [41, 72]. In addition to releasing serotonin and inhibiting its breakdown by monoamine oxidase, 3,4-methylenedioxymethamphetamine blocks serotonin reuptake by the serotonin transporter. In total, these actions lead to an acute increase of monoamines in the synaptic cleft followed by neuronal completion within 4–6 hours [18, 31, 47, 92]. This depletion is exacerbated by its acute inhibition of tryptophan hydroxylase, the rate limiting enzyme in the synthesis of serotonin [16]. The rank order of potency for stimulating monoamine release is norepinephrine = serotonin > dopamine [107]. It is hypothesized that the psychological effects result from 3,4-methylenedioxymethamphetamine's effects on the serotonin system, while its physiological effects are adrenergically mediated [136].

In addition to these amphetamine-like effects, 3,4-methylenedioxymethamphetamine has affinity for serotonin-2, M1-muscarinic, H1-histaminergic, and α2-adrenergic receptors, but the clinical significance of this receptor binding profile is unclear. 3,4-Methylenedioxymethamphetamine also indirectly raises blood levels of adrenocorticotropin-releasing hormone, antidiuretic hormone, cortisol, dehydroepiandrosterone, oxytocin, and prolactin [31, 132]. Oxytocin and prolactin are naturally released following orgasm and childbirth and are thought to facilitate bonding. It has been hypothesized that 3,4-methylenedioxymethamphetamine-mediated release of these hormones results in the sense of intimacy central to the 3,4-methylenedioxymethamphetamine experience [106, 132].

3,4-Methylenedioxymethamphetamine is hepatically metabolized via the cytochrome P450 system [47]. It has saturable kinetics meaning that at higher doses metabolism is slower and toxicity is disproportionably more likely [29, 30, 47]. So far, identified metabolites include 3,4-methylenedioxyamphetamine, 4-hydroxy-3-methoxy-methamphetamine, 4-hydroxy-3-methoxyamphetamine, 3,4-dihydroxyamphetamine (also called alpha-methyldopamine), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine. The contribution of these metabolites to the psychoactive and toxic effects of 3,4-methylenedioxymethamphetamine is an area of active research [138].

3,4-Methylenedioxyamphetamine is known to be psychoactive and like 3,4-methylenedioxymethamphetamine it causes release of serotonin and produces an empathogenic experience [65, 118]. It also resembles the traditional serotonergic hallucinogens in that it has higher affinity for the serotonin-2A receptor and produces more profound sensory disturbances. Much of the toxicity associated with 3,4-methylenedioxymethamphetamine has been attributed to this metabolite [25]. In addition to being a metabolite of 3,4-methylenedioxy-

methamphetamine, 3,4-methylenedioxyamphetamine has been synthesized and is used recreationally under the name "Mellow Drug of America".

Street Information

3,4-methylenedioxymethamphetamine is universally referred to as Ecstasy but its street names includes "XTC", "X", "E", "M", "Rolls", "Beans", "Disco Biscuit", "Adam", "Clarity", "Lovers speed", and "Hug Drug". The practices of combining 3,4-methylenedioxymethamphetamine with lysergic acid diethylamide or psilocybin to produce a more powerful psychological experience are referred to as "Candy Flipping" and "Hippie Flipping" respectively. Mentholated products such as cigarettes or vapor rub are often used to heighten the drug's effects.

Ecstasy is distributed as small single-dose tablets of various colors often decorated with icons or phrases (Fig. 3). These tablets usually contain 15–150 mg of 3,4-methylenedioxymethamphetamine. The tablet form lends a pharmaceutical appearance and a false impression that the contents are safe and uncontaminated. However, pure ecstasy, as described below, is considerably less safe than perceived by most users and often the contents are contaminated with acetaminophen, stimulants or other hallucinogens [40, 46, 122, 146, 148]. Although ecstasy is usually ingested orally, the tablets can be either crushed and snorted or dissolved and injected [89, 113].

Ecstasy is classified with other synthetic drugs such as gamma-hydroxy-butyrate, ketamine, and flunitrazepam as a club drug

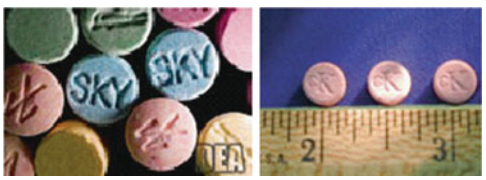


Fig. 3 Photographs of 3,4-methylenedioxymethamphetamine taken from the United States Drug Enforcement Administration Website

because of its popularity at dance parties, raves, and night clubs. In fact, it has been estimated that 3,4-methylenedioxymethamphetamine is present at seventy percent of raves making it the most prevalent club drug [98]. It follows marijuana as the second most commonly used control substance in Europe [26], and in 2004 the United Nations World Drug Report estimated that more than 8.3 million people worldwide had taken ecstasy. In 2007, according to the Monitoring the Future study, 6.5% of 12th graders reported having used ecstasy.

Physiological and Psychological Effects

3,4-Methylenedioxymethamphetamine is structurally similar to both amphetamine and mescaline however it is less stimulating and addictive then amphetamine and produces less profound sensory distortions than mescaline and the other serotonergic hallucinogens [20].

Physiological effects include sympathomimetic symptoms such as tachycardia, mydriasis, diaphoresis, tremor and hypertension [103]. Urinary retention, esophoria (eyes turning inward), trismus, and bruxisms are also common [63]. 3,4-Methylenedioxymethamphetamine users attempt to avoid the latter by sucking pacifiers or lollipops [124]. Interestingly, with repeated administration these adverse effects become more pronounced and the sought after psychological experiences diminish [48].

The psychological experience begins 30–60 min following oral ingestion, peaks at 60–90 min, and last from 4 to 8 h [47, 122]. Users initially feel agitated, have decreased thirst and hunger and experience a distorted sense of time. This is followed by increased energy with euphoria, enhanced sense of intimacy and social tolerance [36, 51, 91]. Its effects on sociality have earned it the vernacular name "the luv drug" and the proposed pharmacological classification as an "entactogen" or "empathogens" [100, 137]. Several days after ingestion of 3,4-methylenedioxymethamphetamine, users tend to experience depressive symptoms, referred to as "the midweek blues" [27, 48, 100, 137, 139].

There is no evidence at this time to suggest that 3,4-methylenedioxymethamphetamine is addictive. As is the case with lysergic acid diethylamide, dependence is unlikely because tolerance develops rapidly [48, 109].

Adverse Consequences

Compared with lysergic acid diethylamide, untoward psychological experiences are less common and less severe. They include over-arousal, sensory illusions, depersonalization, anxiety and occasionally panic attacks [109, 139, 148]. As is the case with the bad trip, benzodiazepines may be helpful [85, 104].

There is much speculation but no definitive evidence of permanent brain damage in humans. The speculation stems from findings in animal studies of an association between 3,4-methylenedioxymethamphetamine and sustained depletion of serotonin and 5-hydroxyindoleacetic acid, inhibition of tryptophan hydroxylase, loss of serotonin receptors and transporters, and loss of fine axons in various brain areas [47]. This evidence for brain damage in non-human species precludes ethical prospective studies in humans. Thus, as with lysergic acid diethylamide, the majority of studies attempting to clarify a relationship between 3,4-methylenedioxymethamphetamine use and long-term sequelae are retrospective and unable to control for poly-drug use or to pre-existing susceptibility to mental illness. Whereas repeated use of straight amphetamine is clearly associated with long-term brain damage, there is no clear evidence for a similar response to 3,4-methylenedioxymethamphetamine; however, only time will tell as the current cohort of club-drug users' age.

Unlike lysergic acid diethylamide, Ecstasy use has been associated with severe life-threatening adverse consequences [111]. The risk of death for first-time users is estimated to be between 1 in 2000 and 1 in 50,000 [45]. 3,4-Methylenedioxymethamphetamine has received much of its notoriety for causing severe hyperpyrexia leading to rhabdomyolysis, disseminated intravascular coagulopathy and multi-organ failure [56]. 3,4-Methylenedioxymethamphetamine, via its affects on serotonin and dopamine, resets the body's internal thermostat. This is compounded by the hot, aerobically intensive dance party venues where it is often used [55] and by the frequent augmentation with diuretics such as alcohol and caffeine.

3,4-Methylenedioxymethamphetamine users are also susceptible to developing another hyperthermic condition, serotonin syndrome, particularly if they have ingested other serotonergic drugs. This is not unlikely given the multitude of drugs with effects on serotonin. Recreational drugs such as amphetamines or cocaine may intentionally be combined with ecstasy. Inadvertent use of prescribed antidepressants as well as purposeful use of these drugs to boost the psychological effects of 3,4-methylenedioxymethamphetamine is also common. Unusual serotonin reuptake inhibitors such as phenylpiperidine opioids (methadone, meperidine, tramadol, propoxyphene) and monoamine oxidase inhibitors such as linezolid and isoniazide and ritonavir in combination with lysergic acid diethylamide might also precipitate a serotonin syndrome [43, 101]. Serotonin syndrome is characterized by muscle rigidity, shivering, tremor and increased deep tendon reflexes. The excessive muscle contraction leads to hyperthermia [43]. The associated mortality rate is 10–15% [51].

3,4-Methylenedioxymethamphetamine is associated with a host of other life-threatening consequences. It directly increases antidiuretic hormone release [54]. This combined with over hydration in response to the well publicized concern of hyperthermia may induce dilutional hyponatremia and subsequent cerebral edema [53, 83]. Symptoms include headache, delirium, irritability, nystagmus, and fatal cerebral herniation [41]. Perhaps because of its sympathomimetic properties, there have been numerous case reports of an association with intracranial hemorrhage, venous sinus thrombosis [44, 52, 62, 114] and sudden death due to cardiac arrhythmias [51, 56, 88, 130]. Interestingly, there also appears to be an

association, for unclear reasons, with pneumothoraces and pneumomediastinaum [11, 14, 84, 110]. Unrelated to hyperthermia-induced multi-organ failure, 3,4-methylenedioxymethamphetamine can cause liver failure that likely is mediated by a hypersensitivity reaction [12, 35, 37]. In individuals under 25 years old, Ecstasy is a common cause of hepatic injury and should be suspected in any young person presenting with liver damage [12].

Management of Acute Toxicity

Activated charcoal may be used in the acute management of 3,4-methylenedioxymethamphetamine toxicity in the unlikely scenario that the individual presents within 1 h of ingestion. Otherwise, management involves fluid replacement in dehydrated patients with hypotension and tachycardia and use of labetalol for tachycardia and hypertension. Antihypertensive medications blocking both α and β adrenergic receptors are preferable. Unopposed β receptor blockade may worsen hypertension due to loss of β adrenergic-mediated vasodilation. Treatment of severe hyperthermia, whether due directly to 3,4-methylenedioxymethamphetamine or 3,4-meth ylenedioxymethamphetamine-induced serotonin syndrome, involves rapid cooling and supportive measures provided in an intensive care setting. Severe cases require sedation, intubation and paralysis to decrease heat production from muscle contraction [51]. It is unclear at this point whether dantrolene is helpful [51].

Conclusions

In conclusion, many serotonergic hallucinogens are naturally occurring compounds that have been used for thousands of years to induce perception altering experiences. They have been an important part of spirituality in many cultures throughout history, likely reflecting the profundity of the experience they elicit. Fascination with these mind altering drugs continues as clandestine chemists persist in synthesizing more varieties. Surprisingly, despite their potent psychological effects, these drugs are considerably safer and less addictive than many other drugs of abuse such as heroin or cocaine. Ecstasy, the most popular of the synthetic compounds, differs considerably from the traditional serotonergic hallucinogens in pharmacology and psychoactive experience. Its empathogenic effects are attractive to young people and lend a false impression of safety as it already appears to be a more dangerous drug than the traditional serotonergic hallucinogens. The long-term effects have yet to be determined as the current 18–25 year olds are the first generation to use it in significant numbers.

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Ketamine and Phencyclidine

Michael F. Weaver and Sidney H. Schnoll

Contents

Introduction

Ketamine and phencyclidine are chemically related to each other and have psychotropic effects similar to other prototypical hallucinogens such as lysergic acid diethylamide. Phencyclidine was developed first as a dissociative anesthetic for animals and humans, but seizures, recreational abuse and unpredictable effects have prevented its therapeutic use. Ketamine was developed after phencyclidine and has similar properties, although it is still used therapeutically as an anesthetic and analgesic in humans and animals. Most ketamine used illicitly is diverted from veterinary supplies. Both drugs have been abused since the 1970s and have become popular again in the 2000s, especially among young adults who are active in the club scene.

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Pharmacology

Mechanism of Action

Ketamine and phencyclidine are arylcyclohexylamines, which are dissociative anesthetics that produce perceptual distortions similar to hallucinogens, as well as other effects, so they are often classified as hallucinogens. Ketamine is a derivative of phencyclidine that is less potent and shorter-acting, and is still used therapeutically in medical settings as an anesthetic and analgesic in humans [7]. Ketamine and phencyclidine selectively reduce the excitatory actions of glutamate on central nervous system neurons mediated by the *N*-methyl-*D*-aspartate receptor complex [3]. These receptors mediate ion flux through

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_28,

channels permeable to sodium, potassium, and calcium, and are involved in synaptic transmission, long-term potentiation, and neuron plasticity. Pharmaco-magnetic resonance imaging has confirmed that the subjective effects of ketamine are mediated by enhanced glutamate release [12]. In addition, phencyclidine affects mu opioid receptors [15], blocks dopamine uptake [4], and inhibits serotonin uptake [43]. Phencyclidine binds to specific receptors in the liver, kidney, lung, heart, and brain [48]. However, the exact mechanism of the effects of ketamine and phencyclidine has not been determined. Metabolism of ketamine and phencyclidine occurs in the liver by oxidation, hydroxylation, and then conjugation with glucuronic acid [49].

Routes of Administration

Ketamine and phencyclidine can be taken orally, inhaled intranasally, smoked, or injected intramuscularly, subcutaneously, or intravenously. Ketamine is obtained primarily in powder form and taken by intranasal insufflation ("snorting") of lines [22], which has a more rapid onset but a shorter duration of effects than when taken orally. Ketamine injection involves particular paraphernalia and high-risk practices [25]. Intramuscular injection is perceived as easier and less threatening than intravenous injection [26].

Phencyclidine is taken as a tablet ("PeaCe Pill," or "PCP"), powder ("angel dust"), or liquid ("whack"). It is smoked alone or when added to tobacco cigarettes or marijuana joints, a combination known as "fry" [35]. The onset of effects when smoked is almost immediate, similar to intravenous administration [30], and is much more rapid than when taken orally (onset takes more than an hour).

Epidemiology

Ketamine

Ketamine was developed in the 1960s as a surgical anesthetic [9]. Recreational use began in the 1970s on the U.S. West coast [36], but it was not registered as a scheduled drug in the U.S. until 1997 or until 2006 in the U.K. The prevalence of ketamine use appears to be stabilizing in the U.S. [23] but is rising in Europe and Asia [22]. There are many different street names for ketamine (Table 1). Nearly all ketamine users are polysubstance users, with 98% using drugs from three or more drug classes, such as inhalants and heroin [50].

Table 1 Street names

Ketamine	Phencyclidine
Cat Valium	Angel dust
K	Animal tranquilizer
Ket	Embalming fluid
Kit Kat	Fry
Special K	Hog
Super K	PCP
Vitamin K	Peace Pill
	Purple Haze
	Whack

The National Institute on Drug Abuse has identified six drugs as club drugs, including ketamine. Club drugs are licit and illicit drugs from different classes that are used primarily by young adults in bars, clubs, concerts, and dance parties or "raves". These substances are used illicitly in those settings due to the perception that they enhance the sensory experience at dance parties where strobe lights, glow sticks, and "techno" music (wordless music with a driving beat) are part of the overall event [46]. Over 40% of those who use club drugs have tried ketamine [28]. Regular ketamine users are older (in 20s as opposed to teens), employed, and better educated compared with most other club drug users [13]. Although ketamine use is very common among club goers—up to 66%—there is a very low prevalence of ketamine use among young people in the general population [50].

Separate from clubs and raves, ketamine is also frequently used in other settings, such as at home or a friend's house. In addition to club goers, it is used by young injection drug users [25], health care workers [32], and men who have sex with men [8].

Phencyclidine

Phencyclidine was first synthesized in the 1950s as a dissociative anesthetic for therapeutic use and originally described as a drug of abuse in the 1960s. Phencyclidine at various times has achieved popularity as a street drug with many different street names (Table 1), and is frequently sold in mixtures with other drugs [41]. Its use waxes and wanes because of its unpredictable effects. Its use increased in the 1970s and peaked in the 1980s but has experienced a resurgence in popularity since the late 1990s [5]. Although not classified as a club drug by the National Institute on Drug Abuse, phencyclidine is used by young adults in settings similar to other club drugs [5].

Trends in the popularity of specific drugs of abuse tend to be cyclic. Relatively large numbers of new users will experiment with a given drug or develop a pattern of recurrent use, often in combination with other substances. With more users, information about undesirable effects spreads among users, or public health concern prompts a response with dissemination of information about abuse and problems. Then the prevalence of abuse may subside for a while. Phencyclidine has gone through previous cycles of popularity because it is relatively easy to manufacture in clandestine laboratories. However, unpleasant effects of repeated use (including propensity to violence and psychotic symptoms, as well as a high frequency of "bad trips") result in a drop in popularity. Phencyclidine use is on the rise again, along with the use of ketamine as part of the club drug scene.

Abuse and Dependence

Diagnostic and Statistical Manual of Mental Disorders Criteria

The criteria in the text revision of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [2] for abuse and dependence for ketamine and phencyclidine do not differ significantly from the general criteria for substance abuse and dependence (Table 2). Ketamine dependence falls under the heading of phencyclidine-like substances in the text revision of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and does not have a separate diagnosis or criteria set. A specific withdrawal syndrome has not been identified for

Table 2 Abuse and dependence criteria

Abuse	Dependence
Maladaptive pattern of use leading to clinically significant impairment or distress, manifested by 1 or more of the following within a 12-month period:	Maladaptive pattern of use leading to clinically significant impairment or distress, manifested by 3 or more of the following within a 12-month period:
1. Recurrent use resulting in failure to fulfill major role obligations at work, school, or home	1. Tolerance, as defined by either: a. Need for markedly increased amounts to achieve the desired effect b. Markedly diminished effect with continued use of the same amount
2. Recurrent use in situations in which it is physically hazardous	2. Often taken in larger amounts or over a longer period than intended
3. Recurrent substance-related legal problems	3. Persistent desire or unsuccessful efforts to cut down or control use
4. Continued use despite recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	4. Great deal of time spent in activities necessary to obtain, use, or recover from the effects of use
	5. Important social, occupational, or recreational activities are given up or reduced because of use
	6. Use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by use

these drugs, which is also the case for other hallucinogens. Therefore, criteria specific to withdrawal are not utilized to determine a diagnosis of dependence for either ketamine or phencyclidine. There are no other unique criteria for abuse or dependence on ketamine or phencyclidine in the text revision of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.

Tolerance and Withdrawal

Tolerance develops rapidly to the desired effects [24], resulting in reduced length of the subjective experience and requiring an increase in dose to maintain the expected effects. Users escalate the amount used to achieve the full hallucinogenic experience, up to seven times the original amount [31]. Use of higher recreational doses can result in more adverse effects, especially physiological side effects. Use of very high doses can result in onset of full anesthetic effects, which may result in an overdose situation for a recreational user. Continued use of ketamine or phencyclidine despite experiencing these consequences constitutes addiction.

A definitive physiological withdrawal syndrome does not appear to develop after stopping use of ketamine or phencyclidine. Phencyclidine users who smoked at least weekly and acknowledge psychological dependence reported no withdrawal symptoms upon stopping [17].

Intoxication

Ketamine

Psychological Effects

Initial use of ketamine is primarily based on desire for experimentation and openness to new experiences, and secondarily for pleasure [31]. Appealing effects described by users include visual hallucinations and out-of-body experiences; undesirable effects include memory loss and decreased sociability [31]. General central nervous system depressant effects include poor concentration and poor recollection similar to alcohol intoxication, which is not unexpected for an anesthetic drug [37].

Ketamine effects include profound changes in consciousness and psychotomimetic effects such as changes in body image (feeling that the body is made of wood, plastic, or rubber) and possible feelings of spiritual separation from the body, including out-of-body experiences. At low doses, users describe mild dissociative effects, distortion of time and space, and hallucinations [31]. However, laboratory administration of ketamine to healthy volunteers resulted in no reported hallucinations [37]. At large doses, users experience severe dissociation with intense detachment such that their perceptions seem to be located deep within their consciousness and reality is far off in the distance; this is called the "K-hole" [31].

The analgesic and dissociative effects may result in injury or even death in users [31]. Emergency department visits associated with ketamine use increased 200 times from 1995 to 2002 [11]. Cognitive impairments can occur even when a user is drug-free, and frequent users have greater impairment than infrequent users when drug-free [10].

Physiological Effects

At low doses, ketamine causes stimulant effects with a temporary increase in blood pressure and heart rate, as well as diplopia and nystagmus [19]. Tachycardia and hypertension are the most common physical findings after illicit use [47]. Other findings of intoxication include pupil dilation and muscle rigidity. Rhabdomyolysis may result from muscle rigidity combined with exertion in severe agitation. Very large doses result in deep anesthesia with coma and respiratory depression [39]. Other physiologic effects of ketamine include severe gastric pain known as "K-cramps", but the etiology of this is unknown [31].

Management

Management of ketamine intoxication is primarily supportive, and adverse effects typically resolve over several hours for mild to moderate intoxication. A thorough history and physical examination, along with toxicological screening for the presence of ketamine, establish the diagnosis. A quiet environment without bright light can help reduce the agitation and psychotic behaviors that are due to overstimulation.

Additional supportive care may be required for severe intoxication or overdose. Benzodiazepines such as lorazepam are helpful for more severe agitation, anxiety, and/or muscle rigidity.

Phencyclidine

Psychological Effects

A reason for initial use of phencyclidine has been described as a desire for enhancement to the user's everyday life [14]. Reasons for continuation of use include feelings of strength, power, and invulnerability, as well as psychic numbing to self-medicate anger and dysphoric symptoms [17]. The phencyclidine experience is regarded as pleasant only half the time and aversive the other half, but some users report that this unpredictability of effects is an attractive feature [6].

Phencyclidine produces brief dissociative psychotic reactions, similar to schizophrenic psychoses. These reactions are characterized by changes in body image similar to those of ketamine as described above. Moderate phencyclidine intake may lead to a catatonic-like picture, with the individual staring blankly and not responding to stimuli; the eyes remain open, even when the individual is in a comatose state. At higher doses, users have great difficulty differentiating between themselves and their surroundings. Some users have religious experiences while intoxicated, such as feelings of meeting God or knowledge of their own impending death [16].

A dissociative phenomenon occurs occasionally, with phencyclidine abusers exhibiting dangerous or violent behaviors [27]. The individual also may appear psychotic. Previous psychiatric history is associated with a higher likelihood for assaultive behavior from phencyclidine use [29]. Levels of consciousness may fluctuate rapidly while the individual is recovering from the intoxication. The effects of phencyclidine can last for several days since it is one of the longest-acting drugs of abuse.

Physiological Effects

In low-dose intoxication, the individual presents with nystagmus, confusion, ataxia, and sensory impairment. This is the only drug of abuse that causes a characteristic vertical nystagmus (it can also cause horizontal or rotatory nystagmus), which helps to identify it as the cause when an individual presents with intoxication by an unknown drug. The text revision of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition provides a specific criteria set for phencyclidine intoxication [2] based primarily on physiological signs and behavioral changes (Table 3). Three stages of phencyclidine intoxication have been described [38], and individuals may fluctuate between the first two stages for several hours; the third stage occurs when individuals take high doses (Table 4).

In high doses, the drug produces seizures and severe hypertension. The hypertension should be treated vigorously since it may cause hypertensive encephalopathy or intracerebral bleeding. Phencyclidine can also cause life-threatening hyperthermia with temperatures over 106°F, which may occur many hours after use.

Management

The most effective treatment of phencyclidine intoxication is increasing its urinary excretion

Table 3 *Diagnostic and Statistical Manual of Mental Disorders* criteria for phencyclidine intoxication

A. Recent use of phencyclidine (or a related substance)
B. Clinically significant maladaptive behavioral changes that developed during or shortly after phencyclidine use. For example: Belligerence Assaultiveness Impulsiveness Unpredictability Psychomotor agitation Impaired judgment Impaired social or occupational functioning
C. Within an hour (less when smoked, "snorted", or used intravenously), 2 (or more) of the following signs: 1. vertical or horizontal nystagmus 2. hypertension or tachycardia 3. numbness or diminished responsiveness to pain 4. ataxia 5. dysarthria 6. muscle rigidity 7. seizures or coma 8. hyperacusis
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

by acidifying the urine with ammonium chloride or ascorbic acid [45]. Urine acidification should only be performed after it is determined that the individual does not have myoglobinuria (indicating rhabdomyolysis) to prevent the development of acute renal failure. Some practitioners feel that the benefits of urine acidification are outweighed by the risks, especially in individuals with hepatic or renal impairment. If the individual is at low risk for hepatic or renal disease, acidification can be initiated. The urine pH should be monitored and kept around 5.5, after which a diuretic can be administered to enhance excretion. The urine should be checked for the presence of phencyclidine to ensure that it is being excreted. Phencyclidine can be deposited in adipose tissue and released over time, which may result in a prolonged state of confusion that can last for weeks; urine acidification may be helpful to deplete the reserve drug.

In an individual who is hypertensive due to phencyclidine, intravenous antihypertensive medications should be administered to reduce blood pressure. Psychotic behavior can be treated with haloperidol. If the individual is severely agitated and poses a potential threat to self or others, haloperidol or lorazepam is effective to control agitation; barbiturates may be even more efficacious [34].

Phencyclidine Intoxication Delirium

Clinical Presentation

The most common psychiatric syndrome that brings phencyclidine users to medical attention is acute delirium. The duration and severity are dose-related, but the acute episode usually lasts 3–8 h. Phencyclidine intoxication delirium is characterized by clouded consciousness that waxes and wanes (Table 5); this fluctuation may be due to periodic gastric secretion with intestinal reabsorption [20]. The individual's mental status fluctuates through paranoia, mania, rapid thought and speech, grandiosity, and emotional lability. All individuals initially experience distortion of body image (loss of body boundaries) and depersonalization (sense of unreality), followed by feelings of estrangement and loneliness; some individuals become catatonic and have dreamlike experiences. Clinically, individuals display insomnia, restlessness, hyperactivity, purposeless or bizarre behavior, perseveration, agitation, and aggression. Phencyclidine intoxication can be differentiated clinically from phencyclidine delirium because phencyclidine intoxication is accompanied by horizontal or vertical nystagmus, ataxia, or slurred speech, and occurs with a clear sensorium (similar to intoxication with other hallucinogens).

Phencyclidine delirium may persist much longer than the acute intoxication episode. There are three phases of phencyclidine delirium: agitated phase, mixed phase, and resolution phase. Each phase lasts around 5 days. The duration is influenced by degree of exposure to phencyclidine, individual susceptibility, dosage of

Table 4 Stages of phencyclidine intoxication

	Stage 1: Behavioral toxicity	Stage 2: Stupor	Stage 3: Coma
Duration	1–2 h	1–2 h	1–4 days
Vital signs			
Blood pressure and heart rate	Mild elevation	Moderate elevation	Significant elevation
Body temperature	98–101°F	101–103°F	103–108°F (malignant hyperthermia)
Respiratory rate	Mild elevation	Moderate elevation	Periodic respirations, apnea
Visual			
Nystagmus	Horizontal, then vertical	Horizontal, vertical, rotary	Horizontal, vertical, rotary
Pupil response	Variable, often miotic	Reactive	Dilated
Gaze	Blank stare	Fixed stare or roving eyes	Disconjugate
Mental status	Poor concentration, repetitive movements, agitation	Catatonic (with eyes open)	Coma
Reflexes			
Deep tendon reflexes	Clonus	Crossed limb reflexes	Absent
Gag reflex	Increased	Repetitive swallowing	Absent
Corneal reflex	Normal	Absent	Absent
Response to pain	Reduced pinprick sensation	Response only to deep pain	No response to deep pain
Drooling	Mild	Moderate	Severe
Nausea	Mild	Moderate	Severe
Spasticity	Rigidity, spasms, ataxia, dysarthria, grimacing, bruxism	Rigidity, twitching, myoclonus, spasticity	Myoclonus, opisthotonos

Table 5 *Diagnostic and Statistical Manual of Mental Disorders* criteria for phencyclidine intoxication delirium

(A) Disturbance of consciousness (reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

(B) A change in cognition (memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.

(C) The disturbance develops over a short period of time (hours to days) and tends to fluctuate during the course of the day.

(D) Evidence from history, physical examination, or laboratory findings of either:
(1) The symptoms in Criteria A and B developed during phencyclidine intoxication, or
(2) Phencyclidine use is etiologically related to the disturbance

This diagnosis is made instead of a diagnosis of phencyclidine intoxication only when the cognitive symptoms are in excess of those usually associated with phencyclidine intoxication and when the symptoms are sufficiently severe to warrant independent clinical attention.

antipsychotic medication given, and whether urine acidification is undertaken.

Management

The hyperactivity, agitation, and aggression displayed by individuals with this condition result in intense physical exertion. Individuals with phencyclidine delirium are usually hospitalized in a closed psychiatric unit, but it is worthwhile to avoid use of physical restraints and to assure adequate hydration. Benzodiazepines and haloperidol may be helpful for phencyclidine delirium. Urine acidification facilitates excretion of phencyclidine and helps to ameliorate more rapidly the psychosis of this disorder. Urine

acidification should continue for at least 3 days after the acute delirium has resolved, and individuals typically require 3–10 days of urine acidification. Electroconvulsive therapy is useful if individuals fail to respond to antipsychotic treatment after a week of inpatient treatment [18, 40].

Phencyclidine Organic Mental Disorder

Phencyclidine organic mental disorder is a mental impairment that may result from chronic phencyclidine use [45]. Characteristics include memory deficits, confusion or reduced intellectual function, assaultiveness, visual disturbances, and speech difficulty. The most common speech difficulty is blocking, which is the inability to retrieve the proper words. The course is variable, but the confusional state may last 4–6 weeks. Urine acidification may shorten the course, although symptoms gradually improve with time if phencyclidine use does not recur.

Management involves protection from injury and helping to deal with disorientation. Excessive stimulation may result in agitation and violent behavior, so stimulation and sensory input should be minimized. A simple, structured, supportive approach works best in a nonthreatening environment with a nonjudgmental staff.

Chronic Use

It can be difficult to differentiate whether specific long-term effects of chronic use of ketamine or phencyclidine are due solely to the ketamine or phencyclidine. Most users of ketamine or phencyclidine are polysubstance users, so attribution of chronic effects is complicated by use of multiple other substances that may produce their own adverse effects. The current generation of ketamine users is the first to have used it long-term. The chronic health effects of ketamine are not known. More research with studies of the effects of chronic use of ketamine and phencyclidine on physical and mental health is necessary. This will help direct future prevention efforts.

Repeated use of ketamine or phencyclidine may result in long-term psychiatric consequences, such as anxiety, depression, or psychosis. The risk of a prolonged psychiatric reaction depends upon the user's underlying predisposition to develop psychopathology, the amount of prior drug use, and the use of other drugs, as well as the dose and purity of the drug taken [44]. Individuals may present with apathy, hypomania, paranoia, delusions, hallucinations, formal thought disorder, or dissociative states. Treatment of prolonged anxiety, depression, or psychosis is the same as when these conditions are not associated with drug use.

Long-term adverse effects of the chronic use of ketamine include psychological problems such as dysphoria, apathy, or agitation, and impairment of short-term memory [21]. Chronic ketamine use results in impairment in semantic memory [33], with greater impairment correlated with more frequent use; this improves with reduction in ketamine use. Impairment in episodic memory, attention deficit, and some schizotypal symptoms (dissociation, blunted affect, and cognitive disorganization) persist after 3 years despite cessation of ketamine use [33]. Long-term adverse effects of the chronic use of phencyclidine include intoxication delirium and organic mental disorder as described above.

The long-term consequence most commonly associated with the use of drugs such as ketamine and phencyclidine is flashbacks. A flashback is an episode in which certain aspects of a previous psychedelic experience are unexpectedly re-experienced. Triggers include stress, exercise, use of other drugs (especially marijuana), or entering a situation similar to the original drug experience; they may also occur spontaneously [46]. The content varies widely and may include emotional or somatic components, but the perceptual distortions are most commonly re-experienced. This may consist of

afterimages, trails behind moving objects, flashes of color, or lights in the peripheral visual fields. These episodes last several seconds to several minutes and are self-limited. The unpredictability of flashbacks often provokes anxiety when they occur. Flashbacks are fairly rare and tend over time to decrease in frequency, duration, and intensity, as long as no additional drug is taken [44]. Flashbacks are unlikely to occur more than 1 year after the original drug experience. Treatment of flashbacks consists of supportive care, including reassurance that the episode will be brief; benzodiazepines help to reduce anxiety. Although much has been written about flashbacks, the phenomenon is poorly understood and there is not universal support for its existence.

Chronic use of phencyclidine or ketamine may result in different physical health problems. Some health effects are related to the route of administration. Intranasal insufflation results in nasal problems according to studies of regular users [31]. Injection (whether subcutaneous, intramuscular, or intravenous) may result in exposure to blood-borne pathogens such as human immunodeficiency virus or hepatitis C virus, subcutaneous abscesses, or bacterial endocarditis. The most common reason for ketamine users to seek medical attention due to ketamine use is from severe gastrointestinal cramping known as "k-cramps". Up to a third of frequent ketamine users experience this [31], but the cause is unknown and no treatment exists currently. A fifth of users have reported bladder problems due to ulcerative cystitis [42]. Another effect of long-term ketamine use is headaches.

Addiction Treatment

The pattern of use of ketamine and phencyclidine is usually intermittent in social settings, so it may be perceived as less of a problem. This may limit willingness to consider addiction treatment by those who abuse these drugs. Adolescents and young adults are the primary users, so family members should be part of the treatment program. Treatment of abuse and dependence is often difficult due to the young age of most users and concurrent polysubstance abuse. Treatment involves similar components to that of other types of substance abuse, including individual counseling, support groups, and 12-step self-help group attendance. There is no pharmacologic treatment available for phencyclidine or ketamine abuse [1]. Treatment settings focus on behavioral components such as individual and group counseling.

Individuals who chronically abuse phencyclidine display characteristics such as impulsiveness and poor interpersonal relationships [45]. This may make successful treatment more challenging, but a treatment environment with a supportive structure can be helpful. Due to the dissociative effects of ketamine and phencyclidine, those who abuse these drugs may have a sense of loss of contact with their bodies. Progressive relaxation techniques, yoga, and regular exercise may help individuals in treatment to focus and improve their concentration [45]. Chronic use of ketamine and phencyclidine may result in cognitive impairments, so a long-term treatment program must take this into consideration to be successful in maintaining abstinence. The treatment environment should provide a supportive structure [45], recognition that initial engagement may be minimal, and utilization of routine and repetition. Treatment staff can improve the chances for a successful outcome by displaying patience and persistence with individuals.

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Part V
Behavioral Addictions and Treatment

The Biology and Treatment of Pathological Gambling

Iris M. Balodis and Marc N. Potenza

Contents

Introduction

Gambling has become increasingly accessible and socially acceptable over the past two decades, with an increasing number of venues and opportunities through casinos, video lottery terminals, sports betting venues, and online poker and other gambling sites. Although most people participate in gambling activities recreationally, some experience gambling problems, including the most severe form, pathological gambling [107]. Pathological gambling has been associated with significant financial debt, family tension, divorce, and criminal activity such as fraud and embezzlement [77, 87]. Extreme cases have involved staged kidnappings and serious child neglect leading to death, murder, and suicide [77].

Pathological gambling is defined as persistent and recurrent maladaptive gambling behavior that jeopardizes personal, occupational, or social functioning [1]. In the text-revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, pathological gambling is classified as an "impulse control disorder not elsewhere classified", a category that also includes disorders such as kleptomania and pyromania. The core feature of these disorders is the failure to refrain from committing a specific act: individuals generally experience a sense of tension or arousal that is relieved by committing the act, typically resulting in pleasure or gratification (e.g., gambling, stealing, or setting fires) [1].

The Psychiatric Nosology of Pathological Gambling

Pathological gambling has been conceptualized as a disorder falling within an

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_29,

obsessive-compulsive spectrum and as a "behavioral addiction" [9, 97]. Studies of impulse control disorders describe clinical elements including an urge to engage in a typically enjoyable yet, in the long term, counterproductive or harmful behavior, a mounting tension until the behavior is completed, a temporary abatement of tension following completion of the behavior, and a return of tension or appetitive urge following varying amounts of time [67]. Impulse control disorders have been described as having elements of impulsivity and compulsivity. Although the underlying motive of pathological gambling is initially pleasure, with increasing frequency individuals may feel "out of control" and their urges may become unpleasant or ego-dystonic [67, 73]. Although some compulsive aspects to gambling are evident, the co-occurrence of obsessive compulsive disorder and pathological gambling is not that common, while comorbidity with substance dependence occurs frequently [22, 55, 88]. The diagnostic criteria of pathological gambling, listed in the text-revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, share similarities with those for substance dependence. Individuals with pathological gambling can demonstrate tolerance and withdrawal symptoms as they gamble with increasing amounts of money in order to achieve the same hedonic experience, and they may become irritable or restless when attempting to cut down on or quit their gambling [1]. Like individuals with drug addictions, those with pathological gambling demonstrate impaired control over their behavior and may hide the extent of their involvement from loved ones or commit forgery or fraud to sustain their gambling [1]. The term problem gambling has been at times used to describe less severe patterns of gambling than exhibited in pathological gambling. This category is conceptually similar to that of substance abuse, although no formal criteria exist for problem gambling [118]. In addition, the term has been used at times inclusive and at other times exclusive of pathological gambling. The most commonly used screening instrument for pathological gambling is the South Oaks Gambling Screen, and this screen queries the types and frequencies of gambling behaviors as well as gambling-related impact on life functioning, particularly with respect to borrowing money for gambling [65]. The South Oaks Gambling Screen is valid and reliable, and a score ≥ 5 signifies probable pathological gambling [65].

Cognitive Distortions

A frequently acknowledged criterion of pathological gambling is the "chasing" of losses, whereby gamblers attempt to regain accumulated losses by returning to a gambling venue shortly following sustaining gambling losses. Nearly winning (e.g., receiving identical symbols on 2 of the 3 reels on an electronic gambling machine) has been suggested to contribute to gambling behaviors [20]. Individuals with pathological gambling, as well as recreational gamblers, may report other cognitive distortions, such as overestimating their chances of winning and their sense of control: "I know what it takes to win this game". In dice gambling and certain other forms, individuals may keep track of previous numbers in order to inform their subsequent bets with the thought that certain numbers will either appear more frequently because they have been observed previously ("hot numbers") or not ("numbers that are due"). Such a "Gambler's Fallacy" ignores laws of probability: that each role of the dice functions independently of the last. Superstitious behaviours ("I only play at nights"), and attributional biases ("That dealer always makes me lose") are also expressed in pathological gambling as well as in recreational gambling groups [120]. Cognitive distortions may represent relevant considerations in the maintenance of pathological gambling, although their frequent occurrence in non-pathological gambling samples questions their centrality to the disorder [74].

Prevalence Estimates and Characteristics

Precise pathological gambling prevalence estimates may be related to assessment measures and other factors. However, most studies report lifetime prevalence estimates ranging from 0.4 to 3% in the general population, representing approximately two to three million adults in the United States [88, 115, 126]. All types of gambling are also not equally represented in pathological gambling populations; one study suggests that pull-tabs, casino gambling, bingo, cards, lottery and sports betting, in descending order, are most strongly associated with pathological gambling [129], and another study found the highest proportion of pathological gamblers at off-track compared with other venues [77]. Pathological gamblers may engage in multiple types of gambling [129]. Factors associated with pathological gambling include male sex, adolescent and young adult age, and presence of other psychiatric disorder(s) [107]. Minorities and those with a lower socio-economic status also appear more likely to gamble and may be at particular risk for pathological gambling [129]. Some studies have found that men and women with pathological gambling show similarities in demographic and clinical features, including time spent gambling, percentage of income lost through gambling and gambling urge severity [40]. Other studies have identified gender differences in manifestations of gambling behaviors that may have significant implications for prevention and treatment strategies. While men constitute about two-thirds of the pathological gambling population and often show a longer duration of onset and begin gambling early in life (childhood/adolescence), women appear more likely to develop pathological gambling later in life and demonstrate a more rapid progression between onset and problematic engagement, a phenomenon observed in substance use behaviors and described as "telescoping" [40, 117, 130]. Gender differences also exist in the types of gambling behavior and in gambling "triggers". Women may report engaging in fewer forms of gambling, mostly bingo and slot machines, and often cite feeling prompted by negative mood states [40]. In contrast, men are more likely to gamble on cards or sporting events and report a greater saliency of sensory cues, such as sounds or advertisement, in their triggers for gambling [40]. Additionally, women, as compared with men with gambling problems, may experience greater psychiatric comorbidity, particularly with mood and anxiety disorders [26, 27, 88].

Pathological gambling frequently co-occurs with other psychiatric disorders [98]. Some studies estimate that up to three-quarters of individuals with pathological gambling report an alcohol use disorder, over 60% are daily tobacco smokers or nicotine dependent, and up to 40% report other drug abuse [56, 88]. About half of individuals diagnosed with pathological gambling also experience a mood disorder, with a particularly high odds ratio of 8.6 for mania, and roughly 40% are also diagnosed with anxiety disorders [88].

Comorbidity is not limited to the Axis I disorders. Estimates of personality disorders range from 29 to 93% in the pathological gambling population, with one study reporting an average of 4.6 personality disorders per person with pathological gambling [11, 81, 88]. While borderline, histrionic, and antisocial personality disorders are most often cited, these may represent a component of an externalizing syndrome [88]. Personality and temperamental factors may play a role in the maintenance of pathological gambling, as pathological gamblers may show high levels of impulsiveness, novelty-seeking, rigidness, extravagance, and harm avoidance combined with low levels of self-directedness [32, 58, 81]. In particular, impulsivity has been investigated as a key underlying construct, and accordingly, in pathological gambling, severity of gambling behavior and psychological disturbances appear related to this measure [112]. Identification of co-occurring disorders is important as the disorders may guide treatment strategies and influence treatment outcome [13].

The Biochemistry of Pathological Gambling

Serotonin

Pathological gambling shares similar biochemical features with substance dependence and other disorders characterized by impulsive features [13]. Low central levels of serotonin metabolites are observed in the cerebral spinal fluid samples of individuals with impaired impulse control including those with pathological gambling [66, 79, 80, 122, 123]. However, the precise nature of central serotonin function in pathological gambling is complicated by findings suggesting increased levels in pathological gambling [80]. Low endogenous levels of serotonin in pathological gambling are suggested by blunted prolactin responses following a pharmacological challenge [75]. Pharmacological challenges using the partial agonist metachlorophenylpiperazine produce a euphoric high in pathological gamblers, a response also observed in individuals with other impulsive disorders [5, 25, 113]. Together, these findings suggest a role for serotonin in pathological gambling, although the precise nature of its involvement requires further investigation.

Dopamine

Given a role for the mesocorticolimbic dopamine system in mediating the reinforcing properties of drugs [60], dopamine has been hypothesized to be involved in gambling behaviors. The maturation of the mesocorticolimbic dopamine and other systems during adolescence may in part explain the high estimates of gambling problems evidenced during this period [16]. Some data suggest that dopamine levels may increase during gambling behaviors [108]. However, ligand-based imaging studies involving pathological gamblers have yet to be published in peer-reviewed journals. Like with serotonin, studies examining dopamine metabolites in pathological gambling populations have generated inconsistent findings. While one study reported alterations in dopamine metabolites suggesting increased dopamine turnover in pathological gambling, this finding was largely mitigated when controlling for cerebrospinal fluid flow rates [6, 79].

During gambling activity, dopamine levels increase after longer playtimes in both recreational and pathological gamblers [72, 108]. Consistent with the idea that gambling and stimulants generate similar effects, priming individuals with the pro-dopaminergic (and pro-noradrenergic) drug amphetamine was associated with an increase in the desire to gamble and reduction in the confidence to resist gambling in pathological gamblers, and pleasurable and motivational responses were positively associated with problem gambling severity [131]. However, the dopamine D2-like receptor antagonist haloperidol was also found to promote gambling thoughts and behaviors [132]. Hence, a precise role for dopamine in pathological gambling requires further investigation.

Individuals with Parkinson's disease, a disorder characterized by dopamine system degeneration, have experienced gambling problems [28, 125, 127]. Dopamine agonists, such as pramipexole, ropinirole, and pergolide, have been associated with impulse control disorders such as pathological gambling in Parkinson's disease [99, 124, 127, 128]. Other factors, including levodopa dosage, age at Parkinson's disease onset, marital status, family history of gambling problems, family or personal history of alcoholism, high levels of impulsivity, and presence of an impulse control disorder prior to Parkinson's disease onset have also been associated with impulse control disorders such as pathological gambling in Parkinson's disease in systematic, cross-sectional studies [99, 128]. As such, the extent to which pathological gambling in Parkinson's disease reflects the pathophysiology of Parkinson's disease, its treatment, a combination thereof, or other factors requires additional research.

Norepinephrine

Norepinephrine, implicated in sensation-seeking and arousal, has also been investigated in the neurobiology of pathological gambling. Although healthy individuals demonstrate increased levels of norepinephrine prior to, as well as during, gambling sessions, pathological gamblers show particularly high levels of this neurochemical [72, 108]. The desire to start or continue gambling positively correlated with norepinephrine levels in one study of pathological gamblers [72]. The report of altered catecholaminergic response patterns in pathological gambling subjects suggests that gambling may represent a compensatory behavior to heightened arousal levels [72].

The Genetics of Pathological Gambling

An elevated frequency of pathological gambling in first-degree relatives of those with the disorder suggests a genetic component to the disorder [8]. Individuals who report gambling problems in their parents are themselves more likely to have higher scores on the South Oaks Gambling Screen; additionally, if their grandparents are also perceived as having gambling problems, these individuals may have a 12-fold higher odds of meeting criteria for pathological gambling [33]. The heritability estimate of a pathological gambling diagnosis from the Vietnam Era Twin registry is 46%, and lifetime prevalence estimates of pathological gambling in identical twins and fraternal twins are 22.6 and 9.8%, respectively [29]. A further analysis of this sample revealed that both identical and fraternal twins with subclinical pathological gambling symptoms were more likely to have a twin with full pathological gambling [109]. These results support a continuity model of pathological gambling, where subclinical gambling and clinical pathological gambling are differentiated by the number rather than the type of contributing factors [110]. Genetic studies provide support for a familial co-aggregation of pathological gambling and other disorders, such as alcohol dependence, antisocial behaviors, and depression, with significant contributions stemming from shared genetic factors [96, 109, 110].

Molecular genetics have inconsistently implicated allelic variants. In one early study of dopamine-related genes, a D2 dopamine receptor gene variant associated with substance dependence [78] was found in 51% of pathological gamblers but only in 26% of controls [18]. Individuals with the most severe pathology and comorbid substance use were more likely to carry the D2A1 gene [18]. Altered distributions of other dopamine receptor gene variants (e.g., those encoding the D1 and D4 receptors) have been reported in pathological gamblers [19]. However, these early studies have been criticized on methodological grounds [51], and a more recent study using a better controlled design and more thorough assessments did not replicate these findings [23]. As such, further research is needed to identify precise molecular genetic contributions to pathological gambling.

There are also suggestive data for serotonergic and noradrenergic genetic contributions to pathological gambling. One study found that men with pathological gambling are more likely to have a shorter variant of the gene coding for the serotonin transporter [84]. Other studies have also reported differential distributions of polymorphisms of monoamine oxidase-A-encoding genes in men with pathological gambling [50, 84]. Larger, genome-wide studies are needed to identify more precisely genes implicated in pathological gambling, and to investigate gene-by-environment and gene-by-gene interactions.

The Neuropsychology of Pathological Gambling

To date, few studies have examined neuropsychological functioning in pathological gamblers. Initial studies suggest deficits in executive functioning, not accounted for by intellectual

differences as assessed by standard intelligence quotient tests, in pathological gambling that are similar to those evidenced in substance dependent populations [32, 35, 37]. Consistent with pathological gambling's classification as an impulse control disorder, pathological gamblers demonstrate impairments on response inhibition tasks. The Stroop task assesses cognitive control involving attention, conflict monitoring, and response inhibition. Participants are required to name rapidly the ink color of matched (congruent) or mismatched (incongruent) color-word pairs. On congruent trials, the word "red" may be written in the color red while on incongruent trials the word "red" may be written in blue ink and, therefore, requires that the individual responds "blue". Not surprisingly, incongruent trials present greater difficulty as individuals are required to inhibit the pre-potent reading response. Pathological gamblers show impairment on this task by producing more errors (i.e., reading the word, rather than naming the word's color) and in taking longer to respond [32, 101, 105]. Modified versions of this task, sometimes referred to as Emotional, Drug, or Gambling Stroop Tasks, use emotional, drug-related, or gambling-related words, respectively. Subjects are presented with neutral or theoretically disorder-valenced words in different colored ink. In affected individuals as compared with healthy controls, the variant Stroop tasks tend to produce further delays and errors in processing. For example, in both recreational and pathological gamblers, when the words are theoretically more emotionally or motivationally salient rather than are neutral words (e.g., "dice" versus "door"), a more pronounced Stroop effect is observed [12, 69]. Such findings suggest not only an attentional bias for disorder-related stimuli, but also a certain level of automaticity in processing [12].

The neuropsychological function of pathological gamblers as compared with other subject groups has been examined [35–37]. Four groups, consisting of individuals with pathological gambling, Tourette's syndrome, alcohol dependence, or no psychiatric disorder, were compared on tasks assessing executive functioning [35, 37]. On tasks involving response inhibition, including the Stroop Task, the three clinical groups performed significantly worse than did healthy controls, but did not differ from one another. This trend was also observed on the Wisconsin Card Sorting Task, a measure of cognitive flexibility. However, on tasks of planning and time estimation, pathological gamblers and alcohol-dependent individuals showed significantly poorer performance relative to healthy control subjects and those with Tourette's syndrome.

The Iowa Gambling Task is a neurocognitive measure assessing risk/reward decision-making where individuals can choose between different decks of cards with varying schedules of reward [4]. Two disadvantageous decks confer high rewards, but also present even higher penalties, thereby resulting in a net loss for players. Two advantageous decks provide low rewards, but even lower penalties. Therefore, consistent selections from these decks produce an overall gain in money. Pathological gamblers and alcohol-dependent subjects demonstrated disadvantageous performance compared with the healthy control group as well as the Tourette's syndrome group. These findings are consistent with prior reports that pathological gamblers show disadvantageous performance on this task [15, 86]. The performance profile of the pathological gambling group also showed that they responded faster, made fewer response shifts following losses and demonstrated less conceptual knowledge about the task than did healthy controls [35].These findings suggest an impulsive and perseverative response style, and this profile may relate to loss chasing or altered reward processing in the pathological gambling group. A separate study examining the psychophysiological correlates on the Iowa Gambling Task showed that, unlike healthy controls, pathological gamblers fail to show increases in skin conductance response or heart rate accelerations prior to making a disadvantageous choice [36]. These alterations in psychophysiological responses suggest an impairment in risk assessment related to disadvantageous risk-reward decision-making [36].

Neurocognitive research findings in pathological gambling should be interpreted cautiously as many studies do not control for comorbidity, medication status, gambling severity, or gambling type or provide comparison control groups [35]. Gambling motivations may also be important to consider when examining neurocognitive performance in pathological gamblers [35]. Whether individuals gamble in order to heighten arousal or relieve their dysphoric mood may relate to their performance and its underlying bio-behavioral substrates. Impaired performance on some neurocognitive tasks assessing inhibition and decision-making may represent phenotypic markers in pathological gambling that have potential in predicting relapse [38]. More research is needed to identify intermediate phenotypic or endophenotypic markers that may be used in the diagnosis and treatment of pathological gambling.

Neuroimaging Studies

Neuroimaging studies suggest altered functioning in frontal, temporal, and limbic structures in pathological gamblers. The first published study using functional magnetic resonance imaging in pathological gambling utilized happy, sad, and gambling videotapes [95]. While viewing the videos, participants reported the onset of an emotional (e.g., feelings of sadness) or motivational (e.g., gambling urge) response by pressing a button. During the gambling scenarios (but not the happy or sad ones), pathological gamblers showed signal decreases in frontal and orbitofrontal cortical areas, thalamus, and basal ganglia. These brain changes occurred prior to conscious awareness of an emotional/motivational response, i.e., preceding the button-press. This activation pattern contrasts with those from symptom provocation studies in obsessive compulsive disorder in which increased activation of cortico-basal-ganglionic-thalamic circuitry is observed [107].

During the viewing of the final portion of the gambling scenarios, when the most robust gambling stimuli were presented, pathological gamblers (relative to controls) showed less activation of the ventromedial prefrontal cortex. Subsequent studies using an functional magnetic resonance imaging Stroop task, a decision-making, and a simulated gambling task have also demonstrated relatively diminished activation of the ventromedial prefrontal cortex in association with pathological gambling [94, 102, 116]. The ventromedial prefrontal cortex has been implicated in mood regulation, decision-making, and impulsivity [3, 7, 13, 68]. The ventral striatum, functionally connected to the ventromedial prefrontal cortex, has also been shown to activate less strongly in pathological gamblers [100, 102]. Activation in the ventromedial prefrontal cortex and ventral striatum correlated inversely with gambling severity in pathological gamblers during simulated gambling, further suggesting the relevance of these regions to clinical aspects of pathological gambling [102]. Similar patterns of brain activations, including relatively diminished activation of ventral striatum, have been reported in cocaine-dependent subjects viewing cocaine tapes and pathological gambling subjects viewing gambling tapes, suggesting similar neural contributions to appetitive urge states across disorders [100]. These neurobiological findings support the conceptualization of pathological gambling as a "behavioral" or non-substance addiction.

Although to date fewer than ten neuroimaging studies examining neural correlates in pathological gambling have been published, studies using healthy controls have investigated intertemporal choice, loss aversion and other components influencing decision-making [53, 104, 119]. One functional magnetic resonance imaging study examining the neural correlates of loss-chasing behavior demonstrated increased ventromedial prefrontal cortex activation when healthy individuals tried to win back money lost on previous gambles [14]. Loss-chasing, therefore, appears linked to brain areas involved in reward processing [59] and raises the possibility that recreational gamblers may chase losses because they believe that winning is imminent [14]. The extent to which these findings relate to

pathological gambling requires further, direct investigation.

Treatment

Few pharmacological and behavioral therapies targeting pathological gambling have been investigated with respect to their tolerabilities and efficacies. It is estimated that only 7–12% of pathological gamblers seek formal treatment for pathological gambling [61, 111]. These individuals may seek treatment for various reasons (e.g., threats of spousal divorce, suicide attempts), and thus treatment-seeking pathological gamblers may differ from pathological gamblers in the general population [40].

Behavioral Treatments

Although Gamblers Anonymous is arguably the most widespread intervention for pathological gambling, questions exist regarding its effectiveness. One study reported that most individuals attend only one or two meetings and less than 10% remain in attendance after one year [114]. Cognitive therapies have shown promise in the treatment of pathological gambling. One cognitive therapy targets erroneous cognitions, such as illusions of control over random events, and was found to be helpful in an initial, small, wait-list-controlled study [62]. Following this treatment, approximately 86% of individuals no longer met pathological gambling criteria, and individuals reported greater self-efficacy and perception of control over their gambling problem. This type of therapy may also be effective in group format, and therapeutic gains appear to be maintained after one year [63]. Cognitive behavioral therapy for pathological gambling identifies gambling triggers and cognitive biases, reinforces non-gambling behaviors, teaches coping skills, and addresses finance management and debt settlement [89]. Individuals receiving cognitive behavioral therapy showed greater reductions in gambling problems and time spent gambling than did those attending Gamblers Anonymous. However, both groups demonstrated improvements over time.

Other psychological interventions have been developed including aversive therapy, imaginal desensitization, motivational enhancement, brief guided therapy, self-help workbooks and eclectic therapies. The effectiveness of psychological interventions has been complicated by differences in assessments used to evaluate treatment outcome [82]. However, a review of behavioral therapy outcome studies showed that these interventions are associated with significant improvement both post-treatment and after long-term follow-up when compared with no treatment [82]. It should be noted, however, that drop-out rates in many studies approach 50% [62]. Future studies should examine the efficacy of combining different therapies that target different cognitive and motivational aspects of pathological gambling.

Pharmacological Treatments

Like in behavioral treatments, the evaluation of the efficacies of pharmacological therapies in pathological gambling is complicated by differences in sample sizes, trial durations, dosing strategies, trial designs, and outcome measures.

The findings of low serotonin levels in pathological gambling and blunted ventromedial prefrontal cortex to serotonergic drugs in impulse control disorders [103] suggest that selective serotonin reuptake inhibitors could potentially be useful therapeutic agents for pathological gambling. Several studies have demonstrated that selective serotonin reuptake inhibitors such as fluvoxamine and paroxetine are associated with short-term improvement in pathological gamblers [24, 47, 49, 57]. However, placebo-controlled trials of fluvoxamine and paroxetine have also yielded negative results [10, 39]. Some variability in outcome may relate to heterogeneity of pathological gamblers, and guiding selection of therapies according to presence

of co-occurring disorders (e.g., selective serotonin reuptake inhibitors for individuals with co-occurring pathological gambling and anxiety disorders) may help improve treatment outcomes [41, 98]. Consistent with this notion, a study examining lithium in the treatment of individuals with co-occurring pathological gambling and bipolar-spectrum disorders found lithium superior to placebo in reducing symptoms of both gambling and mania [48].

Three separate studies have found opioid antagonists (naltrexone and nalmefene) superior to placebo in the treatment of pathological gambling [43, 45, 58]. Individuals with a family history of alcoholism may be particularly responsive to treatment with an opiate antagonist [46]. Medications targeting dopamine receptors directly (e.g., the serotonin/dopamine antagonist olanzapine) have been shown in two placebo-controlled trials not to be superior to placebo in the treatment of pathological gambling [31, 70].

Natural Recovery

Like in drug addictions, untreated recovery appears to occur in pathological gambling. Using cross-sectional data, it has been estimated that most pathological gamblers recover without any therapeutic intervention [111]. These findings suggest that pathological gambling in the community may represent an episodic rather than chronic disorder, and which factors influence its course require further investigation [111, 121].

Prevention Efforts

Few studies have investigated prevention efforts for pathological gambling. Primary prevention efforts for gambling might include more stringent regulation of gambling availability and advertisements and education initiatives on risks associated with gambling. The effectiveness of such interventions requires empirical testing. Given the exposure to nicotine and mutagens in some gambling environments, gambling may be associated with significant health risks [54]. Therefore, the amount of tobacco smoke exposure should be considered in discussions of healthy levels of gambling. A less apparent health risk may be related to the significant increases in autonomic arousal associated with gambling [71, 72]; approximately 83% of casino-related deaths may be attributable to sudden cardiac arrests [52].

Identifying those individuals at greatest risk for developing pathological gambling may be important in developing effective prevention strategies. Many health care providers may not inquire about pathological gambling when assessing patients [17]. Like for substance abuse and dependence, screening tools for pathological gambling may be useful for medical practitioners as associations between medical conditions and pathological gambling have been observed in community and medical clinic samples [26, 83, 90, 91, 93]. As discussed above, individuals with Parkinson's disease should be monitored carefully during the course of their treatment to identify any changes in gambling behaviors.

Other prevention efforts include the use of gambling helplines and self-exclusion policies at casinos where individuals can voluntarily ask that they not be allowed on the gambling site premises [61, 92]. The effectiveness of both of these prevention efforts has received relatively little study, although early analysis of self-exclusion programs suggest that they are associated with a 30% self-reported abstinence of gambling activities [61, 64]. Self-exclusion programs may benefit from more extensive reinforcement through professional follow-up [61].

Research Challenges and Future Directions

Over the last decade, several pharmacological and behavioral treatments of pathological gambling have received initial empirical support [44, 76]. However, multiple questions and potentially confounding factors exist. For example, as relatively few pathological gamblers seek treatment, it is not clear whether those who do are representative of the larger pathological gambling

population [76]. Individuals who seek help may demonstrate ambivalence towards treatment. For example, many individuals may still maintain positive feelings about gambling, and completion of even a short six-week treatment study may be difficult to achieve [121]. The issue of monetary incentives for study participation may raise questions as subjects may be motivated to participate by receipt of financial compensation rather than a genuine desire to stop gambling [121]. Moreover, the impetus for change in many pathological gamblers are financial crises that may not be resolved through psychological or pharmacological treatments [121].

Many early treatment outcome studies have excluded individuals with co-occurring disorders. Given that many pathological gamblers suffer from a co-occurring disorder, questions are raised about the generalizability of such studies [76]. Initial studies suggest that co-occurring disorders influence treatment response [98]. Therefore, common co-occurring conditions should be identified and treatment outcome studies evaluated accordingly [76]. Furthermore, the use of a clinical control group in treatment studies, such as groups with other impulse control disorders or alcohol dependence, could be useful in identifying underlying bio-behavioral factors and assessing similarities with other disorders [34].

There are many unique populations affected by pathological gambling. However, research to date has predominantly included Caucasian males. Racial/ethnic differences have been observed with respect to pathological gambling in Asian [85], Black [2], Hispanic [21], and Native American [30] groups. Differences in clinical characteristics of pathological gamblers have also been found to be associated with sexual orientation [42]. Individuals from minority populations may benefit preferentially from specific therapies. With respect to gender, although males and females with pathological gambling may both be willing to seek treatment, differences in clinical features may be important in guiding treatment [40]. For example, gambling triggers in females may be more strongly influenced by mood state, and thus therapy may preferentially target affective symptoms or mood regulation [40].

Pathological gambling and substance dependence appear to involve similar patterns of dysregulation within ventral components of fronto-striatal circuitry, neurocognitive impairments in inhibition and decision-making and neurochemical and psychophysiological markers suggestive of arousal deficits. The frequent co-occurrence of pathological gambling and substance dependence disorders is consistent with the notion that similar mechanisms may underlie both disorders. Additional research may identify more specifically how pathological gambling relates to substance-based addictions and whether classification of pathological gambling as a non-substance addiction is appropriate.

The continued use of brain imaging techniques and the performance of large genetic studies should help advance the knowledge of the bio-behavioral basis of pathological gambling. The use of neuropsychological, neurochemical, neuroimaging, genetic, environmental, physiological, and self-report measures in treatment and community settings should facilitate integration of clinically relevant information [34, 40]. An improved understanding of the relationship among these different facets should aid in establishing clinically relevant intermediary phenotypes for pathological gambling and advancing efforts in better characterization, diagnosis, and treatment of pathological gamblers.

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An Addiction Model of Binge Eating Disorder

Jacqueline C. Carter and Caroline Davis

Contents

Introduction

The idea of applying an addiction model to eating disorders has been a controversial one (e.g., [116]). While we agree that an addiction model does not adequately address the core clinical features of the two established eating disorders, anorexia nervosa and bulimia nervosa, our aim is to convince readers of the utility of this perspective for the newly recognized "binge eating disorder". Binge eating disorder is characterized as recurrent episodes of binge eating in the absence of the extreme weight control behaviors (e.g., fasting or self-induced vomiting) seen in anorexia nervosa and bulimia nervosa. In this chapter, we argue that conceptualizing binge eating disorder as an addictive disorder would be useful for both researchers and clinicians in understanding the causes of compulsive overeating and in devising more effective treatment interventions. In presenting our case, we will consider clinical and behavioral parallels between binge eating and drug abuse. We will also discuss the similarities in their biological underpinnings and the overlapping risk factors for their development. Finally, we will consider the treatment implications of an addiction model of binge eating disorder and make several recommendations for integrating an addiction approach into established treatments for this disorder.

History and Background

Although people had written about the enslaving properties of opium and alcohol for centuries, it wasn't until the 1800s that the notion of drug abuse as a disease entity—rather than an issue of moral culpability—entered the general parlance of medical professionals [61]. While the original (seventeenth-century) use of the word *addicted* meant "to give over . . . to someone or some practice", its first appearance with specific reference

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_30,

to narcotics was not until the early twentieth century [12], and for most of that time it was largely confined to the misuse of alcohol and the opiates. With the rise in popularity of psychiatry after World War II and the "rediscovery of addiction" [11], other substances such as cocaine, amphetamine, and nicotine were added to the list of addictive drugs. (Although the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition nomenclature does not include the word "addiction", its "dependence" terminology is closest to this condition.)

In recent years, there has been an interesting clinical and scientific shift in perspective, with many believing that addiction should encompass the compulsive engagement in activities such as gaming, internet use, and shopping, in addition to its conventional relation with pharmacological rewards [46, 52, 78, 84]. Current debate has even extended to the possibility that so-called "behavioral addictions" should include the abuse of *natural rewards*—that is, behaviors that are intrinsically necessary for our survival, and in which we freely engage with pleasure and without social sanction.

A few generations ago, it might have seemed heretical to suggest that food could be an addictive substance and overeating could be an addictive behavior. As testament, we were able to find only six published references to such a viewpoint from 1950 to 1970, almost all of them written by T. G. Randolph (e.g., [86]), the well-known founder of environmental medicine. However, a groundswell of change in perspective has occurred in the past few years, as indicated, for example, by the publication of 15 academic papers, in the first two months of 2008, referring to "food addiction". Discussion of this topic has also been matched—probably exceeded—by its frequency in the popular press.

Drugs as Food

Conventional evolutionary "mismatch" views of addiction propose that substance use is a relatively recent phenomenon in the history of our species and that it occurs largely because of the availability of purified and synthetic drugs and their direct routes of administration [77, 93]. In other words, it is the ubiquity and concentrated doses of these substances that have contributed to widespread human drug abuse. By contrast, Sullivan and Hagen pointed out that human beings shared a co-evolutionary relationship with psychotropic plant substances in prehistory for millennia [100]. Indeed, they frequently ate them as food because their ingestion solved a recurrent problem faced by our ancestors.

The neurotransmitters that are essential for normal human functioning—and most implicated in substance use—are dopamine and serotonin, the precursors of which must be provisioned externally from high-quality nutrients such as protein. During most of our history, due to famines and seasonal food shortages, these precursors were nutritionally constrained and, consequently, people experienced neurotransmitter deficits with considerable regularity. Depletions of this sort tend to affect critical behaviors and emotions adversely, including motor activities, cognitive abilities, and mood.

It is also generally believed that over our evolutionary history, certain plants developed chemical defenses against mammalian predators by producing "neurotransmitter substitutes", which had toxic effects when ingested. Sullivan and Hagen argued that in response to this threat, "behaviourally sophisticated hominids" evolved to counter-exploit the potential benefits of plant toxins [100]. For example, because these "neurotransmitter analogues" imparted energy, prevented fatigue, diminished appetite, and increased tolerance for hunger, they helped to avoid the maladaptive "behavioral sequelae of stress" in the absence of adequate food sources. In other words, plant substances served the dual purpose of substituting for more costly energy and buffering against the biological ravages of prolonged stress.

Thus, it seems reasonable and sensible to conclude that organic compounds in our environment can only be categorized as *beneficial* or *harmful* when we take account of "dosage" and

the relevant characteristics of those who partake of them [45].

Food as Drugs

This last point is particularly relevant when considering the typical macronutrient intake in current Western societies. Diets high in concentrated fats and sugars are not only dense in calories, but metabolically efficient because a large proportion of their energy is provided to the consumer. They also tend to elevate mood by releasing neuropeptides, which reinforce their selective preference [55]. Evolutionary biologists believe that "cravings" for sugar and fat evolved to enhance human energy intake in unpredictable nutritional environments, which were universally the norm until relatively recently [45]. However, in the quantities that many people ingest them today, they have an abuse potential rivaling that of popular addictive drugs [96].

The food industry has become especially savvy in exploiting our natural human desire for sugar and fat by increasing many-fold their "dose" in much of our daily foods. For instance, there was a 42% *per capita* increase in the consumption of added fats and a 162% increase in cheese relative to only a 20% increase in fruits and vegetables between 1970 and 2000 [43]. The sharply reduced cost of sugar and vegetable oils worldwide has greatly contributed to the production of highly palatable processed foods [36]. The incidence of snacking, especially in the form of carbohydrates, has also increased over the past 25 years, in tandem with the increase in daily energy intake [90]. "Junk foods", which are the principal type of snack, have little nutritional value, but are highly appealing because of their high fat and sucrose content.

In the case of conventional drugs, greater potency tends to increase their addictive potential. Directly parallel to the notion of "drug dosage" is the size of the meals we are presently served. Wansink and Van Ittersum described the "portion-distorted embarrassment of food" in today's supermarkets and restaurants [109]. To illustrate, a fast-food restaurant meal—a burger, fries, soft drink, and dessert—can provide almost all of one's daily caloric requirements in a single serving. Moreover, the annual growth rate of "fast food" dining has increased 3-fold in the past generation compared with that of at-home consumption [88]. The size of plates, bowls, and glasses in our homes has also steadily increased over the years, and the serving size of some entrees has virtually doubled in recipe books since the 1930s [109].

In summary, just as different drugs promote different degrees of dependence, foods also differ in their capacity to promote abuse [106]. Experts are now confident in claiming that the nutrients composing fast foods are inherently addictive because of their concentration and high volume of fats and sugars. Also, like drugs of abuse, they have the ability to alter brain mechanisms in ways that contribute to their increasingly compulsive use (see [31, 47, 96]).

Clinical and Behavioral Parallels

In making the argument for overeating as an addictive behavior, it is clearly not appropriate to include all cases of excessive food consumption in this taxon. Nor are we claiming that obesity and addiction are one and the same. However, we do believe that binge eating disorder is a phenotype particularly well-suited to such a conceptualization, and that sound clinical and scientific evidence exists to support this viewpoint. Cassin and von Ranson [20] found, for example, that 94% of their adult binge eating disorder sample described themselves as "food addicts" or "compulsive overeaters" and met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for substance dependence disorder [2] when the term "substance" referred to "binge eating". While there is not complete consensus among researchers on the defining features of all addictions, most would agree that there are a common set of defining characteristics. These characteristics include loss of control, tolerance and withdrawal, cravings, and repeated cycles of remission and relapse.

Loss of Control

Perhaps the most clear-cut feature of addiction is the increasingly compulsive use and abuse of the addictive substance or behavior, even in the face of detrimental consequences to health, safety, social relationships, and financial stability. Binge eating disorder is characterized by repetitive and aboulic episodes of overeating, not typically driven by hunger or followed by any compensatory behaviors such as purging, fasting, or excessive exercising. Feeling "out of control" of one's eating behavior is a defining feature of binge eating [2]. Binge eating disorder appears to be a chronic and stable condition [83] with strong links to obesity [32]. Although initially believed to be a disorder of adulthood, there is growing evidence that binge eating disorder also occurs in children and adolescents [17]. In addition to clinical research, there are good experimental paradigms whereby a subset of rats fed an intermittent diet of sugar have developed a pattern of copious consumption resembling human cases of binge eating disorder (e.g., [4, 21]).

Binge eating disorder sufferers typically report distress and guilt about their eating habits, but they have great difficulty controlling these behaviors despite weight gain and ensuing medical problems such as diabetes and hypertension [22]. As a society, we are generally informed and knowledgeable about the negative consequences of poor nutrition and obesity and are sentient of dietary recommendations for good health, so we must conclude that binge eating—like drug addiction—exists despite an awareness of its poor health outcomes.

Tolerance and Withdrawal

In the most general sense, tolerance occurs when a stimulus of a particular magnitude elicits an increasingly diminished response with each repeated exposure and an increasingly higher dose is necessary to achieve the desired effect. This phenomenon is a key characteristic of all drug addictions—and one of the factors that fosters the escalation of intake. Animal studies have demonstrated that a sugar-enhanced diet is associated with increased daily food intake over time [5]. Direct evidence of tolerance in binge eating disorder arises largely from clinical reports of individuals consuming more and more food in each binge as the disorder becomes more chronic. The finding that higher body weight correlates with the frequency and severity of binge eating episodes also provides indirect evidence of tolerance effects [82]. As well, a high proportion of adults with binge eating disorder reported being overweight before the onset of their disordered eating, suggesting that over time, high-calorie diets prompt greater subsequent intake and may contribute to binge eating [87].

The impact of tolerance on the progression of addictive behaviors is made more poignant by its synergy with the debilitating symptoms of withdrawal. Certain foods—particularly sugar—can cause pronounced withdrawal symptoms when removed from the diet, and these effects most clearly resemble the physical signs of distress seen in opiate withdrawal [5]. The most compelling evidence comes from animal research in which rats were initially maintained on a 25% glucose solution (e.g., [5, 110]). Following its removal, they showed aggression, anxiety, a drop in body temperature, teeth chattering, forepaw tremor, and head-shaking—all symptoms associated with withdrawal from drugs such as heroin. While there is also human evidence of "sugar withdrawal", it comes mostly from clinical observation, self-help books, and Internet sites promoting weight-loss diets. They are, however, uniform in describing headaches, irritability, and flu-like symptoms among heavy sugar consumers who become abstinent.

Cravings and Relapse

One of the most distinguishing features of drug abuse is the pronounced sense of craving reported by addicts and their dismal and repeated

failures at giving up the habit. Addiction is rarely an acute illness. A decade ago, Leshner coined the term "chronic relapsing disorder" to describe addictive disorders because total and permanent abstinence seldom occurs after a single treatment episode [59]. For most individuals, there are repeated cycles of cessation and relapse. Human weight cycling is, almost by definition, a sign of repeated defeat in one's effort to curb overeating and is found to be a significant risk factor for the development of binge eating [81].

The addict's powerful cravings that can be elicited from even a small "dose"—as well as from the many conditioned environmental cues—are thought to contribute to poor long-term treatment outcome. Studies have also demonstrated that food cravings are significantly higher in adults with binge eating disorder than in their non-bingeing counterparts of comparable weight [29, 75]. This meshes with other evidence that those with binge eating disorder show enhanced preference for sweet and fatty foods compared with other obese individuals [118]. Craving in animals can only be inferred from their behavior and is typically defined as the enhanced motivation to procure an addictive drug by operant responding [57]. Such behavior has also been observed in rats who lever pressed for 23% more glucose after a 4-week period of a sugar-enhanced diet than at baseline [5].

Neurobiological Parallels

Brain reward circuitry almost certainly evolved to foster our selective engagement in activities like eating, sex, and maternal behavior, which are the essence of our survival as a species. This otherwise highly adaptive neuro-anatomical mechanism is also at the heart of all dependence disorders. Abused substances have psychomotor stimulant properties, which activate the same brain reward pathways as life's natural pleasures. In other words, there is a shared substrate for food and drug reward [79]. Due, however, to the potency of most addictive substances, and to their direct route of administration, the claim that drugs "hijack" the brain has become a popular idiom to describe the downwardly spiralling pattern of drug abuse.

Dopamine neurons in the ventral tegmental area send subcortical projections to striatal regions of the basal ganglia—importantly, the nucleus accumbens—and to various limbic structures such as the amygdala. Ventral tegmental area projections also extend to the prefrontal cortex. This mesocorticolimbic neural network is fundamentally complex and cleverly "designed" to regulate the many emotional, motivational, and cognitive processes involved in reward. For example, our engagement in these behaviors increases our sense of pleasure and well-being—events that galvanize our attention in preference to more neutral, and less essential, activities. Second, we have the desire to repeat these behaviors even in the face of distracting stimuli. They also nurture a strong positive memory, which increases their salience and enhances our appetitive motivation in their direction. Third, we quickly learn the cues in our environment that signal the approach or availability of these rewarding behaviors. Finally, we become resistant (temporarily) to their rewarding properties in order to move on to other activities. Other neurotransmitter systems such as gamma-aminobutyric acid, the opioids, and serotonin are also integral to this process [108]. With respect to food, for instance, dopamine release in the nucleus accumbens is generally associated with its reinforcing effects, while opioid signalling in this area regulates its palatability and hedonic properties [24, 39].

Until relatively recently, the neurobiology of overeating was largely focused on the hypothalamus, while drug addiction research, by contrast, channelled its attention to the mesocorticolimbic pathways [102]. With the increasing sophistication of brain imaging techniques, we are now able to witness the activation of brain reward sites in response to palatable food [6, 92]. Prefrontal systems also play a prominent role in eating and appetite. For instance, increased "dysexecutive" traits have been associated with binge eating and food cravings, just as they are with drug abuse [94].

Experts now generally agree that the reinforcing effects of addictive drugs and palatable foods are regulated, in large part, by the same dopamine pathways [23, 55, 108]. While addictive drugs share with food the property of increasing dopamine in brain reward pathways, the former bypass the adaptive mechanisms of normal reward, such as the habituation that constrains the responsiveness of the brain to food reward [35]. Potent drugs abnormally facilitate Pavlovian incentive learning to drug-conditioned stimuli and sensitize the individual to cravings for the substance [56]. Drugs also cause a tolerance to their rewarding properties by the downregulation of dopamine receptors in the striatum [105] and a decrease in the function of the extended amygdala reward system, which produces the negative affect and anxiety associated with abstinence [56]. There is now compelling evidence that highly palatable foods eaten in abundance have the potential to cause these same neuroadaptations—alterations that increase compulsive use, foster strong cravings, contribute to the symptoms of withdrawal, and make abstinence increasingly difficult [47, 51, 79].

Risk Factor Similarities

Binge eating disorder and drug addiction appear to share certain risk factors for their development. A recent study found significantly higher rates of psychopathology, including substance abuse, in first-degree relatives of women with binge eating disorder compared with relatives of control women [60]. Importantly, however, all the disorders elevated in relatives with binge eating disorder followed a pattern of independent transmission from binge eating disorder, except for substance use disorder, the transmission pattern of which indicated a shared etiology. While the vulnerability for both disorders has many social and cultural parallels, such as availability and cost contributing to their consumption, our review will only focus on certain *psychobiological risks* that they have in common.

Reward Sensitivity

The sensitivity or reactivity of the "common reward pathway" is affected by several biological factors such as the density of dopamine receptors, the amount of dopamine released into the synapse, and the rapidity of its transport back into the cell by the reuptake protein. Individual differences in *reward sensitivity* have been strongly implicated in the risk for drug addictions [15, 58, 62, 76] as well as compulsive overeating [27, 30]. The research is divided, however, about the causal direction of this association.

One argument favors the view that *hypo*-dopaminergic functioning—which has been called a "reward deficiency syndrome"—is a key factor in the development of addiction disorders [13, 53]. The premise is that substances (such as addictive drugs and palatable food) are used as a form of "self-medication" to boost a sluggish dopamine system and increase hedonic capacity. The counterargument is that *hyper*-sensitivity to reward contributes to increased risk for addictive behaviors due to an enhanced motivation to engage in pleasurable activities. For instance, in several studies, heightened reward sensitivity was associated with emotional overeating, preference for high-fat food, binge eating, and food cravings, as well as with hazardous alcohol consumption [26, 41, 62]. One explanation for the apparent disaccord between the two bodies of research may be a *dual vulnerability* to addictions whereby both paths can confer risk, albeit in different individuals and perhaps with different levels of severity.

Impulsivity and Decision-Making Deficits

Poor decision-making skills and difficulties with impulsivity are core symptoms of certain mental health problems but are perhaps most prominently seen in drug dependence [8, 10]. Addicts tend to choose actions that bring immediate

reward, even when this leads to a deleterious later outcome. The human ability to choose *present* options that favorably influence *future* outcomes depends crucially on an accumulated "emotional memory" of the consequences of our *past* interactions with similar events [25]. In other words, we form a probabilistic impression of how a particular action will turn out in the future from an emotionally biasing "gut" feeling, which was generated when that action caused either a positive or a negative reaction in the past. The orbitofrontal cortex, in particular, is critical for activating feelings or emotional states from "thoughts" about rewarding or punishing events that are not currently present in our environment [7, 9].

Much of the early research on decision making came from studying the social impairments of patients with ventromedial prefrontal cortical lesions and observing that their behavioral deficits are typically caused by an inability to assess future consequences advantageously [3, 89]. In other words, they fail to weigh the pros and cons of their actions and to postpone immediate gratification, so their behavior is almost always guided by the negative or positive events present at the moment. A plethora of research using neuropsychological tests of decision-making ability has shown impairment in those dependent on a variety of addictive substances (e.g., [103, 104]). To date, there have been no systematic studies of decision-making deficits in binge eating disorder, although these impairments have been found in individuals with bulimia nervosa and in obese women [14, 16, 28].

Relatedly, *impulsivity*—a personality trait characterized by the diminished ability to inhibit behavior when restraint is the most advantageous and appropriate response in a particular situation—is a key component of decision-making deficits. Impulsive individuals show pronounced weaknesses in learning appropriate associations between reward and punishment, which is essential to making advantageous choices [42]. High expression of this endophenotype has strong links with both binge eating disorder [44, 97] and drug abuse [103, 104]. Due, however, to the difficulties of doing prospective risk-factor research in these areas, it is not clear whether impulsive responding is a precursor to addiction disorders or whether it only occurs because of the brain alterations caused by excessive use.

Treatment Implications

Although binge eating was first identified as a clinically significant pattern of overeating in obesity by Stunkard in 1959 [98], there were no published studies on its treatment until more than 20 years later. Early research suggested that this behavior was associated with higher attrition from weight-loss programs and poorer success rates than obesity without binge eating (e.g., [54]). As a consequence, clinicians such as Marcus and colleagues began to adapt standard behavioral weight-loss treatments to address directly binge eating behavior in an attempt to enhance positive outcomes [67].

Subsequent research found that binge eating in obesity was associated with clinically significant psychosocial distress and impairment and with levels of over-concern about weight and shape similar to that seen in eating disorders (e.g., [63–65]). It was also found to be associated with more chaotic eating habits, more emotional overeating, higher levels of eating disorder psychopathology, and higher rates of psychiatric comorbidity, particularly mood disorders [38, 113, 119]. Binge eaters also reported more social impairment and poorer quality of life compared with obese individuals who did not have binge eating disorder [95]. This evidence stimulated interest in the application of specialized psychological interventions for binge eating disorder, particularly those adapted from treatments for bulimia nervosa. At about the same time, binge eating disorder was included in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [2] as an example of "eating disorder not otherwise specified", inspiring a wealth of further research on its nature and treatment.

Current Treatments for Compulsive Overeating

Because binge eating is a central feature of both bulimia nervosa and binge eating disorder, most controlled treatment studies of binge eating disorder have evaluated interventions with demonstrated efficacy for bulimia nervosa, particularly cognitive behavioral therapy and certain types of medication. The aim of psychological therapy is to interrupt mental and emotional factors that are believed to perpetuate binge eating problems, whereas pharmacological interventions target mood regulation and the neurobiological basis of food intake regulation. In the ideal situation, effective treatments for binge eating disorder would eradicate the core behavior of binge eating, alleviate associated psychosocial problems, and produce clinically significant weight loss.

Psychological Interventions

While randomized controlled trials have indicated that certain psychological interventions for binge eating disorder can bring about substantial, and in some cases sustained, reductions in binge eating and improvements in psychosocial functioning, most participants do not cease binge eating; nor do they achieve clinically significant weight loss (see [48] for a review). The cognitive behavioral therapy approach employed in most binge eating disorder studies is largely based on the treatment manual developed for bulimia nervosa [40], with only minor modifications [63]. This protocol lasts 16 weeks and involves three stages. The first stage focuses on self-monitoring, the establishment of a pattern of regular eating, and the employment of strategies (e.g., distraction and problem-solving skills) to avoid binge eating. The goals of the second stage are to reduce strict dieting, incorporate "binge foods" into normal meals, and reduce over-concern about eating, weight, and shape. The final stage addresses relapse prevention by anticipating future challenges that could trigger a return of binge eating symptoms. The cognitive model views over-concern about body shape, body weight, and strict dieting as the central maintaining factors in eating disorders. In other words, one of the premises of cognitive behavioral therapy is that increased dietary restraint contributes to increased binge eating—an assumption that is irrelevant for individuals with binge eating disorder who are not engaging in food restriction or compensating for their binge eating episodes. In fact, individuals with binge eating disorder tend to overeat between binge episodes.

Studies have found that treatments involving enhanced dietary restraint produce reductions in binge eating behavior in binge eating disorder. Although standard behavioral weight loss treatment does not directly target binge eating, some studies comparing cognitive behavioral therapy and behavioral weight loss treatment have found comparable effects on binge eating, at least in the short term [1, 66]. However, most studies suggest that cognitive behavioral therapy is superior to behavioral weight loss treatment in terms of reductions in binge eating but without producing clinically significant weight loss (e.g., [34, 49, 74]). Moreover, it seems that only those who rapidly become abstinent from binge eating tend to achieve and maintain a significant amount of weight loss with any treatment approach. Cognitive behavioral therapy for binge eating disorder has also been tested in self-help [19, 49] and CD-ROM formats [91] with promising results. In addition, one study found that combining cognitive behavioral therapy with an exercise program resulted in higher abstinence rates and greater weight loss compared with cognitive behavioral therapy alone [80]. Wilfley and colleagues [111, 114] compared cognitive behavior therapy with interpersonal psychotherapy in two trials. Interpersonal psychotherapy focuses on the resolution of interpersonal problem areas that can trigger binge eating. It was found that both treatments were associated with equivalent significant reductions in the frequency of binge eating behavior at the end of treatment and at 1-year follow-up. However, neither treatment produced substantial weight loss. The greatest

reductions in weight occurred among participants who remained abstinent from binge eating at follow-up.

Although the research is scant, dialectical behavior therapy has also been successful in achieving binge abstinence in a significant proportion of individuals with binge eating disorder [101]. This approach, which has been shown to be effective for treating borderline personality disorder, teaches emotion regulation, distress tolerance, and mindfulness skills to cope with the negative emotions that often trigger binge eating. Finally, Overeaters Anonymous is an alternative treatment approach for compulsive overeaters. Overeaters Anonymous is an international network of self-help groups based on the 12-step Alcoholics Anonymous model that was founded in 1960 [99]. It views compulsive overeating as a disease that sufferers are powerless to overcome and recommends "surrendering oneself to a higher power". We wish to emphasize that this approach is quite different from the addiction model of binge eating disorder being advocated in the current chapter, and we are unaware of any controlled studies of its effectiveness.

Pharmacological Interventions

Several medications for binge eating disorder have been evaluated in placebo-controlled randomized trials, including selective serotonin reuptake inhibitors (e.g., [33, 50, 70]), antiobesity agents (e.g., [112]), and anticonvulsant medications such as zonisamide or, more promisingly, topiramate [68, 69, 71, 72]. There is some evidence that fluoxetine produces reductions in binge eating behavior. However, two recent studies found that cognitive behavioral therapy was superior to fluoxetine for binge eating and weight loss [33, 50]. On balance, sibutramine—a serotonin and norepinephrine reuptake inhibitor alleged to modify internal signals of hunger and satiety—has the best evidence for use in the treatment of compulsive overeating to date [107, 112]. In a recent large multicenter trial, Wilfley and colleagues found that sibutramine was superior to placebo in reducing binge eating and producing clinically significant weight loss over a 24-week period [112].

Integrating an Addiction Perspective

While there is strong empirical support for the use of cognitive behavioral therapy in the treatment of both binge eating disorder and drug addiction [18, 115], a substantial proportion are non-responders, and the rate of relapse is significant. We believe that the clear parallels between drug addiction and compulsive overeating, outlined earlier in this chapter, can provide a helpful framework for developing more effective treatments for binge eating disorder. Importantly, however, a major limitation for compulsive overeaters is the impossibility of completely abstaining from the "addictive substance" as is often recommended for drug addiction. Presenting individuals who have binge eating disorder with an addiction model of compulsive overeating—with the implicit message that they may be fighting a strong neurobiological drive to overeat in an environment that exploits these urges—may help foster a therapeutic sense of self-empathy as well as an understanding that treatment is likely to involve learning effective strategies and enduring lifelong efforts to resist overeating and prevent relapse.

All addictive behaviors may be used to increase positive feelings or sensations. For compulsive overeaters, the rewards may include the pleasant taste, the increased energy from rises in blood glucose, and an improved mood. Recognition of these effects points to the importance of helping individuals with binge eating disorder find alternative sources of reward and pleasure in their lives besides food and eating. Clinical experience suggests that individuals with binge eating disorder often report an overemphasis on food as the only source of enjoyment in their lives.

On the other hand, negative emotions are also major triggers for both binge eating and substance use since both food and drugs can also dull or distract from emotional distress.

Overcoming an addiction requires an individual to learn to tolerate negative emotional states, including cravings and urges for the addictive substance, without acting on them. That is why the development of emotion regulation and distress tolerance skills is central to the treatment of both binge eating disorder and drug addiction. Emotion regulation skills are strategies used to calm oneself down and feel better without engaging in self-destructive behaviors such as substance abuse or binge eating. Similarly, distress tolerance skills involve learning to sit with upsetting feelings and let them pass without acting on maladaptive urges. Those with binge eating disorder find it particularly distressing to experience a food craving or the urge to eat—even when not physically hungry—without acting on it. This is a skill that they must learn to master.

Drug addiction and compulsive overeating also require the interruption of deeply ingrained learned habits and stimulus preferences that are maintained by the reinforcing properties of powerful rewards. Both behaviors are conditioned responses to certain triggers and are generally followed by highly reinforcing consequences. Use of stimulus control strategies, such as limiting the availability of "binge foods" and confining eating to only one place in the house, may be helpful. As in drug addiction, it is possible that the consumption of "binge foods", typically high-calorie, high-fat foods, has a priming effect that can trigger compulsive overeating [106]. Whereas the cognitive behavioral therapy model recommends incorporating binge foods into one's daily meal plan, from an addiction perspective, avoiding trigger foods is the recommended course of action for binge eating disorder. As impulsivity is strongly associated with compulsive overeating and binge eating disorder (see earlier review), effective treatments also need to address problem-solving and decision-making skills to improve impulse control.

A final area worthy of further study is motivational interviewing—a client-centered but directive approach designed to help individuals explore and resolve ambivalence about change, thereby increasing intrinsic motivation to change problematic behaviors [73]. Ambivalence about change is common in both binge eating disorder and drug addiction. This is because, despite its negative consequences, the addictive behavior typically has many benefits for the individual. In the addiction field, it was shown that 4 sessions of motivational interviewing were superior to 12 sessions of cognitive behavioral therapy for alcohol abuse [85]. To our knowledge, only one study has examined motivational interviewing for binge eating disorder [37]. In this study, a single session of motivational interviewing plus unguided self-help was compared with self-help alone. No differences were found in terms of compliance with the self-help program or binge eating outcome. However, this may be because a single session was not of sufficient intensity to produce an effect. In order to recover, individuals with binge eating disorder, like those with drug and alcohol addictions, must resist strong biologically based urges to consume substances with powerful reinforcing properties. Enhancing and maintaining the motivation to do this in the long term is likely to be as important to the treatment of binge eating disorder as it has been shown to be in the treatment of drug and alcohol addiction.

Summary and Conclusions

In this chapter, we have presented an addiction model of compulsive overeating and binge eating disorder. We have reviewed evidence for this perspective, including overlapping clinical features, shared neurobiological mechanisms, and risk factor similarities. In addition, we have presented several recommendations for integrating this perspective into established treatments for binge eating disorder.

To date, studies on the psychological treatment of binge eating disorder have found that rapidly achieving and maintaining abstinence from binge eating is a crucial first step in achieving effective outcomes. While cognitive behavioral therapy may be the most widely used psychological treatment, an important limitation of

this approach is that it does not produce significant weight loss, does not sufficiently address the lack of dietary restraint in binge eating disorder, and results in a substantial proportion of non-responders [117]. As outlined in this chapter, we believe that integrating an addiction perspective that considers the similarities between treating drug addiction and treating compulsive overeating will improve outcomes.

Pharmacological treatments of binge eating disorder, particularly topiramate and sibutramine, have also had some success, but research in this area is limited by short treatment duration, small sample sizes, and lack of follow-up data following medication discontinuation. Currently there is no convincing evidence that combining medication with psychotherapy provides any added benefit beyond that afforded by psychotherapy alone.

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Compulsive Buying

Joanna M. Marino, Troy W. Ertelt, James E. Mitchell, and Kathy Lancaster

Contents

Introduction

Kraepelin and Bleuler first identified "oniomania" or the "urge to buy" in the early 1900s [9, 35]. Today, compulsive buying is likely a much different phenomenon from what it was when Kraepelin and Bleuler first conceptualized the disorder. In the United States, and likely in all industrialized nations, consumer spending takes place in both public places such as shopping centers, discount stores, or rummage sales and in private homes through the use of online shopping and television shopping networks. The set of symptoms known as compulsive buying, pathological buying, or buying disorder has recently received increased attention in both the consumer and mental health literatures although data on the topic remain limited.

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Diagnosis and Classification

Characteristics of compulsive buying include disinhibition or limited control over buying behavior [5]. Compulsive buying is not included in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision; however, McElroy and colleagues [42] have outlined criteria consistent with the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision format, and these have been widely adopted in defining and studying compulsive buying (Table 1).

Some have suggested that compulsive buying fits into the grouping of addictive and impulsive behaviors [29]. An individual with compulsive buying behavior may experience a cycle of urges and impulses, followed by pleasure or euphoria while shopping, and guilt after purchasing items, along with a drive to continue the behavior [29, 51]. Impulse control disorders involve impulses or drives that the individual cannot

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_31,

Table 1 Diagnostic criteria for compulsive buying

Diagnostic criteria
(1) Maladaptive preoccupation with buying or shopping, or maladaptive buying or shopping impulses on behavior, as indicated by at least one of the following:
(A) Frequent preoccupation with buying or impulses to buy that is/are experienced as irresistible, intrusive and/or senseless.
(B) Frequent buying of more than can be afforded, frequent buying of items that are not needed, or shopping for longer periods of time than intended.
(2) The buying preoccupations, impulses or behaviors cause marked distress, are time consuming, significantly interfere with social or occupational functioning, or result in financial problems (for example, bankruptcy).
(3) The excessive buying or shopping behavior does not occur exclusively during periods of hypomania or mania.

Adapted from McElroy et al. [42]

resist, and these urges are harmful to oneself or another person [51].

According to its current classification, compulsive buying is a "disorder of impulsive control-not otherwise specified" due, in part, to the limited research on this topic [5]. Some researchers have hypothesized that compulsive buying falls onto a spectrum since the urge to buy may be variable in some individuals, or increasing and decreasing in certain situations, and the onset of compulsive buying behavior may be gradual [12].

However, research has yet to determine whether compulsive buying fits better with obsessive-compulsive, addictive, or impulse control disorders. Black [4] conceptualized compulsive buying as obsessive thoughts followed by the compulsion to buy, and Frost and colleagues [23] found that compulsive buyers had higher scores on an obsessive-compulsive symptomatology scale when compared with controls. Christenson and colleagues [11] also suggested that compulsive buying might have features of both impulsive and compulsive disorders. Further research needs to delineate the relationship of compulsive buying to each of these theories.

Common factors among compulsive buying behavior are the desire, relief, and feeling of well-being that come from purchasing. Compulsive buyers may believe that their material possessions, not necessarily their personal characteristics, determine their identity. By purchasing, such individuals may feel that they are presenting a more desirable self to the world while hiding their shame over their debt and ongoing purchases. In addition, some research has suggested that a better conceptualization of compulsive buying may include compulsive acquisition, meaning that some individuals who exhibit compulsive buying behavior may feel the need to pick up or gather free items such as brochures or fliers [23].

Individuals who exhibit compulsive buying behavior often appear to be upset over their own lying, such as hiding new packages from a spouse. For many compulsive buyers, the act of purchasing, rather than what they buy, is what leads to gratification [12]. Many who suffer from compulsive buying do not use the items that they purchase [20]. Some individuals may return or sell the item, though many keep the items [11, 26]. This collection of items can lead to clutter or result in hoarding behavior. Some individuals with compulsive buying disorder spend their money on themselves, while others buy gifts [20]. Some have reported that their urge to shop has led them to seek out and rummage trash cans and dumpsters.

Prevalence Rates and Subject Characteristics

The available data on prevalence rates of compulsive buying have proved to be variable. Koran

and colleagues [33], after conducting phone surveys, found a point prevalence of 5.8% in the United States, with female prevalence rates somewhat higher than males, at 6.0 and 5.5%, respectively. These numbers decreased to 1.4% point prevalence when the Compulsive Buying Scale cut-off score was increased. Compulsive buying respondents tended to be middle-aged, to have incomes below $50,000, to be more likely to make minimum payments on credit cards, and to be within $500 of maximum credit limits [33]. Individuals with compulsive buying behavior also usually spend over $100 during compulsive buying episodes [11]. Christenson and colleagues [11] found that most individuals who exhibited compulsive buying behavior were experiencing indebtedness and that an average of almost half of the household's income went toward attempts to resolve debt caused by compulsive buying behavior. Differences in shopping tendencies between genders, among individuals of varying incomes, and during special events (e.g., holidays, birthdays, or anniversaries) are important considerations in studying compulsive buying behavior [5].

One additional key feature of compulsive buying is the use of credit cards. O'Guinn and Faber [52] found that individuals who exhibited compulsive buying behavior, on average, tended to have more credit cards than general consumers and that more compulsive buyers' credit cards were within $100 of their limit. Access to credit cards is abundant in the United States, and cognitions associated with the use of credit cards (e.g., "I'm not paying for this right now", "I can afford this next month", or "I can pay off this credit card with another card") can often lead to the cycle of overspending. Additionally, the desire for and value placed on the need to attain and have the most items possible are likely key aspects for many compulsive buyers. Others diagnosed with compulsive buying disorder may feel driven to purchase items because they have a "collection" of specific items. Still others feel the allure of the sense of "saving" when they see a sales rack, even when they spend money on an item that they do not need.

Economics and Consumerism

Economists have long studied the behavior of buyers. Some believe that it is best to conceptualize compulsive buying on a continuum with "normal" spending. However, compulsive buying is a disorder involving more than just indebtedness. Whereas individuals with compulsive buying behavior do have control over their spending, there are other factors influencing and sustaining the impulse to buy that make those with compulsive buying disorder feel that they can no longer control their buying.

External forces may have etiological importance in the development of compulsive buying. For example, in the United States, there appears to be a sense of importance attached to having higher end goods such as new, expensive cars and designer fashions. Others may feel pressures from the American culture's pursuit of "youth". Individuals may experience a sense of psychological well-being when purchasing objects that fall into these categories and may think that these objects will make others perceive them as successful. Nevertheless, each individual may feel driven by a different factor or factors, and the concept of "success" may be different among individuals in different socioeconomic strata. Indeed, compulsive buying appears to affect individuals in varying socioeconomic categories [12].

Shopping in the United States is a somewhat gender-specific leisure activity. Black [5] suggested that compulsive buying behavior and compulsive gambling behavior might be gender-specific variants of the same underlying pathology, with compulsive buying behavior manifesting itself in women and compulsive gambling behavior being more prevalent among men. Those with compulsive buying disorder often find themselves drawn to shopping for clothing, shoes, music CDs, jewelry, makeup, groceries, and décor for the home [4, 44]. Larger items such as cars are also possible purchases, and for this reason, purchases differ depending on access to disposable income.

Etiology and Course

No one has examined extensively the possible etiologies of compulsive buying, although it will likely fit into a biopsychosocial etiological model [19]. The course for compulsive buying is probably chronic, with one study finding the mean age of onset in late adolescence to be about 18 years [11]. Identification of the buying as a problem tends to occur later, in one's late twenties or early thirties [11]. In many cases, the main thing that identifies compulsive buying is the large debt that subjects have accrued, followed by feedback from friends or family, legal problems, or guilt [11].

Levels of materialism and youth are predictors of compulsive buying tendencies [16]. Women are more likely to be diagnosed with compulsive buying disorder, perhaps since predominantly females hold the "shopping" role in families [11, 16, 42, 57]. Indeed, women are more likely to carry a diagnosis of compulsive buying. Additionally, women have had higher scores on compulsive buying inventories, suggesting that compulsive buying may be more severe in females [12]. Compulsive buying is also related to low self-esteem and to problem credit-card use [12, 13, 20, 52, 56].

Several variables may be important in determining etiological factors for compulsive buying behavior as well as differences in compulsive buying among younger individuals. Survey results of adolescents suggest a positive relationship between hours of television viewed per day and compulsive buying behavior. This may be due to the influence of materialism viewed on television [13]. There is also a significant correlation between compulsive buying behavior in adolescence and perceptions of parental compulsive buying behavior, possibly suggesting that compulsive buying is a learned behavior identified through modeling [13]. Adolescent girls also have had higher compulsive buying scores than boys, which speaks to the differences in diagnosis or shopping behavior between the genders [13]. Predictive modeling of adolescent compulsive buying behavior suggests that gender, younger age, peer influence, parents' compulsive buying behavior, tangible family resources, family stressors, and lesser family communication may predict compulsive buying [13, 25]. Others have found significant relationships between compulsive buying behavior and risk-taking behaviors such as smoking, alcohol and drug use, and unsafe sexual practices [53], which may speak to the relationship of impulsivity to compulsive buying behavior.

Developmental learning may also affect the formation of compulsive buying. In examining retrospective recall of childhood buying behavior, d'Astous [12] found that the likelihood of compulsive buying increased in individuals who reported a history of being likely to spend money quickly after receiving it in childhood, as well as when they reported their parents buying "everything" they wanted [12]. Additionally, susceptibility of influences from friends or social situations (e.g., feeling important when making a purchase, frustration when having fewer things than others do) was related to compulsive buying behavior [12]. Further research could better assess similarities in childhood experiences or modeling that may be precursors to compulsive buying.

There has been little research regarding the personal financial costs of compulsive buying. Miltenberger and colleagues [44] found that debt ranged from $0 to $30,000 in a small sample of individuals who exhibited compulsive buying behavior. Compulsive buying episodes can vary in duration from less than an hour to hours of shopping [44].

A range of emotions can lead to compulsive buying episodes. Individuals with compulsive buying symptoms suggest that they often experience negative emotions before shopping, though some report elation, power, and joy beforehand [11]. Miltenberger and colleagues [44] also found that ratings of sadness or depressed mood were significantly higher before shopping when compared with mood during the shopping episode. Faber and Christenson [19] also reported that boredom, depressed mood, and anxiousness were moods experienced prior to shopping. Euphoria and excitement ratings were

significantly higher during shopping episodes than afterwards [44]. These findings suggest that a negative mood state occurs before shopping and that shopping leads to a more positive change in an emotion. After shopping, a negative mood state is likely to emerge as individuals realize they are unable to afford the purchased items. In most cases, negative emotion (e.g., tension/anxiousness, anger/irritation, self-criticalness, and boredom) scores were highest before shopping and decreased during and after the shopping episode [44]. This model of negative reinforcement may sustain compulsive buying behavior [44].

Researchers have attempted to connect obsessive-compulsive spectrum disorders or impulse control disorder to compulsive buying, considering the possible role of serotonin in compulsive buying symptoms. In the only study directly examining this relationship, no differences emerged between compulsive buying participants and control participants in the rate of occurrence of two polymorphisms related to the serotonin transporter [15].

Comorbidity

A number of studies have examined the relationship of compulsive buying with other psychiatric disorders. The most commonly reported comorbidities include mood disorders, anxiety disorders, substance use disorders, impulse control disorders, and eating disorders [19, 42, 57]. For example, when compared with control groups, it appears that those with compulsive buying disorder are more likely to have a mood disorder or another psychiatric disorder than would be expected in the general population [7]. In individuals with compulsive buying disorder and their family members, depression and anxiety appear to be common [7, 20, 23].

The relationship between compulsive buying and mood disorders is reasonably well established. In his examination of several case series, Black [5] identified comorbidity rates for compulsive buying disorder and mood disorders ranging from 28 to 95%. It is important to note that compulsive buying behavior is distinct from the symptoms of a manic or hypomanic episode. Additional research on how spending and buying differ in manic episodes compared with compulsive buying episodes would be useful in understanding the distinction.

Researchers have drawn a strong link between compulsive buying disorder and binge eating disorder [21]. Faber and colleagues [21] performed two studies to assess the link between these two disorders. In the first study, they examined compulsive buying in women diagnosed with binge eating disorder. The authors found that the women diagnosed with binge eating disorder had significantly more symptoms of compulsive buying than did matched controls. In the second study, the authors compared a group of participants (mostly women) with compulsive buying behavior with a group of participants whose buying behavior was normal. The authors found that those with compulsive buying behavior were significantly more likely to engage in behaviors characteristic of binge eating disorder. Additionally, McElroy and colleagues [43] contributed a theoretical link between compulsive buying disorder and binge eating disorder, in that both disorders likely belong on the compulsive-impulsive behavior spectrum. Concerning other eating disorders, no one has shown a strong link between compulsive buying disorder and anorexia nervosa or bulimia nervosa [45].

As mentioned previously, some have suggested that compulsive buying disorder is part of the obsessive-compulsive spectrum [5]. Interest in the obsessive-compulsive spectrum has increased over the last several years, and some have suggested that up to 10% of the population in the United States has an obsessive-compulsive spectrum problem that includes intrusive thoughts and/or repetitive behaviors [28]. However, the relationship of compulsive buying disorder to obsessive-compulsive disorder and obsessive-compulsive spectrum disorders is unclear. For example, Bienvenu and colleagues [3] examined a sample of individuals diagnosed with obsessive-compulsive disorder and their first-degree relatives. They

identified only one case where compulsive buying disorder co-occurred with obsessive-compulsive disorder. Additionally, Jaisoorya and colleagues [30] examined a large sample of individuals with obsessive-compulsive disorder and found only one individual with comorbid compulsive buying disorder. While compulsive buying disorder symptoms seem to relate to the general symptoms of obsessive-compulsive disorder, it appears that the relationship between compulsive buying disorder and obsessive-compulsive disorder may be unremarkable.

Some have identified a relationship between compulsive buying disorder and kleptomania. McElroy and colleagues [43] presented a theoretical paper closely linking kleptomania and compulsive buying disorder. Lejoyeux and colleagues [40] identified a relative risk of comorbid kleptomania of 8.5% for those with compulsive buying disorder. It also seems possible that behaviors associated with kleptomania (e.g., shoplifting) may become more common in those with compulsive buying disorder as their financial situations deteriorate and they are unable to purchase the goods that they are compelled to obtain. Another disorder that some have speculated is closely related to compulsive buying disorder is pathological gambling. As noted above, Black [5] has conceptualized compulsive buying and pathological gambling as being gender-specific manifestations of a similar underlying psychopathology. In a sample of pathological gamblers, 23% had a lifetime history of compulsive buying disorder [6]. Christenson and colleagues [11] found no difference between individuals who exhibited compulsive buying behavior and age-matched control subjects across trichotillomania, pyromania, kleptomania, intermittent explosive disorder, or pathological gambling. However, compulsive buying subjects were more likely to have any impulsive control disorder when compared with the age-matched control group [11]. Further research about the comorbidity among compulsive buying, kleptomania, and pathological gambling could help to explain the complex relationship observed among these disorders.

Schlosser and colleagues [57] reported on a sample of 46 individuals who met criteria for compulsive buying. Participants completed two assessments (Structured Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised, Personality Disorders and Personality Diagnostic Questionnaire Revised), and the authors examined the extent to which the two instruments identified the same personality pathology. The most frequently identified personality disorder within the sample was obsessive-compulsive personality disorder. Twenty-two percent of the sample met the criteria for obsessive-compulsive personality disorder on both the Structured Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised, Personality Disorders and Personality Diagnostic Questionnaire Revised. Avoidant personality disorder and borderline personality disorder were both present in 15% of the sample. Overall, 59% of the sample met criteria for a personality disorder on both the Structured Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised, Personality Disorders and Personality Diagnostic Questionnaire Revised [57].

The literature on hoarding is too large to review in this chapter; however, the literature regarding compulsive buying and hoarding is worth mentioning. Frost and Hartl [22] identified several important features of compulsive hoarding, including the acquisition of seemingly useless possessions and the inability to discard them, the negative effect of clutter created from compulsive hoarding on the activities of daily living, and the distress and impairment experienced because of compulsive hoarding. Others have suggested that those who compulsively hoard possessions attach sentimental meaning to items while others do not [59]. Hoarding behavior is more likely in those with compulsive buying disorder compared with a non-compulsive buying group [23]. No one thus far has proposed a diagnostic specifier for identifying hoarding behavior in compulsive buying; however, it may be that a hoarding specifier could help in differentiating compulsive buying disorder subtypes.

That is, those with compulsive buying disorder who choose to give their items away may differ from those buyers who hoard items or see some sentimental value in the possession [23]. Indeed, Mueller and colleagues [48] suggested that compulsive buying behavior might be more severe in those compulsive buying subjects who hoard compared with those who do not hoard items. Moreover, compulsive buying subjects with hoarding behavior are more likely to have an affective disorder, substance use disorder, eating disorder, or anxiety disorder than those subjects who only hoard, suggesting more comorbid psychopathology in those with both hoarding and compulsive buying behavior [48]. Further research is needed to identify whether those individuals with hoarding traits are different from those with compulsive buying without hoarding behavior and to determine how treatment may differ between these two groups.

Almost half of one compulsive buying sample had a substance abuse problem, with most subjects abusing or dependent on alcohol [23]. Researchers have shown that substance abuse is comorbid with compulsive buying behavior, although no research to the authors' knowledge has directly examined the relationship between the two disorders.

Cultural Considerations

Researchers have investigated compulsive buying in several countries, including the United States, Canada, Germany, Belgium, and the United Kingdom, with prevalence rates from 2 to 10% found in the United States, United Kingdom, and Germany [50]. Compulsive buying increased in Germany from 1991 to 2001 [50]. Research in other countries has not yet determined whether compulsive buying behavior is on the rise.

Data comparing American and German samples suggest that the severity of compulsive buying in both samples is largely equivalent [49], while German buyers were more likely to have a current or past psychiatric disorder and have a history of more psychiatric disorders, especially affective and anxiety disorders [49]. Substance abuse and binge eating were also highly comorbid disorders in the German sample [49]. Gwin and colleagues [25] have identified some significant predictors (e.g., gender, parents' compulsive buying, tangible family resources, communication style, and family stress) for compulsive buying tendencies in an adolescent sample from Mexico.

A study in South Korea comparing compulsive buying in American and South Korean college students revealed some similarities in their behavior [38]. However, different patterns emerged when the authors administered the Diagnostic Screener for Compulsive Buying, as developed by Faber and O'Guinn [18], to samples from both the United States and South Korea. In the United States, the Diagnostic Screener for Compulsive Buying is unidimensional; however, in South Korea, the authors observed a bidimensional structure of the same measure [37]. The two dimensions suggested for the South Korean samples related to "financial outcomes" and "unfettered spending" [37]. The authors interpreted this difference in response to the Diagnostic Screener for Compulsive Buying as being indicative of culturally different manifestations of compulsive buying disorder.

In an analysis of Israeli consumers, Shoham and Brenčič [58] found that predictors of compulsive shopping behavior included unplanned purchasing, the tendency of consumers to buy items that were not on a list, and gender (i.e., females). The authors concluded that the "in-store decision-making" might lead to compulsive buying behavior.

Assessment

When assessing for compulsive buying, several factors are important to consider. First, the behavior cannot be better accounted for by another disorder such as mania or bulimia nervosa (in which individuals may buy large quantities of food to eat) or by an organic problem such

Table 2 Instruments useful in the assessment of compulsive buying

Instrument
Addictive buying indicator [56]
Buying cognitions inventory [39]
Buying impulsiveness scale [55]
Compulsive acquisition scale [23]
Compulsive buying scale [18]
Compulsive buying scale [17]
Credit card use scale [54]
Minnesota impulsive disorder interview [11]
The compulsive buying scale [60]
Yale-Brown obsessive-compulsive scale-shopping version [47]

as a brain injury [5]. Several instruments used in research and designed to characterize compulsive buying behavior (Table 2) also would be helpful in clinical populations.

Treatment

Impulse control disorder treatment often involves problem solving, learning and employing alternative behaviors, cognitive restructuring, and relapse prevention interventions [27]. Compulsive buying has its own complexities, as buying behavior cannot ever be fully eliminated [52]. Randomized controlled trials in either individual or group formats of cognitive therapy have yet to be conducted, and no self-help manuals have been studied in the treatment of compulsive buying disorder; however, research in this area is developing.

Mitchell and colleagues [46] have created a self-help and group therapy manual that appears to be beneficial in the treatment of compulsive buying disorder. The following outline would typify a 10-week treatment plan:

- Week 1: Individuals are encouraged to calculate current debt, which is also essential in order for participants to determine a plan to resolve the debt that they have accrued. Many times, credit counselors are options for participants who are overwhelmed by their debt.
- Week 2: Like most cognitive-behavioral models, compulsive buying disorder treatment begins by encouraging individuals to identify their problem buying behaviors and the cues that lead to these behaviors (Fig. 1). Each week, subjects are required to complete a purchasing record to aid in the identification of problematic buying behavior.
- Week 3: Individuals who exhibit compulsive buying behavior are coached on how to avoid problematic situations, restrict their stimulus field (e.g., stopping only at specific, "low-risk" stores), and increasing more desirable behaviors and activities. Delaying the response to buy by waiting at least 24 h can work to remedy impulse shopping.
- Week 4: Compulsive buying participants learn cash management techniques such as carrying small amounts of cash, paying off credit card debt, determining how much money they should place in a savings account each week, and balancing a checkbook. Following an introduction to healthy buying behavior, participants begin to identify hoarding behavior as well as how to resolve this behavior.
- Week 5: There is a discussion of thoughts, feelings, and behaviors related to compulsive buying. Participants identify how cues lead to specific emotions, behaviors, and thoughts, and what consequences ensue.
- Week 6: There is a discussion of cognitive restructuring, especially challenging nonproductive thinking (e.g., "I can't live without my credit card" or "I have to go to the mall to feel better").
- Week 7: There is an examination of self-esteem, especially in relation to shopping and self-image.
- Weeks 8 and 9: In addressing exposure, stress managements, and problem solving skills, participants are encouraged to allow themselves into situations where they can identify and control their urge to buy and implement a new strategy for dealing with negative mood states.
- Week 10: In a discussion of relapse prevention plans, individuals learn to identify

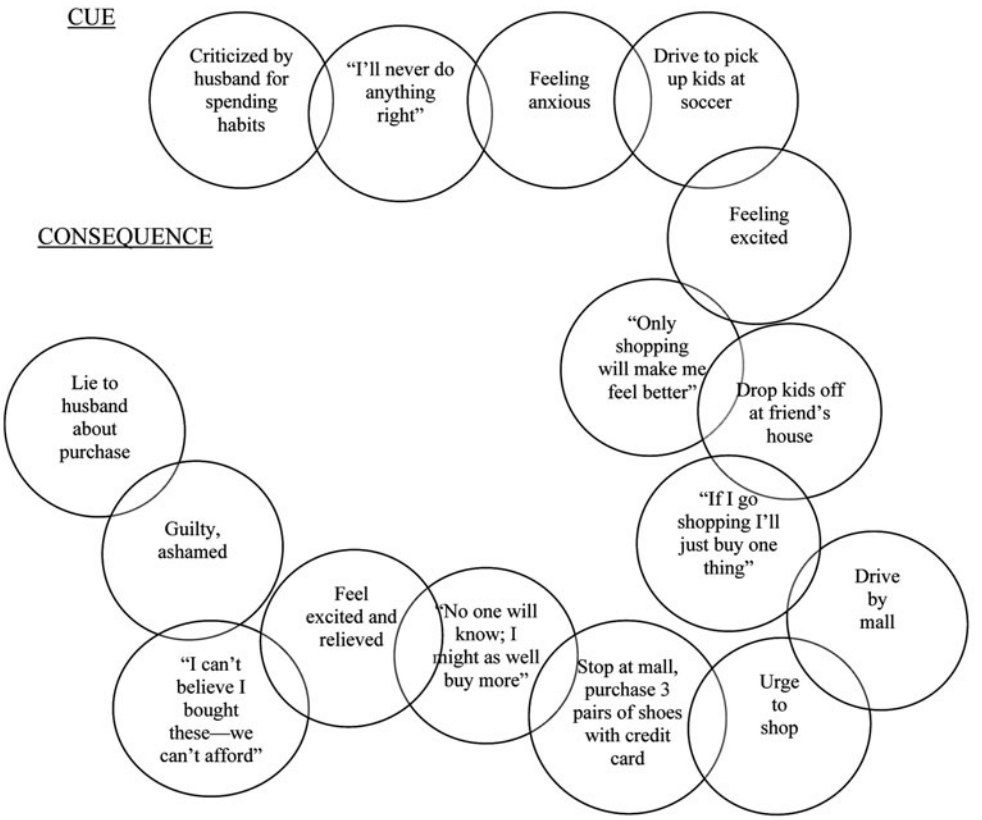

Fig. 1 Cue and consequence diagram

high-risk situations that may lead to lapses in compulsive buying behavior. They also identify how they can respond if a setback in buying occurs.

An examination of this cognitive-behavioral type therapy approach suggests positive results at the end of treatment and a 6-month follow-up, although the sample size in this pilot study was small [46]. Education about credit card use may be the key, as the use of cash and debit cards may have a very different impact on continued compulsive shopping, when compared with the continuing use of credit cards [12, 46]. Post-treatment debts may be a concern in the resolution of mood symptoms [46]. Authors have also concluded that materialistic feelings and attitudes may be important predictors and subsequently important treatment factors in compulsive buying therapy [16].

Additionally, a small case series ($n = 4$) of individuals with compulsive buying symptoms was treated with psychoanalysis [36]. The author suggested that internal emptiness is what created and maintained the compulsive buying behavior. There were no specific outcome data reported for this case series.

Support groups for treating addictions, such as Alcoholics Anonymous for alcoholism, have long been in use. Compulsive buying support groups have not become as common as other treatment groups although Debtors Anonymous has been able to assist in debt management [41]. Additionally, Brazer [10] outlined his method for aiding individuals with "money disorders", which includes the use of Debtors Anonymous in combination with psychoeducational group formats that discuss the disease model of addictions, educate individuals on debtors, deal with negative emotions such as anger and depression,

improve self-esteem, and plan for the future. One major concern with using Debtors Anonymous is the group's limited number of locations. Black [4] also noted that several self-help books have been developed [2, 14, 61].

Research on pharmacological treatment interventions has been mostly inconclusive although researchers have studied several classes of medication. Case studies have suggested that naltrexone may be beneficial in the treatment of compulsive buying since the medication specifically targets the urge to shop [24].

Fluvoxamine has treated several psychological disorders including obsessive-compulsive disorder and depression. Black and colleagues [8] found similar and substantial improvement in a 9-week, double-blind comparison of fluvoxamine and placebo in compulsive buying subjects. Ninan and colleagues [51] found equivocal results between the control and fluvoxamine groups. However, in both studies, the authors suggested that psychoeducation related to compulsive buying symptoms and nonspecific therapeutic variables may have aided in the improvement of subjects [8, 51]. These results suggest that self-help manuals or generalized therapeutic attention via more cost-effective support groups may be beneficial for individuals with compulsive buying disorder.

Koran and colleagues [34] investigated the use of escitalopram in conjunction with relapse prevention in compulsive buying and found that a similar number of both placebo and escitalopram subjects experienced relapses. Many of the subjects who relapsed in both groups appeared to have comorbid depression symptoms at the time of relapse or at baseline, suggesting the possibility of negative mood states as an etiological factor to compulsive buying [34].

Koran and colleagues [31] also reported on open-label trials using citalopram for compulsive buying. The results appeared positive as all subjects showed decreased scores on the Yale-Brown Obsessive-Compulsive Scale-shopping version and a depression scale [31]. Again, these authors suggested that the attention that individuals exhibiting compulsive buying behavior received in a clinical setting or the shopping logs that they completed might have had an important impact in the resolution of the compulsive buying systems, and that research with citalopram treatment alone is needed [31]. In a later study, Koran and colleagues [32] again found beneficial outcomes for all seven individuals randomized to the citalopram group in a double-blind study.

Aboujaoude and colleagues [1] conducted a 1-year follow-up with individuals who had exhibited compulsive buying behavior in Koran and colleagues' [31] sample. At 3, 6, 9, and 12 months, over 70% of initial responders to citalopram were in remission [1]. Yale-Brown Obsessive-Compulsive Scale-shopping version scores appeared to increase somewhat in those who initially responded to citalopram, while total debt and shopping expenditures decreased [1]. Those who did not appear to respond to citalopram during the initial study showed poorer long-term outcomes [1].

One clear problem with the pharmacological treatment studies thus far is small sample sizes. Further research clearly needs to determine how individuals will respond to varying selective serotonin reuptake inhibitors and other agents and what impact clinical attention has in these studies.

Future Research

Compulsive buying, while first identified nearly a century ago, apparently has become an increasingly common problem. This has led to increases in research in this area, but further study of the problem will need to determine which individuals on the compulsive buying spectrum will benefit from cognitive-behavioral therapy, behavioral therapy, or medication. Current literature on compulsive buying examines only cognitive-behavioral interventions; therefore, future research should likely examine other treatment interventions such as interpersonal therapy or behavioral therapy. Additionally, compulsive buying treatment will likely need to address compulsive buying comorbidity. Finally, there needs to be further

delineation of possible compulsive buying subtypes. The current chapter identified the state of research in this area, and further advances will help to identify and treat more appropriately those struggling with compulsive buying.

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Sexual Behavior as an Addictive or Compulsive Phenomenon

Kimberly R. McBride, Michael Reece, and Brian Dodge

Contents

Introduction

Due to the magnitude of the human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) epidemic, and its profound impact on public health and social structures, an emphasis on the behavioral, social, and cultural factors associated with sexual risk and its relation to HIV transmission has been essential. However, an unanticipated artifact of disease-focused research is that much of the contemporary knowledge related to sexual behavior has been constructed in the context of HIV. Apart from Kinsey and colleagues' pioneering studies [42, 43] and a series of national health surveys which contain items on sexuality, scientists still know relatively little about sexuality issues in the general population in comparison with other aspects of health and human behavior [45].

This void of knowledge has led to an increase in the "pathologizing" of sexual behaviors that are viewed as "atypical" or "amoral", with little empirical evidence from representative studies [34]. A vivid example of this phenomenon can be seen in the recent social construction of "sexual addiction" as a clinical disorder. Although there has been substantial debate and skepticism surrounding the nature and existence of sexual addiction (or sexual compulsivity) as a pathological condition, the concept has been widely studied and measured in recent sexological, psychological, and public health research [46]. In addition, numerous clinicians and self-help groups have increased awareness of, and "treatments" for, sexual addiction and sexually compulsive behavior. As yet, however, studies of sexual compulsivity and its associations with sexual behavior have been primarily assessed

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_32,

among individuals who are already considered to be at "high risk" for sexual health problems. Additionally, researchers have rarely focused on relations between sexual compulsivity actual negative health outcomes (physical or otherwise). Indeed, research on the topic to date has thus far raised more questions than answers.

History of Sexual Addiction and Sexually Compulsive Behavior

The earliest descriptions of sexually compulsive behavior can be traced to Greek myths of satyrs and stories of the god Dionysius [26, 51]. The term "nymphomania", used to describe female sexual excess, is derived from Greek. In the nineteenth century, the term "Don Juanism" was used in reference to male sexual excess [26]. In the late nineteenth century, Krafft-Ebing presented one of the first case studies detailing the effects that compulsive or "out-of-control" sexual behaviors had on the life functioning of a male client [44].

The notion that sexual behavior can be conceptualized as an addiction or compulsion warranting psychiatric treatment is relatively recent [31, 41]. During the mid-to-late twentieth century, case reports were published describing similar clinical presentations from individuals reporting out-of-control sexual behaviors; however, the terms used to describe the behavior and the conceptualizations of etiology varied widely [3, 17, 22, 24, 35, 53, 54, 62]. Terms ranged from nymphomania and Don Juanism to perversions and paraphilias, compulsive sexual behavior, impulse control disorders, sexual addiction, and sexual compulsivity.

Currently, a universally accepted term and a clear definition of out-of-control sexual behavior do not exist. The terms most often used by researchers and clinicians in reference to out-of-control sexual behavior include: compulsive sexual behavior; sexual addiction; sexual compulsivity; sexual impulsivity; and hypersexuality [7, 12, 13, 18, 27, 33, 36, 50, 60]. In general, these terms are used to describe sexual behavior that is beyond an individual's control which leads to impairment in life functioning and a range of negative outcomes. There is no single treatment strategy that is widely accepted, rather approaches range from cognitive behavioral therapy to the use of selective serotonin reuptake inhibitors and naltrexone to 12-step group interventions.

Sex Outside the Norm

Over the past 30 years, the idea that sexual behavior can become a clinical disorder leading to significant impairment in life functioning has appeared in the scientific literature with increasing frequency. Prior to the emergence of HIV and AIDS in the late 1970s and early 1980s, interest in the phenomenon of out-of-control sexual behavior was primarily limited to psychological researchers and clinicians. It was not until the early 1980s that the terms "sex addict" and "sexual compulsive" were used in scholarly writing and popular culture to refer to individuals whose sexual behaviors rested outside of accepted socio-cultural norms. However, the emergence of HIV brought attention to sexual behaviors that increased the likelihood for transmission. Among the factors that were identified as high risk was sexual behavior that is perceived to be beyond an individual's control.

In the decades following the initial HIV crisis there has been a rapid proliferation of research aimed at understanding the etiology and consequences of out-of-control sexual behavior as well as approaches to treatment. Much of the existing research has focused on the sexual behaviors of gay men, clinical samples of pedophiles and self-identified "sex addicts", and, in particular, sexual risk-taking behaviors such as unprotected intercourse. Fewer studies have focused on identifying sub-clinical levels of out-of-control sexual behavior and non-clinical populations, particularly women. However, researchers have devoted a significant

amount of attention to studying the relationship between out-of-control sexual behavior and sexual health outcomes, such as the transmission of HIV and sexually transmitted infections. Research has linked out-of-control sexual behavior to participation in high-risk sexual behaviors following an HIV diagnosis, the acquisition of sexually transmitted infections, substance abuse disorders, and psychiatric comorbidity [8, 36, 37, 55, 57–59].

While documentation linking out-of-control sexual behavior to psychological distress and sexual health consequences exists, the construct remains controversial within the scientific community. Scholars have argued that definitions of normative sexual behavior are subject to social and psychological theories unique to culture and time in history and often reflect socio-cultural mores governing behavior [29, 41]. Much of this debate centers around fundamental issues associated with defining out-of-control. Until recently, the universal gold standard for identification was behavioral frequency. Sex researcher John Bancroft and colleague Zoran Vukadinovic wrote a critical review of the construct of out-of-control sexual behavior, calling for scientific evidence that the behavior is qualitatively different from normative sexual behavior that occurs at the high end of the continuum. In their article, Bancroft and Vukadinovic maintain that it is negligent to assume that engaging in frequent sexual activity is inherently risky or problematic without documenting the occurrence of negative consequences [4].

Others have argued that perceptions of control over sexual behavior are social constructions, and that the importance and meaning of "out-of-control" models might reflect notions of self-control and self-consciousness unique to the American culture [32, 61]. It has been suggested that the idea of diagnosis, and subsequent labeling, reflect attempts to pathologize and medicalize sexual behaviors [32]. These scholars often cite the fact that homosexuality was listed as a mental disorder in the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association until the late 1970s. This point is central to understanding the lack of consensus among the scientific community given the rapidly emerging possibilities for the expression of sexuality and the diverse range of sexualities that exist in contemporary society. There remains a need for research that takes into account that sexual behaviors and norms vary among individuals and cultural groups. Indeed, what may be viewed as problematic for one individual, or within one culture, may be normative within another. Such variations in sexual behavior and behavioral frequency make it critical to link behavior to the actual occurrence of negative outcomes, and to understand the role of associated factors, in order to avoid errors in identifying and treating problematic sexual behaviors.

Clinical Criteria

While researchers and clinicians have identified out-of-control sexual behaviors as problematic and have linked such behaviors to negative psychological and sexual health outcomes, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition has no specific diagnostic criteria or category for classification [1]. Rather, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, out-of-control sexual behaviors can be classified under one of three major categories: paraphilia, either one or more specifically identified or paraphilia not otherwise specified; impulse control disorder not otherwise specified, or sexual disorder not otherwise specified. The absence of an accepted nomenclature and diagnostic criteria limit the diagnosis and treatment of problematic behavior.

Despite the ambiguity surrounding diagnosis, there is an over-whelming consensus among researchers regarding the comorbidity of sexual compulsivity with psychological and substance abuse disorders. The literature consistently links out-of-control sexual behaviors to psychological distress and substance use and dependency [19, 38, 39, 56, 58, 64, 65]. Benotsch et al.

found that among their sample ($N = 294$), individuals with higher sexual compulsivity scores also scored higher on indicators of depression, anxiety, borderline personality traits, obsessive-compulsive personality traits, and hopelessness [8]. Likewise, Wan et al. found that 39% of their treatment sample ($N = 59$) reported at least one pre-existing psychiatric diagnosis [64]. Kalichman and Cain found that higher levels of sexual compulsivity were linked to higher usage rates of alcohol, powder cocaine, crack cocaine, and inhalants [38]. Bancroft and Vukadinovic reported that among their sample of self-identified sex addicts ($N = 31$), one-third reported other addictive patterns, including alcohol, drugs and alcohol, overeating, computer games, and shopping [4].

The above studies represent only a few examples of published findings describing the comorbidity of psychiatric disorders and substance abuse disorders and out-of-control sexual behavior. However, findings from additional studies consistently report similar links. These findings raise questions for some about whether such associations provide evidence that out-of-control sexual behavior is a unique disorder or condition, or whether it should be conceptualized as the behavioral expression of another underlying disturbance. While it is possible that out-of-control sexual behavior does warrant its own classification, it is also possible that individuals who suffer from other disturbances use sex as a means of self-medication to alleviate or temporarily escape discomfort deriving from underlying distress. This point becomes particularly important when we consider the notion of excessive sexual behavior among non-clinical samples, as studies have shown that non-clinical negative mood states can influence sexual interest among some individuals.

The way in which psychological disorders or mood states affect sexual behavior is somewhat unclear. For example, it has long been established that clinical depression and anxiety can lead to a decrease in sexual interest and response, however recently attention has been given to the idea that among non-clinical samples depression and anxiety may actually serve to increase sexual interest [2, 5, 6, 47]. A recent study which looked at the relationship between mood and sexuality in heterosexual men and women found that 10% of men and 9.5% of women reported increase sexual interest when feeling depressed, and 25% of men and 23% of women reported an increase in sexual interest when feeling anxious [47]. A similar study investigating the relationship of mood and sexuality in heterosexual men found that 12% of the sample reported increased sexual interest when depressed [6]. The increase in sexual interest was markedly greater for anxiety, with 23% of the sample reporting higher levels of sexual interest during times of anxiety or stress. Among gay men, similar patterns have been noted. A study that explored mood and sex among a sample of gay men found that 21% of men reported an increase in sexual interest when depressed, while 17% reported an increase in sexual interest related to anxiety or stress [6]. Finally, a study investigating sexual functioning and self-reported depressive symptoms among a sample of college women found that women with higher levels of depression reported significantly more desire for masturbation when compared with controls, though desire for sex with a partner did not differ significantly [30].

Exploring out-of-control sexual behavior among both clinical and non-clinical samples may help clarify the relationship between psychological disorders, and/or mood states, and sexual behavior. Whether out-of-control sexual behavior is understood as a distinct psychological disorder, the symptom of underlying pathology, or a coping mechanism for alleviating non-clinical negative mood states has important implications for how such behavior is explained theoretically.

Etiology

Several researches have attempted theoretical explanations of out-of-control-sexual behavior and, as a result, various theories and models of

causation exist. Among the most widely cited etiological explanations are Carnes' Addiction Model, Coleman's Compulsive Sexual Behavior Model, and Kalichman's Impulse Control Model [14, 19, 39]. Each of these conceptualizations provides theoretically based explanations of etiology; however, overwhelming empirical support favoring any of these explanations is markedly absent. In fact, there is a clear divide among the research community on whether or not the phenomenon exists at all, with some scholars arguing that more substantial and convincing evidence is needed to support the notion of out-of-control or compulsive sexual behavior.

Carnes' Addiction Model

Carnes believed that sexual addiction is a chronic illness, and defined it as an extremely intense sex drive or obsession with sex [14]. Further, sex becomes the most important need, driving the individual's behaviors [15]. Carnes operationally defined sex addiction as a pathological relationship with a mood-altering experience, and believed that the hallmark of sexual addicts is the lack of ability to control their sexual feelings, thoughts, and behaviors [16, 63]. Rather than sex being a pleasurable act for the individual, Carnes asserted that for the addict, sex becomes a tool to ameliorate pain and relieve stress; at the core of the addiction is the fear of abandonment and shame [14, 15]. Carnes, and others who have supported his addiction model, likened the biological, neurological, and physiological responses that result from sexual stimulation to responses resulting from the consumption of alcohol and other drugs [25, 65].

In terms of treatment, Carnes advocated a 12-step approach adapted from the Alcoholics Anonymous model. The underlying premise of the approach is that the individual is an addict and is, therefore, powerless over the amount or type of sexual activity in which he or she engages [14, 51]. A key component to this approach is the belief that the individual is overwhelmed by shame, and in order to recover must progress through the 12-step process.

Coleman's Compulsive Sexual Behavior Model

Coleman first introduced the Compulsive Sexual Behavior Model of sexual compulsivity in 1990. Coleman theorized that compulsive sexual behavior is a disorder in which the individual experiences intense sexually arousing fantasies, urges, and associated sexual behaviors that are intrusive, driven, and repetitive [19]. Individuals with compulsive sexual behavior are described as being unable to control their sexual behavior and may perceive their behavior as excessive. Further, these individuals often experience serious co-morbid symptoms and associated consequences including, anxiety; depression; somatic complaints; alcohol or drug abuse or dependency; HIV or other sexually transmitted infections; unwanted pregnancy; relationship problems; domestic violence; sexual dysfunction; or child abuse [20]. According to Coleman et al., compulsive sexual behavior may lead to ethical, social, and legal problems, as well as psychological distress [20].

Coleman conceptualized compulsive sexual behaviors as fitting into one of two distinct categories, either paraphilic or nonparaphilic. Whereas paraphilic compulsive sexual behavior is comprised of non-normative sexual behavior that involves both distress and recurrent fantasies, nonparaphilic compulsive sexual behavior involves the excessive and compulsive engagement in normative sexual behaviors [19]. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, classifies eight paraphilic disorders: exhibitionism, fetishism, frotteurism, pedophilia, sexual masochism, sexual sadism, transvestic fetishism, and voyeurism. While there have been attempts to declassify a number of these paraphilias, Coleman et al.

pointed out that in order to meet clinical criteria an individual must experience sexually arousing fantasies, sexual urges, and behaviors that cause clinically significant distress in social, occupational, or other important areas of functioning [1, 20]. Coleman et al. asserted that, by nature, paraphilic behaviors impair an individual's ability to form reciprocal love relationships and sense of well-being [20]. The term "nonparaphilic compulsive sexual behavior" was used by Coleman to refer to the phenomenon under investigation in this study. There is no clear diagnostic category for nonparaphilic compulsive sexual behavior listed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [1]. However, Coleman et al. contended that an example can be found under the category "sexual disorder not otherwise specified" [20]. The example referred to by the author's states: "distress about a pattern of repeated sexual relationships involving a succession of lovers who are experienced by the individual only as things to be used." Nonparaphilic compulsive sexual behavior is thought to have at least 7 subtypes: compulsive cruising and multiple partners, compulsive fixation on an unattainable partner, compulsive autoeroticism (masturbation), compulsive use of erotica, compulsive use of the internet for sexual purposes, compulsive multiple love relationships, and compulsive sexuality within a relationship [11, 20]. Nonparaphilic compulsive sexual behavior is thought to lead to serious mental, sexual and physical health problems.

Coleman et al. acknowledged that there is no clear division between subclinical symptoms and a diagnosable clinical condition, and that individuals may experience problematic sexual behaviors without meeting the clinical threshold for compulsive sexual behavior [20]. Despite the lack of clear demarcation, Coleman et al. provide clinical criteria for diagnosing compulsive sexual behavior [20]. According to the guidelines, criteria for compulsive sexual behavior are met when the individual has recurrent and intense normophilic or paraphilic sexually arousing fantasies, sexual urges, and behaviors that cause clinically significant distress in social, occupational, or other areas of functioning; and these fantasies, sexual urges, and behaviors cannot be accounted for by another medical condition, substance use disorder, Axis I or II disorder, or developmental disorder. Further, gender, sexual orientation, and sociocultural norms must be taken into account.

The etiology of compulsive sexual behavior is described as complex and likely involving a variety of physiological and psychological factors [20, 56]. Coleman discussed links to both neuropsychiatric conditions such as temporal lobe lesions, epilepsy, and head trauma, as well as psychological disorders, particularly anxiety and depression. Coleman contended that neuropsychiatric causes should be considered when the onset of compulsive sexual behavior is subsequent to a trauma, surgery, illness, or the use of a substance (prescribed or not). If neuropsychiatric causes are ruled out, it is important to consider psychological factors [20, 56].

The suggested treatment for compulsive sexual behavior is a combination of pharmacotherapy and psychotherapy. According to Coleman's treatment paradigm, psychotherapy for compulsive sexual behavior explores environmental and psychodynamic stressors that contribute to the behavior. In addition, clients are taught coping mechanisms to manage stress, anxiety, and depression. A group treatment approach is recommended however such groups are not widely available. Because there are many types of compulsive sexual behavior, Coleman suggested tailoring therapy to individuals within the group setting [20]. Couples and/or family therapy, in conjunction with individual or group treatment, may help facilitate healthy sexual and/or intimacy functioning. Favored pharmacological interventions include the use of selective serotonin reuptake inhibitors or naltrexone. The body of evidence supporting the efficacy of selective serotonin reuptake inhibitors for treating compulsive sexual behavior comes from several small sample studies and case reports [10, 11, 21, 35]. Likewise, there have been few studies examining the efficacy of naltrexone for treating compulsive sexual behavior [56]. Instead, much of the literature supporting the efficacy of

naltrexone studied a variety of other disorders, including: alcoholism, cocaine abuse, eating disorders, and pathological gambling.

Kalichman's Impulse Control Model

Kalichman's primary interest in the notion of out-of-control sexual behavior grew out of the desire to understand mediating factors associated with HIV risk and the resistance to adopting risk reduction strategies [40]. According to Kalichman, sexual compulsivity is a heterogeneous psychological construct that can include a preoccupation with sexual desires and behaviors to the degree that disruptions in social relationships, occupational difficulties, and problems in daily living are experienced by the individual [38]. Further, Kalichman denoted that this conceptualization of sexual compulsivity is not synonymous with sex addiction, hypersexuality, or other clinically defined categories [38]. Kalichman defined sexual compulsivity as the propensity to experience sexual disinhibition and under-controlled sexual impulses and behaviors as self-identified by the individual [38]. In addition, Kalichman believed that sexual compulsivity most likely has multiple forms and etiologies.

Because Kalichman's conceptualization of sexual compulsivity is non-clinical, the bulk of his work on the topic has been devoted to documenting the relationship between sexual compulsivity and HIV/sexually transmitted infection risk, rather than trying to articulate theoretical underpinnings. Simply, he believes that individuals can only be identified as sexually compulsive when they self-report multiple markers of sexual preoccupations and under-controlled sexual impulses, and that this is likely related to a lack of impulse control [8, 38].

Measurement

A range of measures have been developed and used in research related to sexually compulsive behaviors. The primary measures include the Compulsive Sexual Behavior Inventory and the Sexual Compulsivity Scale [19, 36]. More recently, a new scale has been developed to assess whether one's sexual behaviors are associated with the negative cognitive and behavioral outcomes that have been proposed by groups such as the Society for the Advancement of Sexual Health [48, 49].

Compulsive Sexual Behavior Inventory

The Compulsive Sexual Behavior Inventory was developed in response to the lack of existing scales that attempted to identify individuals with compulsive sexual behavior [19]. According to the authors, previous attempts to develop such a scale failed to incorporate all of the major components of the phenomenon. The Compulsive Sexual Behavior Inventory was intended to create a standardized, reliable, and valid assessment tool for clinicians and researchers. For validation purposes, it was hypothesized that groups of individuals with paraphilic and nonparaphilic compulsive sexual behavior would not differ significantly on the measure but would differ significantly from controls.

The preliminary study of reliability and validity of the Compulsive Sexual Behavior Inventory included three groups, individuals diagnosed with paraphilic compulsive sexual behavior recruited from a sex-offender treatment program ($N = 35$), individuals with nonparaphilic compulsive sexual behavior recruited via advertisements ($N = 15$), and control participants recruited via advertisements ($N = 42$). The initial inventory consisted of 42 items related to sexual control and various aspects of behavior associated with both paraphilic and nonparaphilic compulsive sexual behavior [19]. Participants were directed to rate their responses to items on a scale ranging from 1 = Very frequently to 5 = Never. A principal components factor

analysis using varimax rotation was performed on the data. Factor loadings that exceeded 0.60 after rotation were retained for the final scale. The reliability of the retained factors was tested using Cronbach's alpha and the data were tested using linear discriminant function analysis to determine the scale's ability to differentiate individuals with compulsive sexual behavior from controls. In addition, three analyses of variance were conducted to explore mean differences for each group on the identified subscales. A plot of data from the entire sample indicated that a three-factor solution had the best fit. The three-factor solution accounted for 58% of the variance in the data, with the first factor explaining 42% of the variance. The second factor explained 10.1% of the variance (eigenvalue = 4.26), and the third factor accounted for 5.9% of the variance (eigenvalue = 2.46). The retention of items on each factor was determined by the magnitude of the factor loading and subsequent assessments of face validity. A total of 28 items were retained, and the factors appeared to measure control, abuse, and violence.

Initial tests of validity were conducted using linear discriminant function analysis, testing the scale's ability to distinguish between groups believed to have compulsive sexual behavior versus those who did not. The classification matrix was reported to have correctly identified 92% of cases, with one normal control being incorrectly classified as compulsive and six compulsives being identified as normal. Further explorations of validity used the three subscales as independent variables in analyses of variance to explore group differences. The findings revealed significant effects for group on the control subscale. Further, pairwise comparisons demonstrated that pedophiles scored significantly lower on the subscale when compared with the other two groups. A significant main effect was also found for the violence subscale, and subsequent pairwise comparisons revealed that controls differed significantly from pedophiles. Table 1 provides the measures contained in the Compulsive Sexual Behavior Inventory.

Sexual Compulsivity Scale

Kalichman posited that intrinsic factors such as personality disposition might play a role in HIV risk behaviors; particularly, he was interested in Zuckerman's work on sensation seeking. Based on findings from previous studies that linked sensation seeking to high-risk sexual behaviors, Kalichman theorized that sensation seeking might be an important predictor of HIV risk and resistance to behavioral change [28, 40, 52]. In order to test his theory, Kalichman adapted the Sensation Seeking Scale to measure sensation seeking specific to sexual behavior and, in addition, developed a measure of sexual compulsivity [66].

The Sexual Compulsivity Scale was designed to measure two aspects of sexuality: hypersexuality and sexual preoccupation, and items reflect "excessive preoccupation with sex acts and encounters" [36]. The scale has been widely used to investigate high-risk sexual behaviors. The scale consists of 10-items and directs respondents to indicate the extent to which they agree with statements ranging from "not at all like me" to "very much like me". The 10 items used in the Sexual Compulsivity Scale were derived from a 12-step self-help recovery manual for sex addicts [16, 53].

Scale reliability and validity were tested in two samples. The first sample consisted of self-identified gay men ($N = 286$). Sixty-three percent of the sample was white, and 72% reported an annual income over $20,000. Participants were recruited through fliers were placed in bars and social organizations in Milwaukee, Wisconsin. The second sample consisted of inner-city men ($N = 60$) and women ($N = 98$) at high-risk for HIV. Ninety-five percent of the sample identified as African-American, and 94% reported an annual income of less than $20,000. Participants in this sample were recruited through local community agencies in Milwaukee, Wisconsin. Tests of reliability were performed by computing alpha coefficients. Internal consistency for sample 1 was reported to be alpha = 0.86, and for sample 2 to be

Table 1 Compulsive sexual behavior inventory

Please mark the response that best describes your behaviors or experiences[a]:
How often have you had trouble controlling your sexual urges?
Have you felt unable to control you sexual behavior?
How often have you used sex to deal with worries or problems in your life?
How often have you felt guilty or shameful about aspects of your sexual behavior?
How often have you concealed or hidden your sexual behavior from others?
How often have you been unable to control your sexual feelings?
How often have you made pledges or promises to change or alter your sexual behavior?
How often have your sexual thoughts or behaviors interfered with the formation of friendships?
How often have you developed excuses and reasons to justify your sexual behavior?
How often have you missed opportunities for productive and enhancing activities because of your sexual activity?
How often have your sexual activities caused financial problems for you?
How often have you felt emotionally distant when you were engaging in sex with others?
How often have you had sex or masturbated more than you wanted to?
Were you sexually abused as a child?
Were you physically abused as a child?
Other than parents or siblings, did you experience sexual activity as a child with someone more than 4–6 years older than you?
Did you have sexual experiences with any of your siblings?
Have you been forced to have sex with a stranger, casual acquaintance or friend?
How often have you been arrested or legally apprehended for your sexual behavior?
Have you forced anyone against his or her will?
Did you have sexual experiences with either of your parents?
Have you ever hit, kicked, punched, thrown, chocked restrained or beaten any of your sexual partners?
Have you given others physical pain for sexual pleasure?
In fighting, have you been hit, kicked, punched, slapped, thrown, chocked, restrained or beaten by your current or most recent partner?
Have you received physical pain for pleasure?
Have you received money to have sex?
Have you been forced to have sex with your husband, wife, or lover?
Have you been watched masturbating or having sex without giving permission?

Adapted from Coleman et al. [19]

[a]Measured with a five-point response scale that includes: very frequently, often, occasionally, rarely, never

alpha = 0.87. A 3 month retest was performed on both groups. For sample 1 (N = 195) alpha = 0.64, and for sample 2 (N = 52) alpha = 0.80. Construct Validity was established by exploring associations between scores on the Sexual Compulsivity Scale and risk behaviors. For sample 1, positive associations were found between scores on the Sexual Compulsivity Scale and substance use and sexual risk-taking behaviors, and inverse associations with self-esteem and the intention to reduce risk-taking behaviors. In sample 2, positive associations were found between increased frequencies of unprotected sex, higher number of sexual partners, and were associated with pleasure activities. In addition, an inverse association was found with the intent to reduce risk. Follow-up studies using the Sexual Compulsivity Scale have reported similar results [8, 9].

The Sexual Compulsivity Scale has not been without critique in the literature. For the most part, since its initial publication, the scale has only been used to assess sexual compulsivity and its relations to "risky" sexual behaviors among individuals who are members of "high-risk" groups for HIV infection (i.e., men who have sex with men, heavy substance abusers, etc.) or who are already HIV positive. In an attempt to examine how the scale functions in a more "general population," Dodge et al. found support for reliability and construct validity of the Sexual Compulsivity Scale in a sample of nearly 900 heterosexual college students [23]. Construct validity was substantiated by the presence of significant relationships of sexual compulsivity with higher frequencies of solo and partnered sexual behaviors and numbers of sexual partners. The scale was also displayed

relations to gender and age, such that men and younger individuals scored higher on the Sexual Compulsivity Scale. As in "high-risk" samples, sexual compulsivity scores were associated with higher frequencies of unprotected sexual behaviors. Relationships between sexual compulsivity and solo, partnered, and unprotected sexual behaviors remained significant after controlling for demographic variables. Although the researchers found support for construct validity of the Sexual Compulsivity Scale in this sample, they also noted that it is not clear whether the scale distinctly measures sexual compulsivity or taps into other constructs, such as sexual desire and sexual exploration. Table 2 provides the items of the Sexual Compulsivity Scale.

Cognitive and Behavioral Outcomes of Sexual Behavior Scale

The Society for the Advancement of Sexual Health has offered a list of outcomes that could suggest that a person or their behaviors are sexually compulsive. The outcomes outlined by the Society for the Advancement of Sexual Health span six domains of life functioning: social, emotional, physical, legal, financial/occupational, and spiritual. An outcomes-based understanding of sexual compulsivity would suggest that individuals and their behaviors could be considered sexually compulsive if they find that their sexual behaviors (including behaviors that they do alone such as masturbation and those that they do with other people such as having intercourse) are leading to negative consequences in various areas of their lives. For example, that a person spends a great deal of time viewing sexually-explicit materials on the Internet may not necessarily be indicative of sexual compulsivity, but if that behavior results in the individual's inability to relate to a romantic or relational partner or creates other challenges then it might indicate that their Internet-based sexual activities have become problematic [9].

Recently, scales assessing cognitive and behavior outcomes of sexual behavior were developed to assess both the extent to which a participant was concerned about negative outcomes resulting from their sexual behaviors, and the extent to which such outcomes were actually experienced by participants [48, 49]. The scales were constructed based on 6 domains of impact of sexually compulsive behaviors identified by the Society for the Advancement of Sexual Health. The 6 domains are identified as: financial, legal, physical, psychological, spiritual, and social. The cognitive outcomes scale, consisting of 20 items, asks participants to rate on a four-point scale ranging from "never" to "always" the extent to which they worry that the things they have done sexually may result in a specified outcome. The 16 behavioral outcome items are measured dichotomously "yes" or "no" using 16 items to assess whether a participant

Table 2 Sexual compulsivity scale

Please indicate the extent to which the following statements apply to you[a]:
My sexual appetite has gotten in the way of my relationships.
My sexual thoughts and behaviors are causing problems in my life.
My desires to have sex have disrupted my daily life.
I sometimes fail to meet my commitments and responsibilities because of my sexual behaviors.
I sometimes get so horny I could lose control.
I find myself thinking about sex while at work or in class.
I feel that my sexual thoughts and feelings are stronger than I am.
I have to struggle to control my sexual thoughts and behavior.
I think about sex more than I would like to.
It has been difficult for me to find sex partners who desire having sex as much as I want to.

Adapted from Kalichman and Rompa [36]

[a]Measured with a four-point response scale that includes: never applies to me, sometimes applies to me, often applies to me, always applies to me

has actually experienced an outcome. Cognitive subscale scores were created from mean scores of the items making up each factor. Behavioral outcome scores were the sum of the "yes" (1 point) versus "no" (0 points) answers to the items for each factor.

Tests of scale reliability and validity were conducted in a cross-sectional sample of 391 young adults, largely comprised of women (70.3%, $N = 274$). The sample was chosen to explore whether negative cognitive and behavioral outcomes associated with sexual behavior could be detected in a non-clinical population at sub-clinical levels. The majority of participants were 21 years of age or younger (86.2%, $N = 336$) and identified as heterosexual (95.4%, $N = 372$).

Analyses were conducted to assess the psychometric properties of the Cognitive and Behavioral Outcomes of Sexual Behavior Scale and the extent to which those in the sample reported experiencing negative outcomes resulting from their sexual behaviors. Reliability of the Cognitive and Behavioral Outcomes of Sexual Behavior Scale was assessed using Cronbach's Alpha for internal consistency reliability; separate analyses of the cognitive and behavioral items were conducted. Internal consistency for the 20-item cognitive scale was high ($\alpha = 0.89$) with a slightly lower level of reliability ($\alpha = 0.75$) for the 16-item behavioral scale. However, given that the response scale for the behavioral items was "yes" or "no"; this level is quite acceptable.

Construct validity for the 20 cognitive outcomes items was tested using a Principal Component Analysis with varimax rotation, specifying six factors because items were constructed to focus on the six outcome categories articulated by the Society for the Advancement of Sexual Health. Overall, the six-factor solution explained 74.8% of the total variance. The inter-item correlation matrix did not yield correlations high enough to suggest that the scale is unidimensional. Separate reliability estimates were calculated for each of the six factors (or subscales). Cronbach's Alpha for internal-consistency was found to be high for all of the factors, or subscales, indicating scale reliability in this sample. Table 3 contains the Cognitive and Behavioral Outcomes of Sexual Behavior Scale.

Implications for Clinical Practice

Recent research indicates that, at some point, sexual behavior can lead to negative outcomes that include sexual risk-taking behavior and psychological distress [48, 49]. These findings have important implications for the prevention of HIV and other sexually transmitted infections, as well as negative consequences beyond risks to sexual health. In fact, it may be that an outcomes focused assessment tool is most appropriate for screening individuals with sub-clinical levels of sexual compulsivity and populations whose clinical presentations may be different from those traditionally studied in sexual compulsivity research. For example, research indicates that women may experience negative outcomes in the form of psychological, spiritual, and social distress suggesting that practitioners may need to reconceptualize their approaches to both assessment and treatment [48, 49]. Research indicates that men may primarily manifest sexual compulsivity in terms of physical outcomes, particularly those related to disease and pregnancy.

However, there is also evidence to suggest that young men experience disruptions in their social lives and other areas of functioning. Therefore, it may be appropriate to develop risk-reduction and intervention strategies aimed at sexual-risk taking, while providing other forms of treatment, such as psychotherapy, to address the psychological and social aspects of out-of-control sexual behaviors.

Regardless of theoretical orientation, the majority of practitioners favor approaches that incorporate cognitive and behavioral dimensions related to developing and maintaining control. This being the case, the Cognitive and Behavioral Outcomes of Sexual Behavior Scale may serve as a useful tool, used in conjunction with other screening measures, for clinical

Table 3 Cognitive and behavioral outcomes of sexual behavior scale

Cognitive Outcomes
Below is a list of things that some people worry about as a result of their sexual activities (including things people do alone and those they do with others). Please indicate the extent to which the following apply to you. I am worried that the things I have done sexually[a]:
Might have placed me or one of my sex partners at risk for pregnancy.
Might have placed me or one of my sex partners at risk for a sexually transmitted infection (like herpes, gonorrhea, or crabs).
Might have placed me or one of my sex partners at risk for HIV.
Might have caused one of my sex partners to experience pain, injury or other problems.
Might have resulted in pain, injury or other problems for myself.
Might have presented the potential for serious physical injury or death.
Might be leading to problems with my friends.
Might be leading to problems with my family members.
Might be leading to problems with my boyfriend/girlfriend/spouse.
Might have placed me at risk of being arrested.
Might have been against the law.
Might have led to financial problems.
Might have caused me to waste my money.
Were interfering with my ability to complete tasks for work or school.
Might have had presented the potential for me to lose my job.
Could lead to school-related problems, such as probation, expulsion or other sanctions.
Were inconsistent with my spiritual beliefs.
Were inconsistent with my religious values.
Were making me feel guilty.
Were making me ashamed of myself.
Behavioral Outcomes
Below is a list of things that sometimes happen to people as a result of their sexual activities (including those they do alone and those they do with others). Please indicate whether these things have happened to you during the last year as a result of your sexual activities. In the past year, as a result of the things you have done sexually, did the following happen to you[b]:
I or my sexual partner (s) became pregnant.
I contracted a sexually transmitted infection.
I contracted HIV.
I gave someone else a sexually transmitted infection.
I gave someone else HIV.
I caused pain, injury or other physical problems for myself.
I caused pain, injury or other physical problems for a sex partner.
My relationships with friends and/or family members were damaged.
My relationships with a spouse or other relationship partner were damaged.
I was arrested.
I experienced financial problems.
I experienced problems at school.
I experienced problems at work.
I experienced spiritual distress.
I was embarrassed or ashamed of myself.
I felt guilty.

Adapted from McBride et al. [48]

[a]Measured with a four-point response scale that includes: never, sometimes, often, always

[b]Measured with a dichotomous response scale that includes: yes, no

practitioners, as it would allow them to identify areas on which to focus treatment. Further, because research indicates gender differences in negative outcomes associated with sexual compulsivity, clinicians may need to take different approaches to assessment and treatment of sexual compulsivity in women and men. The literature consistently reports that women score lower on measures of sexual compulsivity and less often present for treatment. It may be that

women are less likely to self-report problems related to out-of-control sexual behavior due to social and cultural stigma related to high levels of sexual frequency or the behavioral expression of sexuality. Clinicians must take these issues into consideration, and ensure that they are conducting adequate assessments. While a body of research indicates that selective serotonin reuptake inhibitors and naltrexone may enhance the efficacy of treatment outcomes when used in conjunction with cognitive behavioral therapy, additional documentation is necessary as these studies were limited to small samples and case reports [10, 11, 21, 56].

Many providers may have little or no training in the identification and treatment of sexual compulsivity. Because mental health professionals play a critical role in promoting health and well-being, it may be necessary to provide specialized training on the assessment and treatment of sexual compulsivity, particularly in terms of identifying negative consequences resulting from behaviors. Not only do providers need to be aware of the obvious risks to sexual and psychological health, but also the potential for negative consequences in a variety of life domains.

Implications for Future Research

Until recently, sexual compulsivity has been primarily conceptualized as a phenomenon leading to sexual risk-taking behavior with little focus on consequences beyond sexual health. Recent research findings provide support for construct validity and, further, suggest that qualitative differences exist. Further, research indicates that negative outcomes related to sexual behavior that may be indicative of sub-clinical levels of sexual compulsivity occur in non-clinical populations. Thus, it may be useful to conduct longitudinal studies to determine whether those who score high on measures of sexual compulsivity show a progression in their experiences of negative cognitive and behavioral consequences. It may be that sexual compulsivity exists on a continuum, whereas initially individuals experience minor consequences, primarily limited to cognitive distress, and later progress to experiencing negative behavioral consequences as the level of compulsivity increases. Studies including clinical measures of psychological distress may provide insight into psychiatric comorbidity that many have suggested is linked to sexual compulsivity. If sexual compulsivity is, indeed, a mechanism of mood regulation or "self-medication" for underlying psychiatric condition, such studies might further our understanding of these associations.

Last, more studies are needed to determine the practical significance of sexual compulsivity in diverse populations [23]. These studies should evaluate the presence of actual negative health outcomes in individuals who score higher on measures of sexual compulsivity and who engage in more frequent sexual risk behaviors so that health professionals may develop and tailor HIV/STD education and intervention efforts as needed. Researchers should also design, test, and refine potential therapeutic treatments and interventions for sexual compulsivity, as its existence as a clinical condition becomes clearer through further scientific inquiry.

Summary

The idea that sexual behavior can go beyond the control of an individual has received a great deal of attention over recent decades, particularly in the context of sexual risk-taking behaviors that present the potential for the transmission of HIV and other sexually transmitted diseases and infections. Though many scientists and researchers support the notion that sexual compulsivity exists, others have argued that no such phenomenon exists but, rather, that normative sexual expression at the high end of the behavioral continuum is being pathologized. To complicate the issue, the opportunities for the behavioral expression of individual sexuality continue to broaden, with technological advances such as the Internet presenting new

avenues for sexual engagement. Further, shifting cultural and social norms allowed for more open expressions of a range of sexualities and sexual behaviors, calling into question previous understandings of human sexuality and blurring the boundaries of "normal".

Despite these changes, there has been evidence to suggest that there is a point where sexual behavior becomes out-of-control, leading to negative consequences for the individual. However, until now, there has been virtually no evidence to document the occurrence of negative consequences above risks to sexual health. The results from recent research suggest that, indeed, a variety of negative consequences are associated with sexual behaviors and perhaps is therefore a more solid criteria for establishing the point at which a behavior becomes "out-of-control." Such findings are an important first step to understanding the phenomenon and provide evidence to support the validity of the construct. Clearly, the results suggest that individuals experience a sense of loss of control associated with their sexual behaviors or the outcomes of those behaviors. Further, recent findings have provided documentation that indicates sexual compulsivity can impact several dimensions of a person's life. For example, impairment in social functioning and psychological distress were found to be associated with out-of-control sexual behavior. Whether these are simply outcomes resulting from the behavior, or underlying etiological mechanisms that influence the development of sexual compulsivity, remains to be determined.

An outcomes-focused approach to understanding sexual compulsivity may move us in a new conceptual direction. Engaging in frequent sexual encounters is not inherently problematic, particularly if an individual uses appropriate protection. Therefore, the disease-focused arguments relating to out-of-control sexual behavior are limited to sexual compulsivity as it influences instances of unprotected sex. An outcomes focus broadens the conceptualization, as an individual who experiences a loss of control may have little risk for disease but may be experiencing negative consequences in other areas, such as financial problems resulting from the use of online pornography, or psychological distress relating to uncontrolled masturbation. Adopting a broader, outcomes-focused approach to understanding out-of-control sexual behavior will allow scientists and practitioners to obtain a more thorough understanding of the phenomenon, and hopefully lead to better screening tools and treatment strategies.

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Instant Messaging Addiction Among Teenagers: Abstracting from the Chinese Experience

Hanyun Huang and Louis Leung

Contents

Introduction

Instant messaging is a computer application that allows synchronous text communication between two or more people through the Internet. Such communication can be characterized in that parties at both ends of a conversation see each line of text right after it is typed (line-by-line), thus making it more like a telephone conversation than an exchange of letters [3]. Instant messaging is also a computer-based, one-on-one communication tool—a hybrid of e-mail, chat room, pager, telephone, voice mail, caller ID, and bulletin board with a multiparty "chat" model [13]. The instant messaging systems discussed in this chapter include MSN Messenger, QQ (Oh I Seek You), ICQ (I Seek You), and Yahoo!Messenger, Skype, as well as other instant messaging applications. QQ is the most popular instant messaging channel in China, like ICQ in the West.

As a relational maintenance tool, instant messaging has been used for entertainment, work, and team relationships [22, 41, 44]. Instant messaging has been found useful when discussing topics that are uncomfortable to talk about in face-to-face situations [31]. As Internet and computer-mediated communications undergo further development, instant messaging is becoming even more popular among Internet users. As this continues, teenagers could become more vulnerable to being addicted to this widely adopted social interaction tool.

Traditionally, the concept of addiction was based on a medical model and was properly reserved for bodily and psychological dependence on a physical substance. Other scholars have argued that the concept of addiction should be widened to cover a broader range of behaviors [30, 39, 49]. Griffiths proposed

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_33,

the concept of "technological addiction", which is non-chemical but behavioral addiction that involves excessive human-machine interaction [17]. It can be either passive, such as television viewing, or active, such as computer games or online chatting, and usually comprises inducing and reinforcing features that may contribute to the promotion of addictive tendencies [17]. It also features the core components of addiction, including salience, mood modification, tolerance, withdrawal, conflict, and relapse [18]. It has been argued by Griffiths that any behavior that fulfills these criteria can be operationally defined as addiction [18]. Some other research also supports the notion that excessive use of technology can be considered problematic [20, 50]. Using pathological gambling as a model, Young proposed that Internet addiction could be defined as an impulse-control disorder, which does not involve an intoxicant [60]. Previous studies examining Internet addiction have found that the use of synchronous communication applications on the Internet, such as instant messaging, by Internet-dependent students is significantly higher than among non-dependent individuals [2, 47, 59, 62]. As instant messaging has become extremely popular in recent years, whether instant messaging addiction exists among teenagers—as well as what symptoms and addict characteristics can be identified—is a research area with significant theoretical and policy implications.

Previous research has also investigated the relationship between psychological variables, such as shyness and alienation, and Internet addiction. For example, Chak and Leung indicated that there is a correlation between shyness and one's tendency to be addicted to the Internet [11]. Jansen and Clafton also reported on the rising phenomenon of Internet addiction in Australia and found that many people are dependent on the Internet for most of their social interaction [25]. As a result, these people are increasingly alienating themselves from the offline community. Other studies also indicated that pathological Internet use is problematic to teenagers' academic performance [37, 47, 48].

Internet and Instant Messaging Penetration in China

According to "The 21st Statistical Survey Report on Internet Development in China", published by the China Internet Network Information Center, there were 210 million Internet users and 170 million instant messaging users in China in 2007 [15]. Among Internet users, 28.8% were students and 19.1% were teenagers under 18 years of age. Of the teenage Internet users, junior high school students (Grades 7–9) spent, on average, about 7.5 h every week on the Internet, whereas senior high school students (Grades 10–12) spent 12.3 h weekly. The report pointed out that 18.2% of senior high school students and 9.6% of junior high school students spent more than 20 h every week on the Internet. These findings suggested that teenagers may be experiencing some degree of Internet dependence. The report further revealed that 85% of teenage Internet users were instant messaging users, whereas 81% of all Internet users used instant messaging. These figures illustrated that instant messaging has become so popular that many teenagers may become easily addicted.

In 2006, the China Internet Network Information Center released "The Survey Report on Chinese Instant Message Market" [14]. The report showed that 73.4% of instant messaging users regarded instant messaging as necessary. Instant messaging tools impacted other communication methods—over 40% of the users regarded instant messaging as their "most frequently used communication channel". Because of its convenience and low cost, over 60% of the instant messaging users reduced their use of e-mail, and over 70% of MSN users and nearly two-thirds of QQ users reduced their telephone use. QQ dominated 84.4% of the instant messaging market in 2006, and MSN ranked second, accounting for 13.9% of the market. These figures indicated that instant messaging is prevalent among Internet users in China, especially teenagers.

Internet Addiction

Derived from the substance-dependence criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) [1], Internet addiction disorder, the first listed Internet-related disorder, is defined as a behavioral addiction consisting of six core components: salience, mood modification, tolerance, withdrawal symptoms, conflict, and relapse [18]. Griffiths has suggested that the source of this addiction can originate from one or more aspects of Internet use including the process of typing, the medium of communication, the lack of face-to-face contact, Internet content, or online social activities. Young characterized Internet addiction as staying online, for pleasure, largely in chat rooms, for an average of 38 h or more per week, and concluded that Internet addiction can shatter families, relationships, and careers. Utilizing an adapted version of the criteria for pathological gambling defined by the DSM-IV, Young developed eight criteria to provide a screening instrument for addictive Internet use. Individuals have to meet five of eight criteria for Internet addiction to be considered an addict. The criteria are: (1) preoccupation with the Internet; (2) a need for longer amounts of time online; (3) repeated attempts to reduce Internet use; (4) mood modification from Internet use; (5) staying online longer than intended; (6) loss of a significant relationship, job, or educational or career opportunity; (7) deception about the time spent online; and (8) use of the Internet as a way of escaping from problems [14]. Several other studies on Internet addiction have been conducted during the past decade [5, 6, 11, 19, 34, 47, 61].

Instant Messaging Addiction

Instant messaging has penetrated young people's lives, and its use continues to grow. As early as 20 years ago, Shotton suggested that people might experience computer-mediated communication dependence [50]. Scherer's research indicated that Internet-dependent students are almost three times more likely than non-dependent students to use synchronous-communication Internet applications [47]. According to Young, 63% of "avid Internet users" are more likely to use synchronous Internet applications as compared with 12% for non-dependent users [59]. Similarly, Anderson reported that the daily use of synchronous-communication Internet applications among Internet-dependent students is nearly 10 times that of non-dependent students [2]. Yuen and Lavin's research also showed that Internet-dependent individuals spend twice as much time on instant messaging as non-dependent individuals [62]. According to Leung, college students indicated that relaxation, entertainment, and fashion are instrumental motives for ICQ use, while inclusion, affection, sociability, and escape are the intrinsic motives [32]. Students who are heavy users of ICQ are motivated by affection and sociability. The lonelier, more dishonest, and more negative students are, the less truthful they are in self-disclosure concerning their ICQ interactions [33]. Leung also found that being emotionally open on the Net and heavy use of ICQ are the most influential criteria in predicting abuse of the Internet among the "Net generation" [34]. This finding reinforces Wellman's research that Internet-dependent individuals spend most of their time in the synchronous-communication environment engaging in interactive activities, including ICQ, for pleasure-seeking or escape [57]. What's more, research conducted by the organization known as "Breakthrough" found that about 5% of the respondents, who were secondary school students, were addicted to ICQ [7]. These students showed low self-esteem and had less parental and peer support than non-ICQ addicts. They were also weaker in self-expression, listening, and a willingness to express their viewpoints. However, most of these studies conceptualized Internet addiction as a unidimensional construct; almost no research has been conducted on instant messaging addiction from a multidimensional symptomatic perspective.

Shyness and Internet Use

Shyness is a form of social anxiety that interferes with a person's ability to participate in social situations. It is a fear of meeting people and a discomfort in the presence of others [42, 63]. At its core is the anxiety of being evaluated by others and consequently rejected [43]. Shyness can lead to a range of social problems, including self-consciousness, poor self-projection, and deficient communication [29]. Compared with others, shy people are more likely to regard their offline networks as unsupportive and unsatisfying and are happy to be by themselves or to participate minimally in social encounters [40]. What's more, shy people have less social support, smaller friendship networks, and less friendship satisfaction, are more passive, and have fewer interactions in their offline lives than people who are not shy [26].

Recent research has shown that the unique attributes of computer-mediated communication—i.e., it is mediated, low in social cues, and sometimes anonymous—may provide new ways for shy people to communicate with the outside world with less risk of being embarrassed. One study showed that correlations of shyness with aspects of involvement in online relationships are greater than those with involvement in face-to-face relationships [56]. Another study investigated whether the Internet promotes or impedes social interactions and found that shy people feel much less inhibited in social interaction online compared with offline, and consequently they are able to form a number of online relationships [45]. Stritzke and colleagues suggested that some individuals, particularly shy people, prefer to interact in an online environment as opposed to traditional face-to-face interactions [53]. Similarly, McKenna and colleagues pointed out that the Internet helps those people who are shy, lack social skills, or have social anxieties in forming relationships [36]. These people can enjoy aspects of the Internet that allow them to meet, socialize, and exchange ideas through the use of e-mail, ICQ, chat rooms, and newsgroups, which in turn allows them to fulfill unmet emotional and psychological needs that are more intimate and less threatening than real-life relationships [21]. In line with these findings, Caplan confirmed that people who have higher levels of depression, shyness, and loneliness and lower self-esteem have a greater preference for online conversation [10].

Furthermore, Yuen and Lavin studied the role of shyness in Internet dependence and found that Internet-dependent individuals' shyness is greater in face-to-face interactions relative to online interpersonal exchanges, and they discussed how instant messaging can be used to ameliorate shyness and how such reinforced behavior could foster dependence [62]. People who are addicted to the Internet make intense and frequent use of the Internet, especially for online communication via e-mail, ICQ, chat rooms, newsgroups, and online games [11].

Alienation and Internet Use

Alienation refers to a sense of social estrangement, an absence of the support of meaningful social connection, lacking a sense of belonging, and feeling cut off from family, schools, and friends [9, 35]. It directly represents social dysfunction and a failure to bond effectively with prosocial institutions such as the family and school, or even with individuals such as one's peers [38].

No previous studies have examined alienation and instant messaging use, but some studies have explored alienation and Internet use. One study found that Internet sites have the potential to create a sense of community in cyberspace, which could be attractive for alienated youth seeking alternative socialization sources [55]. In a study of alienation and the use of violent Internet sites, it was revealed that alienation from both family and school can predict the use of violent Web sites [51, 52], suggesting that youth who feel disconnected from family or school would be likely to turn to antisocial media content,

particularly on Web sites. These findings demonstrate the attraction of the Internet as an interactive medium for alienated youth.

Furthermore, the Internet itself may "reproduce" alienation. Despite the fact that most Internet use is devoted to active social communication, researchers discovered that such use counter-intuitively takes time away from face-to-face contacts and replaces stronger ties with weaker ones [27]. As a result, interaction quality decreases, resulting in feelings of loneliness, depression, and a lowered sense of belonging, especially for those who are new to the Internet.

Along this line of research, other researchers have found that ostracism (the act of ignoring and exclusion) is as powerful on the Internet as it is in a physical presence [58]. When participants in the research were cyber-ostracized, their sense of belonging and inclusionary status was reduced significantly, which in turn worsened their mood and increased their feelings of exclusion.

In instant messaging, people can talk not only to friends but also to strangers. People can also make new friends through instant messaging. Thus, teenagers who feel alienated from family, friends, and school might tend to seek social support or friendship online through instant messaging.

Internet Use and Academic Performance

Whether academic performance and use of the Internet are interrelated has long been of interest to researchers. A 16-month field study conducted by Jackson and colleagues discovered that children from low-income families who used the Internet more had higher scores on reading achievement tests and obtained higher overall grades than children from low-income families who did not use the Internet very much [24]. Interestingly, a follow-up study based on these findings concluded that academic performance predicts subsequent Internet activities, whereas Internet activities predict subsequent academic performance [23]. However, Barber reported that 86% of teachers responding to a survey believed that Internet use by children does not improve performance, probably due to the fact that the information that the Internet contains is highly disorganized and unrelated to school curricula [4].

Previous researches have studied the relationship between Internet abuse or Internet dependence and academic performance. Scherer and Bost surveyed 531 students about their Internet use, using a checklist of ten clinical symptoms to parallel the symptoms of substance abuse and dependence. Results indicated that 13% of the sample reported that Internet use interfered with their academic work, professional performance, or social lives [48]. An online survey and two campus-wide surveys conducted at the University of Texas at Austin and Bryant College further documented that Internet abuse is problematic for academic performance [8, 37, 47]. Scherer concluded: "Excessive Internet use is problematic when it results in impaired functioning such as compromised grades or failure to fulfill responsibilities [47]."

Studies also have been done to evaluate the relationship between the use of instant messaging (or similar applications) and academic performance. Kubey and colleagues revealed that heavy leisure Internet use is highly correlated with impaired academic performance, particularly when the use is with synchronous-communication applications such as chat rooms and Multiple User Dungeons [28]. The researchers proposed that the unique social qualities of such applications represent a most significant utility for lonely individuals who can be with friends at any time, resulting in many users staying up late at night and feeling tired the next day, which in turn affects their academic performance.

Another study on ICQ (a specific medium of instant messaging) was conducted in Hong Kong to examine the effects that it has on adolescents [12]. The study reported that 38% of the respondents indicated that using ICQ has an effect on their academic performance. However, whether such effects were positive or negative, as stated

by the researchers, could not be determined through the self-report questionnaires. Cheuk and Chan remained optimistic by concluding that if the participants used ICQ for academic issues such as a discussion of homework, then ICQ's effect would be positive.

Studies also have been conducted on the relationship between teenage alienation problems and their effects on academic performance. Coleman discovered that intellectualism is not the sole determining variable in the academic performance of students. The rewards from their social systems, including their achievements in other areas such as sports, and how well they get along with each other are also very important in affecting their performance in school [16]. In the study on Swedish teenagers by Roe, it was discovered that those who feel alienated from classmates and the school subsequently achieve lower levels of academic results [46]. The research conducted by Sugarman yielded a similar outcome. He stated that students having a lower commitment to their "pupil role" achieve less academically than those who are more committed to the role of student [54].

An Empirical Study of Instant Messaging Addiction in China

To continue this line of research, this chapter reports a questionnaire survey research conducted in November 2007 in a middle school in Xiamen, China. A stratified random sampling method was used to select 330 students in Grades 7–12 (aged 12–19) to participate. The aims of the study were to examine: (1) whether instant messaging addiction exists among Chinese teenagers, and, if so, who the addicts are, what their symptoms are, and to what extent they are addicted; (2) whether psychological variables such as shyness and alienation can predict instant messaging use or addiction, among teenagers, and (3) whether instant messaging use and addiction can impair the academic performance of teenagers in China.

The majority of the participants (95.8%; $n = 316$) indicated that they use instant messaging. Only 4.2% of the participants indicated that they had never used instant messaging before. Of the 316 instant messaging users, 70.6% of them indicated that they always or often log onto instant messaging software once they go online. Over 86% of instant messaging users reported that their most frequently used instant messaging function is text chatting, while 89.9% said that they almost always chat with friends as opposed to relatives, teachers, or strangers.

Instant Messaging Addiction and Addiction Symptoms Among Teenagers

Using the classic definition of Internet addiction by Young, 9.7% of the teenagers in our sample could be classified as instant messaging addicts. The results show that instant messaging addicts spend more hours every week on instant messaging and spend significantly longer hours each time they use it.

The study in China also yielded four instant messaging addiction symptoms among teenagers: (1) *Preoccupation with instant messaging* (alpha = 0.82) revealed whether the lives of the teenagers were preoccupied by instant messaging; the teenagers act annoyed when they are interrupted during online chats; they feel preoccupied by online chatting and fantasize about chatting online when offline; they feel depressed and moody when they cannot chat online; they sacrifice sleep to chat online; and they need to increase instant messaging time to achieve satisfaction. (2) *The loss of relationships* due to overuse of instant messaging (alpha = 0.77) reflected that addicted teenagers hide their time spent on online chatting; try to cut down their use but fail; choose to spend more time chatting online rather than going out with friends; and

jeopardize friendships or educational opportunities because of online chatting. (3) *The loss of control* (alpha = 0.73) illustrated that teenagers cannot control the time they spend on instant messaging. This shows that they always spend more time on instant messaging than they intend; they neglect other things they have to do because they are chatting online, and their relatives and friends complain about this. (4) *Escape* (alpha = 0.68) indicated that teenagers use instant messaging as an alternative way to escape from responsibilities; they chat online when they are in a dysphoric mood, and they always anticipate chatting online again. These four symptoms are consistent with most of the "substance dependence" symptoms proposed by the American Psychiatric Association, which include "withdrawal, tolerance, preoccupation with the substance, loss of control over the substance, more use of the substance than intended, continued consumption of the substance despite adverse consequences, and loss of interest in other social, occupational, and recreational activities" [1].

Among the four symptoms, "loss of control" was a significant factor to predict level of instant messaging use and was the most powerful variable to predict academic performance decrement. This indicates that teenage addicts were relatively young and less self-disciplined, and it was not easy for them to control the time spent on instant messaging when they used it to chat online and neglected their homework or daily life duties, thus resulting in academic performance decrement. The four addiction symptoms formed the most powerful group in hierarchical regression to predict teenagers' academic performance decrement; all four were significant predictors. This indicates that teenagers, who showed more severe symptoms in instant messaging addiction, were more likely to suffer from academic performance decrement. This result underscores the harmful effects of instant messaging addiction on teenagers' academic performance and suggests that if teenagers exhibit any of the above instant messaging addiction symptoms, teachers and parents should pay attention to their academic performance.

Effects of Shyness and Alienation on Instant Messaging Addiction and Academic Performance

The study in China also revealed that the shyer the teenager, the higher his or her level of instant messaging addiction. Teenagers who are more alienated from family, peers, and school are more likely to suffer from a higher level of instant messaging addiction. To differentiate between addicts and non-addicts, discriminant analysis found that the instant messaging addicts were heavy users of instant messaging and had more years of online experience; they tended to be shyer and more alienated from peers, school, and family. Teenagers who are heavy users of instant messaging and who suffer from higher level of instant messaging addiction are more likely to have academic performance decrement. These findings are consistent with and reinforce previous research that the higher the tendency for a person to be addicted to the Internet, the shyer the person is; people who are addicted to the Internet make intense and frequent use of it especially for online communication via ICQ [11].

Alienation also showed significant and positive correlations with level of instant messaging addiction and all three alienation dimensions were significant predictors to discriminate instant messaging addicts and non-addicts. That is, teenagers who were more alienated from family, peers, and school were more likely to become instant messaging addicts. Such a result indicates that teenagers who suffered alienation from family, peers, and school tended to seek care, friendship and social support through instant messaging.

Instant Messaging Use and Academic Performance Decrement

Both the level of instant messaging use and level of instant messaging addiction have

significant and positive bivariate correlations with academic performance decrement. This finding suggests that teenagers' instant messaging use did impact their academic performance. The more they used it, the more they would be dependent on instant messaging, and the more they might experience a decrease in academic performance. These findings were in agreement with Cheuk and Chan's study that using ICQ had an effect on adolescents' academic performance in Hong Kong [12]. Therefore, parents and teachers should pay close attention and provide proper guidance or mediation for teenagers' instant messaging use.

Demographics and Instant Messaging Use

Age was a significant negative predictor for level of instant messaging use and a significant positive predictor for level of addiction and academic performance decrement. These findings are interesting, and they suggest that the younger the teenagers, the less self-disciplined they were, and the more they would use instant messaging. At the same time, older teenagers were more mature and have more things to share with friends, such as relationships, affairs, gossips, and issues that are difficult to talk about face-to-face, so they might have been more addicted to instant messaging. This might, therefore, have had a negative impact on academic performance decrement. Older teenagers might have been more rebellious. Teachers and parents might have thought that they were grown-ups and had less control over them. As expected, these results suggest that teachers and parents should pay more attention to older teenagers as they may be most vulnerable to instant messaging addiction.

Gender was not a significant predictor of the level of instant messaging use and addiction. This indicates that gender difference in computer-mediated communication use is narrowing. Years of instant messaging use was significant in predicting level of instant messaging addiction, which indicates that those who have been using instant messaging for a longer time might find more advantages of instant messaging, and thus may become addicted more easily.

Conclusions

Teenagers today are immersed in interactive media. Their lives are dedicated to many of the emerging communication technologies—the Internet, interactive games, mobile phones, SMS, MP3, iPods, and conversing in instant messaging services such as MSN, QQ, ICQ, and Yahoo!Messenger. Many policymakers and critics have voiced fears about what these personal communication technologies are doing to teenagers, especially those consumed in their own privacy. This chapter examined the multidimensional addiction symptoms of instant messaging, together with shyness and alienation, to explore their relationships with instant messaging behavioral patterns. Furthermore, it also investigated the consequences of instant messaging use as related to academic performance among teenagers in a middle school in China. Instant messaging can have a positive, as well as negative, influence on social behaviors and intellectual development. The use of instant messaging is not necessarily an isolating event for young people. For many, it has become an important social activity. In their own space, they appropriate their private time to help them make sense of their lives. However, few parents know for sure what their children are doing with the Internet in their bedroom or private space—often because young people know more than their parents about the Internet. With whom are they chatting using instant messaging, and with what consequences? How can teenagers, along with parents, prevent excessive use and abuse? This research in China provides an additional perspective. In fact, knowing how instant messaging addiction affects academic performance among teenagers in these fundamental ways will help

parents, educators, technology designers, and policymakers to set priorities and effective decisions about mediating teenagers' use of instant messaging services.

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Hoarding as a Behavioral Addiction

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Contents

Overview

Compulsive hoarding is defined as the acquisition of—and inability to discard—possessions of limited value, to a degree that precludes appropriate use of living spaces and creates significant distress or impairment in functioning [23, 24]. Hoarding can interfere with an individual's ability to work, interact with others, and perform basic activities, such as eating or sleeping. In severe cases, it may lead to dangerous, even life-threatening living conditions. Hoarding also is associated with a profound public health burden. In a survey of local health departments, 64% of health officers reported receiving hoarding complaints, some of which resulted in a significant cost to the community [32]. More recently, a large Internet survey of self-identified hoarding participants ($N = 864$) and family members ($N = 655$) revealed that compulsive hoarding is related to poor physical health, social service involvement, and significant occupational impairment [89].

Hoarding has been linked to anxiety disorders, specifically obsessive-compulsive disorder, although its diagnostic status is plagued with controversy [95]. Consistent with prominent models of anxiety disorders [4], individuals who compulsively hoard frequently report feelings of anxiety when they are asked to discard or organize their possessions. They also may demonstrate avoidance and safety behaviors connected to their hoarding-related beliefs and fears [82]. There is, however, a pleasurable or gratifying component associated with acquiring, collecting, and saving possessions that distinguishes hoarding from other anxiety-related problems.

This appetitive aspect of hoarding suggests that there are similarities between hoarding and behavioral addictions, which include several impulse control disorders (pathological gambling, pyromania, and kleptomania).

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_34,

In behavioral addictions, individuals experience pleasurable or gratifying feelings while engaging in the target behavior, followed by a decrease in arousal and feelings of guilt and remorse [52]. An individual who compulsively collects items from yard sales and thrift stores may similarly feel a rush of positive emotion upon finding an item that she feels is unique or valuable, followed by feelings of regret when she reflects upon how much the clutter is overtaking her home and negatively impacting her life. While the anxiety-related aspects of hoarding have been the subject of several investigations [24], the appetitive nature of this syndrome has been relatively understudied. Although hoarding behavior is sometimes motivated by a desire to reduce anxiety, there are cases in which hoarding appears to be driven by anticipation of pleasure and impaired self-regulation [44]. There also may be cases in which both anxiety and approach behaviors play a role. From a clinical perspective, this underscores the importance of functional analysis in determining motivation for hoarding and, more specifically, acquisition behaviors.

Classification and Comorbidity

As previously noted, hoarding has been considered to be a dimension or subtype of obsessive-compulsive disorder in much of the recent research [82]. Findings of moderate frequencies of hoarding behavior in obsessive-compulsive disorder populations, ranging from 18 to 33%, support this association [29, 73]. Moreover, several studies have found that individuals who hoard report more obsessive-compulsive disorder symptoms than non-hoarding individuals [23, 29]. Frost and colleagues [31] compared individuals with obsessive-compulsive disorder who exhibited compulsive hoarding symptoms versus those who did not, and found that the two groups did not differ on the number of obsessive-compulsive disorder symptoms displayed, although they both reported more obsessive-compulsive disorder symptoms than did anxious and nonclinical control participants.

Despite this association, there is mounting evidence that hoarding is distinct from other obsessive-compulsive disorder symptom dimensions. Most factor analyses of obsessive-compulsive disorder symptoms have found that hoarding constitutes a separate factor from other obsessions and compulsions [10, 44, 58, 63, 73]. Furthermore, hoarding behavior has been reported in a variety of psychiatric disorders besides obsessive-compulsive disorder, including schizophrenia [62], organic mental disorders [43], eating disorders [22], brain injury [16], and dementia [18]. Finally, hoarding is typically a poor predictor of treatment outcome in both psychological and pharmacological treatments for obsessive-compulsive disorder [11], although several recent studies have not confirmed this association [2, 15, 77, 81]. In light of the conflicting evidence regarding the diagnostic status of hoarding, Wu and Watson [95] examined the relationship between obsessive-compulsive disorder and hoarding in two large samples. They found that hoarding correlated only modestly with other obsessive-compulsive disorder symptoms, which reliably correlated with each other. Further, hoarding was no more strongly associated with obsessive-compulsive disorder symptoms than other dimensions of psychopathology, such as depression.

It is significant that not all individuals who hoard have comorbid symptoms reflective of typical obsessive-compulsive disorder [44]. In addition, hoarding beliefs and behaviors do not always fit the obsessive-compulsive disorder model. Steketee and Frost [82] noted that hoarding thoughts may not always impel the associated compulsive behaviors, may not be as intrusive as typical obsessions, and are not always viewed as ego-dystonic by the individual. Additionally, many hoarders lack insight into the severity of the consequences of their behaviors and experience attenuated levels of distress compared with obsessive-compulsive disorder clients [82]. The ego-syntonic nature of hoarding is similar to that observed in some addictive and impulse control disorders.

Hoarding and Impulse Control Disorders

Most relevant to the current chapter is the association between hoarding and the spectrum of impulse control disorders. Impulse control disorders are positively reinforcing to the individual and are associated with a wide variety of emotional states, including pleasure or gratification. They are characterized by repetitive behaviors and impaired inhibition of these behaviors and include pathological gambling, skin picking, and trichotillomania. Researchers have suggested that impulse control disorders may best be conceptualized as part of an obsessive compulsive spectrum [51, 65] as the urges and subsequent behavioral responses observed in impulse control disorders appear, at least superficially, similar to the excessive rituals observed in obsessive-compulsive disorder [8]. Problems removing unwanted thoughts and deficits in decision making may also represent commonalities between obsessive-compulsive disorder and impulse control disorders.

A key difference between impulse control disorders and obsessive-compulsive disorder, however, is that an individual with an impulse control disorder experiences feelings of pleasure and gratification while engaging in the target behavior, in contrast to the anxiety experienced when individuals with obsessive-compulsive disorder engage in a compulsion [39]. For example, the repetitive and often harmful rituals performed in obsessive-compulsive disorder may appear similar to the wagering behaviors of compulsive gamblers. When significant monetary losses fuel chasing behavior, a compulsive gambler may feel compelled to gamble to avoid negative consequences in much the same way that rituals in obsessive-compulsive disorder are performed in an effort to alleviate negative emotional states such as anxiety, shame, and guilt [87]. However, gambling behaviors are clearly pleasurable and reinforcing [40]. Individuals who hoard also derive a sense of pleasure and gratification from their acquisition behaviors, which may suggest that hoarding fits better among the impulse control disorders than its common conceptualization as a subtype of obsessive-compulsive disorder.

Compulsive hoarding has been linked to impulse control disorders in a variety of studies, suggesting the possibility of a common diathesis underlying both hoarding and certain impulse control disorders. Samuels et al. [73] reported a greater frequency of trichotillomania and skin picking among hoarding compared with non-hoarding individuals with obsessive-compulsive disorder. In addition, Frost et al. [33] found that pathological gamblers reported significantly more hoarding symptoms than light gamblers and speculated that both hoarders and gamblers may share similar concerns about the loss of potential opportunities. Compulsive hoarders believe that items may be needed for some future use and, therefore, fear discarding items as this would represent a lost opportunity for the item's use [33], with some research suggesting that even the sight of a possession can trigger this fear [26]. Frost and colleagues [33] have suggested that pathological gamblers may have difficulty refraining from purchasing chances because of similar beliefs and fears about losing an opportunity to gain financial benefit. Although Grant et al. [41] found a low prevalence of impulse control disorders overall among individuals with obsessive-compulsive disorder, obsessive-compulsive disorder participants with a lifetime and current impulse control disorder were more likely to report hoarding symptoms. In addition, some research suggests that beliefs about possession and about buying are similar to the beliefs of those with compulsive hoarding [55]. The association between hoarding and impulse control disorders is consistent with McElroy and colleagues' conceptualization of a compulsive-impulsive spectrum [66] but requires further exploration.

Hoarding and Compulsive Acquisition

Compulsive acquisition is a central component of compulsive hoarding [23, 24] that is of particular significance when considering hoarding as

a behavioral addiction. The compulsive acquisition component of hoarding consists, in part, of compulsive buying, which is classified as an impulse control disorder [66]. Compulsive buying has been defined as chronic, repetitive purchasing behavior in response to negative events and or/feelings that is difficult to stop and results in harmful consequences [17]. Similar to other impulse control disorders, compulsive buying is associated with a pattern of tension, pleasure, and subsequent feelings of guilt and remorse [12].

A high level of compulsive buying has been found among individuals who hoard [30], and, conversely, a high level of hoarding symptoms have been found in compulsive buyers [34]. A study comparing compulsive buyers with non-compulsive buyers found that compulsive buyers scored higher on both obsessive-compulsive disorder and hoarding symptoms, but the relationship between buying and obsessive-compulsive disorder was mainly mediated by hoarding [34]. Interestingly, this study found that while not all compulsive buyers suffer from compulsive hoarding, nearly all hoarding participants suffer from compulsive acquisition. Compulsive acquisition in hoarders, however, is not limited to buying, but includes collecting free things that are being given away or have been discarded by others. However, Frost et al. [30] found that these behaviors were related; a measure of compulsive buying behavior was associated with a compulsive acquisition of free items.

The relationship between compulsive hoarding and buying may be accounted for by shared cognitive deficits and biases. Both hoarding and compulsive buying appear to be closely related to impaired mental control [30] and fears about decision making [55]. Additionally, evidence suggests that similar cognitive biases about the meaning of possessions exist in both hoarders and compulsive buyers [56]. Although O'Guinn and Faber [68] suggested that compulsive buyers may derive more emotional pleasure from the process of acquiring items, in contrast to hoarders, who retain a sense of satisfaction from items even once ownership has been established, Kyrios et al. [56] found that compulsive buyers did hold beliefs about possession similar to those reported by hoarding participants. These beliefs included fears over lost opportunities to obtain objects, erroneous beliefs about the inherent value of possessions, and beliefs about personal responsibility for objects [55]. Research on compulsive hoarding has suggested that the sight of a possession activates the fear of losing an opportunity [26]. Collectively, these findings suggest a diagnostic overlap between compulsive hoarding, obsessive-compulsive disorder, and impulse control disorders. Steketee and Frost [82], however, in a review of these findings, concluded that limitations such as selection of appropriately defined samples, methodological concerns, the absence of formal diagnostic interviews, and inadequate measurement of hoarding constrain conclusions about whether hoarding is best conceptualized as a sub-syndrome of obsessive-compulsive disorder, as an impulse control disorder, or as a separate clinical construct.

Etiology/Biobehavioral Underpinnings of Hoarding

In the last 5 years, much new evidence has emerged regarding the biological/neural underpinnings of compulsive hoarding. Several case reports have described cases of pathological collecting and saving that began after a brain injury, typically along with other changes in personality and social functioning [16, 46]. These cases suggest that hoarding may be related to frontal lobe dysfunction. Other evidence for the biological correlates of hoarding has come from two sources: neuroimaging studies and genetic research.

Neuroimaging Research

Several recent studies have investigated a possible neural basis of compulsive hoarding. Anderson et al. [3] conducted a study in which

13 of 86 individuals with focal lesions exhibited abnormal collecting behavior. All 13 of these individuals had damage to the mesial frontal region of the brain, including the anterior cingulate region. Further, in the first study using positron emission tomography to examine compulsive hoarding, Saxena et al. [76] found that compared with non-hoarders who had obsessive-compulsive disorder, individuals with both compulsive hoarding and obsessive-compulsive disorder had significantly lower glucose metabolism in the anterior and posterior regions of the cingulate gyrus. The authors posited that lower activity in these regions may mediate the deficits in motivation, attention, memory, and decision making that are associated with compulsive hoarding. Underactivity in these regions also has been observed in cocaine addicts and alcoholics regardless of whether they were continued users or had abstained for a lengthy period [90–92].

Finally, Mataix-Cols et al. [64] conducted a functional magnetic resonance imaging study in which individuals with obsessive-compulsive disorder were presented with pictures containing various types of obsessive-compulsive disorder-related stimuli, including hoarding-related images (old newspapers, clothes, etc.). Participants were told to imagine that the items belonged to them and that they would have to discard them later. During this provocation, participants demonstrated greater activation than controls in the left precentral/superior frontal gyrus, left fusiform gyrus, and right orbitofrontal cortex. Collectively, results of these studies provide evidence that the hoarding symptom dimension may reflect the dysregulation of a specific neural system.

Genetic Research

Findings of several recent genetic studies also support the notion that hoarding represents a unique symptom subtype in obsessive-compulsive disorder with a distinctive psychobiological profile. Lochner et al. [59] genotyped individuals with obsessive-compulsive disorder and control participants of Afrikaner descent to investigate certain polymorphisms in genes hypothesized to be relevant to obsessive-compulsive disorder. They reported that there may be a relationship between variation in the Catechol-*O*-methyltransferase gene and compulsive hoarding. (Catechol-*O*-methyltransferase is an enzyme involved in the degradation of dopamine, a neurotransmitter with increased activity in obsessive-compulsive disorder.) In another genetic study, Samuels et al. [74] treated compulsive hoarding as the phenotype of interest and stratified families with obsessive-compulsive disorder into those with and without two or more relatives affected with compulsive hoarding. Results of the study suggested that a region on chromosome 14 was linked with compulsive hoarding behavior in families with obsessive-compulsive disorder. Finally, Zhang et al. [96] conducted a genome scan of the hoarding phenotype on 77 sibling pairs who were concordant for a diagnosis of Gilles de la Tourette syndrome. Results of this study suggested joint effects for the hoarding phenotype of specific loci on 5q and 4q. While the findings of these studies have not been conclusive, collectively they highlight possible regions of interest with respect to genetic correlates of compulsive hoarding.

Cognitive-Behavioral Theory and Evidence

Current cognitive-behavioral conceptualizations [24, 26] specify a multidimensional model to explain the core manifestations of compulsive hoarding. Hoarding is posited to develop as a result of conditioned emotional responses associated with certain thoughts and beliefs concerning items or possessions. Acquisition and failure to discard possessions represent avoidance of the anxiety associated with discarding and decision making. In addition, similar to other behavioral addictions, excessive saving behavior

is positively reinforced because the possessions attain a pleasurable or comforting quality. The prominent model of compulsive hoarding proposed by Frost and Steketee [26] consists of four main components: information-processing deficits, beliefs about and emotional attachments to possessions, and emotional distress and avoidance behaviors that develop as a result.

Information-Processing Deficits

The cognitive-behavioral model of hoarding suggests that individuals who hoard may possess information-processing deficits that result in confusion or misinterpretation about the value of possessions and difficulty organizing and discarding. Several neuropsychological studies of compulsive hoarding support the notion that there are cognitive deficits associated with this syndrome.

Grisham et al. [45] compared a compulsive hoarding group with a mixed clinical group and a community control group on a number of measures for attention, working memory, and verbal and nonverbal intelligence. They found that those in the hoarding group had intact verbal intelligence and working memory but were impaired on measures of attention and nonverbal intelligence. They also were slow to initiate responses and had difficulty inhibiting impulsive responses. Similarly, Hartl and colleagues [50] found that hoarding adults displayed symptoms consistent with attention-deficit/hyperactivity disorder on a self-report measure. Weaknesses in these neuropsychological domains of attention and nonverbal intelligence may, therefore, limit hoarders' ability to sustain attention during a task (e.g., when deciding what possessions to save or discard) and to organize their possessions and reduce clutter. Other studies have found evidence for indecisiveness [25] and deficits in verbal and nonverbal memory [49].

Hoarding behavior also appears to be associated with specific deficits in organizing and categorizing common objects [61, 93]. Wincze et al. [93] compared the performance of hoarders with the performances of non-hoarders who had obsessive-compulsive disorder and control participants on a sorting task. They found that participants in the hoarding group were under-inclusive (i.e., they sorted the objects into a larger number of categories) compared with control participants. They also took a longer time than the controls to decide in what category the objects belonged, and they reported more distress during the sorting task. This was only true, however, when they were sorting personally relevant objects. These results suggest that the information-processing deficits due to an under-inclusive categorization style are not global but are specific to relevant objects. Wincze at al. [93] suggested that hoarders' difficulty categorizing objects may be due to the meaning attached to objects, which influences what features of the object are attended to during a sorting task. Luchian et al. [61] replicated this study with nonclinical hoarding and control participants and found similar results.

There are some inconsistencies in the research on hoarding and associated neuropsychological deficits. While Grisham et al. [45] found that hoarders displayed relatively intact decision making on a gambling task, Lawrence and colleagues [57] found that hoarding symptoms were associated with specific decision-making impairments on the same gambling task, in addition to poor set shifting on a sorting task. Lawrence et al. [57] suggested that hoarders have difficulty deciding whether to save or discard a possession due to these difficulties in decision making. Additionally, the risky behaviors exhibited by hoarding participants suggest that problems with impulse control may contribute to difficulties in decision making. Grisham et al. [45] did observe greater impulsivity in the hoarding group on measures of attention. The discrepancies between these studies are likely due to differences in the samples selected. In the Grisham et al. [45] study, the hoarding group consisted of participants who met the criteria for compulsive hoarding, regardless of whether they had obsessive-compulsive disorder, while the hoarding group in Lawrence et al. [57] comprised

individuals with obsessive-compulsive disorder who also displayed hoarding behaviors.

The recent findings on specific neuropsychological characteristics associated with hoarding may elucidate the relationship between hoarding and addictions. Addictive disorders are characterized by repeated behaviors that are pleasurable to perform. Hoarding may similarly be associated with a pleasurable state upon acquisition of new items, but hoarding behaviors are also viewed as an attempt to avoid the emotional distress associated with discarding [24]. Although the motivations behind the behaviors (pleasure seeking vs. distress avoiding) may vary, there is a degree of overlap that may be accounted for by similar neuropsychological deficits. Lubman et al. [60] argued that problematic drug use is associated with decreased inhibitory control, thus compromising decision-making ability. The poor inhibition and decision making are also evident in compulsive hoarding [45]. The deficits observed in hoarding participants on the gambling task [57] have also been found with drug-addicted individuals. Furthermore, these individuals show behavioral responses similar to the hoarders observed by Lawrence et al. [57] and individuals with lesions to the orbitofrontal cortex [5], the same region implicated in positron emission tomographic studies of hoarders. Drug-addicted individuals also show deficits in response inhibition [37] similar to those observed by Grisham et al. [45] with compulsive hoarding participants.

Emotional Attachment to Possessions

Maladaptive beliefs and excessive emotional attachment to possessions are also posited to play a central role in the maintenance of compulsive hoarding [26, 86]. The beliefs and cognitions associated with excessive saving range from exaggerations of common beliefs, e.g., "I need these sentimental possessions to remind me of important events in my life" to more idiosyncratic reasons for saving, e.g., "These used Band-Aids® are a part of me because they contain my blood." The individual's unrealistic beliefs about possessions are associated with excessive emotional attachment to objects, which leads to delaying or avoiding the process of making decisions and discarding [23]. Research suggests that these beliefs cluster into four basic types: emotional attachment to possessions, memory-related concerns, responsibility for possessions, and control over possessions [86].

Excessive attachment to possessions can lead to a sense of grief and loss when individuals with compulsive hoarding are forced to discard items [13]. These reactions can even be comparable to the grief experienced due to the death of a loved one [24], a finding that accords with a tendency for hoarders to imbue their possessions with human qualities, thereby anthropomorphizing them [42]. As these reactions can inevitably provoke anxiety, avoidance of discarding is negatively reinforced because it prevents the experience of these emotions. Anxiety can also arise when others attempt to arrange or utilize a hoarder's possessions. Control over possessions appears to be partly related to a heightened sense of responsibility for keeping objects intact and to a sense of personal responsibility for being prepared in the event that an object is required at some point in the future [28].

Assessment of Compulsive Hoarding

Despite growing interest and research in the area, there is still a paucity of measures specifically designed to assess compulsive hoarding. Several measures of obsessive-compulsive disorder include hoarding subscales, such as the Yale-Brown Obsessive Compulsive Scale [38], the Obsessive Compulsive Inventory [20], and the Obsessive Compulsive Inventory-Revised [21]. Many studies of hoarding have used the two Yale-Brown Obsessive Compulsive Scale items assessing hoarding obsessions and compulsions. Some researchers have raised concerns about using these items [82] due to questions about

the definition of a hoarding obsession and the inability of these two items to assess many crucial aspects of hoarding behavior. One recent study of hoarding [70] used the Dimensional version of the Yale-Brown Obsessive Compulsive Scale [71]. This version was designed to assess obsessive-compulsive disorder dimensions (contamination, cleaning, harm, hoarding, symmetry, sexual/religious, and miscellaneous obsessions and compulsions). The Dimensional version of the Yale-Brown Obsessive Compulsive Scale includes a series of clinician-administered scales that can be used to assess the presence and severity of each symptom dimension.

The Obsessive Compulsive Inventory and Obsessive Compulsive Inventory-Revised include several symptom subscales including Washing, Checking/Doubting, Obsessing, Mental Neutralizing, Ordering, and Hoarding. Both measures are somewhat better than the Yale-Brown Obsessive Compulsive Scale at assessing hoarding; however, the Hoarding subscales of both the original Obsessive Compulsive Inventory and the revised inventory are still problematic. This subscale failed to distinguish clinical from non-anxious controls adequately in the original Obsessive Compulsive Inventory [20], and the revised inventory has demonstrated weak internal consistency [47]. Additionally, Abramowitz and Deacon [1] found that the Obsessive Compulsive Inventory-Revised hoarding subscale correlated only weakly with the other Obsessive Compulsive Inventory-Revised subscales and did not correlate with the Yale-Brown Obsessive Compulsive Scale in a clinical sample of anxious participants. These findings raise concerns about the appropriateness of utilizing obsessive-compulsive disorder measures to index hoarding thoughts and behaviors.

The first systematic attempt to design a scale solely to measure hoarding symptoms was the Hoarding Scale [23], a 22-item self-report questionnaire that assessed discarding behaviors, emotional reactions to discarding, problems with decisions regarding discarding, concerns over future use of discarded items, and sentimental attachment to possessions. The Hoarding Scale was found to be both reliable and valid in college, clinical, and community samples. In addition, it was able to discriminate between individuals who reported experiencing hoarding tendencies and community controls [23]. Although it possessed sound psychometric properties, the Hoarding Scale had inherent limitations as subsequently identified by the primary author [35]. Given the limited information about hoarding behaviors at the time of its development, the Hoarding Scale did not assess all of the components that are now known to be important facets of hoarding, such as excessive acquisition. The scale also confounded beliefs about possessions with behavioral symptoms and included items about specific types of possessions that were not applicable to every individual with hoarding tendencies [35]. In addition, the Hoarding Scale did not adequately assess distress or impairment at the clinical/severe level [82].

The recognition of the Hoarding Scale's limitations led to the development of a revised measure to address these concerns, the Saving Inventory-Revised [35]—a 23-item self-report questionnaire with three subscales assessing: (1) excessive acquisition of purchased and free items, (2) saving and discarding behaviors, and (3) excessive clutter as a result of these behaviors. The Saving Inventory-Revised has been shown to discriminate between identified hoarders and both non-hoarding controls and non-hoarding obsessive-compulsive disorder cases [35]. The subscales have been shown to correlate with additional indices of hoarding interference, such as activity dysfunction and both self- and observer ratings of clutter in the home [13, 35, 88].

There are several other self-report measures of hoarding. One commonly used measure, the Saving Cognitions Inventory [86], is a 24-item self-report inventory that assesses beliefs and attitudes experienced when trying to discard possessions. Participants rate the extent to which a thought influences their decision about whether to discard a possession on a 7-point Likert scale. The four subscales assess emotional attachment to objects, beliefs about objects as memory aids, responsibility for not wasting possessions, and

the need for control over possessions, respectively. In addition, a few studies have employed the Yale-Brown Obsessive Compulsive Scale: Acquisition and Saving Version [84], a 10-item self-report measure that is modeled on the Yale-Brown Obsessive Compulsive Scale. The Acquisition and Saving Version indexes the severity of hoarding thoughts and behaviors and the subsequent interference and avoidance. Questions address time spent, distress, interference, and effort and success in resisting thoughts and hoarding behaviors. Finally, the Activities of Daily Living-Hoarding Subscale [83] is a 16-item inventory designed to assess interference in daily activities such as bathing, dressing, and preparing and cooking food due to clutter within the home. Items also assess general conditions within the home such as the presence of rotten food and associated safety/health issues (fire hazard, unsanitary conditions). The Activities of Daily Living-Hoarding Subscale is particularly useful when completed by two raters (e.g., by the hoarder and family member or clinician) as discrepancies between the two ratings can be indicative of poor insight.

Poor insight poses a problem for the assessment of hoarding when using measures that rely on self-disclosure of beliefs and behaviors. As noted previously, individuals with compulsive hoarding demonstrate limited recognition of the problem [11, 14, 19, 42, 80], with as many as 50% failing to recognize their behaviors as being problematic [31, 85]. The validity of self-report inventories may, therefore, be compromised. In an effort to address this concern, Frost et al. [36] developed a pictorial measure to index the extent of clutter within the home. The Clutter Image Rating [36] includes nine pictures that vary in rating from 1 (no clutter) to 9 (severe clutter) for a kitchen, a living room, and a bedroom, with a mean composite score calculated across the three rooms (range 1–9). Respondents select the picture that most closely matches each room to provide a rating of the amount of clutter associated with that room.

In addition to the measures described here, many studies have also used their own clinician-administered interviews to assess the presence and severity of hoarding (cf. [45, 77, 79]). The lack of uniformity across studies underscores the need for the development of a standardized structured interview to aid in future investigations of the parameters associated with compulsive hoarding, particularly one that can be used as a treatment outcome index.

Treatment of Compulsive Hoarding

The presence of hoarding symptoms is often a negative predictor of treatment outcome for current treatments that are effective in treating obsessive-compulsive disorder [11]. This is true for both pharmacological and psychological treatments [7]. It has been suggested that this is because those with hoarding problems often refuse treatment and/or are less motivated to engage due to poor insight. It is usually a family member or spouse that pressures the hoarder to seek treatment. Kozak and Foa [54] suggested that traditional treatments for obsessive-compulsive disorder may be less effective because hoarders often display perfectionistic thinking and magical ideas that interfere with the treatment components.

Biological Treatments

Most biological treatments have examined the effect of serotonergic medications on symptoms of compulsive hoarding. In a study by Mataix-Cols et al. [63], 150 individuals with obsessive-compulsive disorder were treated with serotonergic reuptake inhibitors across six placebo-controlled medication trials. The authors examined whether different factor structures on the Yale-Brown Obsessive Compulsive Scale checklist predicted treatment response after controlling for baseline severity of symptoms. Only the hoarding dimension of the Yale-Brown Obsessive Compulsive Scale was associated with poorer outcomes on obsessive-compulsive disorder symptom

measures, suggesting that hoarding symptoms predict poor treatment outcome.

Winsberg et al. [94] investigated treatment outcome following treatment with serotonergic reuptake inhibitors in a sample of 20 compulsive hoarders. Of the 18 participants who received an adequate trial, half showed an improvement by at least 25% on the Yale-Brown Obsessive Compulsive Scale, with one showing a marked response. It is unclear, however, whether these changes occurred in hoarding symptoms. All participants in the trials had other obsessive-compulsive disorder symptoms, and the improvement in Yale-Brown Obsessive Compulsive Scale scores may have been due to changes in these symptoms. The nine individuals in the study who received cognitive behavioral therapy intervention for hoarding based on the treatment outline provided by Hartl and Frost [48] appeared to show somewhat greater improvements than those treated with medication alone. In another treatment study by Black et al. [7], medication and cognitive behavioral treatments were compared with placebo. In a sample of 38 non-depressed individuals with obsessive-compulsive disorder, approximately 18% of those who reported hoarding symptoms responded to treatment, compared with 40% of treatment responders in the non-hoarding group. These results are in accord with the suggestion that hoarding symptoms negatively predict treatment response.

Nevertheless, there is some promise for biological treatments for hoarding as recent studies [15, 77] have found that hoarders do respond, at least to some degree, to medication. Saxena et al. [77] found that hoarders with obsessive-compulsive disorder responded as well to the serotonergic reuptake inhibitor medication paroxetine as did those with obsessive-compulsive disorder but no hoarding symptoms, although the treatment response of both groups was not optimal. Other studies have found that early onset, poor insight, somatic obsessions [15], sexual obsessions [2], and comorbidity [81] are predictors of poor treatment response to medications and not hoarding symptoms. One of these studies [15], however, did find a statistical trend suggesting that hoarding may have been a negative predictor of treatment response.

Psychological Treatments

Current cognitive-behavioral techniques have had some success for the treatment of compulsive hoarding (e.g., [84]). This treatment approach is largely based on the model of compulsive hoarding described by Frost and Hartl [24]. The treatment usually comprises a group program with additional individual sessions that involve therapists visiting clients' homes to complete exposure and discarding exercises. Treatment usually lasts from 6 months to a year.

Cognitive behavioral therapy for hoarding covers five general themes: education about hoarding, improving decision-making capacity, development of an organizational system for possession, graded exposure to avoidance behaviors, and cognitive restructuring around beliefs about possessions [27]. The exposure sessions are conducted both during sessions, with clients bringing in a selection of possessions, and within the home. Clients are expected to practice making decisions about the category to which possessions belong (i.e., discard, save, or retain for sorting later) and to follow through with these decisions. This exposes them to the emotional distress of discarding and challenges fears about making a mistake, missing information, and being responsible for discarded items. Therapists never touch clients' possessions without permission so that the client is entirely responsible for the decision-making process. Clients are taught to challenge their beliefs about the emotional significance of their possessions, the cost of making a mistake, the need for perfectionism, and the importance of remembering/having access to information. They are also required to create an organizational system and to categorize possessions that they decide to save based on this system in order to reduce clutter.

There is some evidence indicating that treatments based on the cognitive-behavioral model are effective for compulsive hoarding. Hartl and

Frost [48] conducted a multiple baseline experimental case study involving an individual with a long-standing hoarding problem. Therapy consisted of the strategies outlined above delivered in weekly 2-h sessions combined with regular homework tasks. After 9 months, there was a reduction in hoarding symptoms, indecisiveness, and non-hoarding obsessive-compulsive disorder symptoms. After 18 months, the targeted living spaces were almost completely free of clutter. Steketee et al. [84] conducted a larger-scale study for seven individuals over 20 weeks. Six of them attended group therapy and had individual home visits, while the seventh received individual home visits using a similar individual treatment applied by Hartl and Frost [48]. Scores on the Yale-Brown Obsessive Compulsive Scale showed some improvement after 15 sessions of treatment. Self-report ratings also improved on recognition of irrational reasons for saving, organization, and decision making, although clutter was slow to improve. Scores on the Yale-Brown Obsessive Compulsive Scale and self-report measures improved further for participants who continued fortnightly treatment for a year.

Saxena et al. [75] reported similar improvement in a group of 20 compulsive hoarders with obsessive-compulsive disorder. A large group of individuals with non-hoarding obsessive-compulsive disorder symptoms also received treatment. This included 6-week daily multimodal therapy involving cognitive behavioral therapy, selective serotonin reuptake inhibitor medications, and psychosocial rehabilitation. Scores on the Yale-Brown Obsessive Compulsive Scale following treatment showed improvement for both the hoarding and non-hoarding groups, although the improvement was less marked for the hoarding group. Importantly, improvements in mood and psychosocial functioning were similar for both groups.

Overall, research findings indicate that compulsive hoarders do respond to cognitive behavioral therapy, although improvements are moderate in comparison with gains observed in non-hoarders with obsessive-compulsive disorder. There are a number of methodological limitations, however, that temper these findings. First, there is a lack of properly controlled treatment studies that involve allocation to treatment (cognitive behavioral therapy or medication) and a placebo group. Also, the lack of specificity of the measures used to index symptoms makes it difficult to determine whether improvements are due to changes in hoarding symptoms or other non-hoarding obsessive-compulsive disorder symptoms. Reliable measures of symptoms specific to hoarding need to be used to determine whether treatment is actually targeting hoarding.

Compulsive hoarders may be responding relatively poorly to treatment due to a lack of insight and motivation to engage in treatment [24]. It may, therefore be advantageous to incorporate a motivational interviewing component into treatment to increase individuals' insight into their hoarding problems. Tolin et al. [88] reported that homework adherence was a positive predictor of treatment outcome, highlighting the importance of insight and motivation to overcome hoarding problems. Motivational interviewing [67] is often used in the treatment of addictions to resolve ambivalence about change and to help individuals identify the discrepancy between their current behavior and their goals for the future. A meta-analysis of randomized controlled trials examining the efficacy of motivational interviewing [9] found that this technique alone was as effective as other active treatments for problems involving drugs and alcohol, diet, and exercise. Tolin et al. [88] suggested that a motivational interviewing component could be integrated into treatment for compulsive hoarders when motivation wanes.

Future Directions in Hoarding Treatment Research

In a large survey, Kessler et al. [53] found that adult attention-deficit/hyperactivity disorder was highly comorbid with other mental disorders and substance use problems. They suggested

that treating attention-deficit/hyperactivity disorder successfully may have an impact on the development of other comorbid disorders. Indeed, there is evidence that adult attention-deficit/hyperactivity disorder is a risk factor for substance use disorders [6]. Among other neuropsychological deficits, individuals with hoarding display a deficit in sustaining attention. Hartl et al. [50] found that hoarding participants displayed symptoms consistent with attention-deficit/ hyperactivity disorder in adults on a self-report measure. Weaknesses in attention may limit hoarders' ability to sustain attention during a task (e.g., when deciding what possessions to save or discard), organize their possessions, and reduce clutter.

Treatment for attention-deficit/hyperactivity disorder is usually stimulant medication [69]. Cognitive behavioral treatment for attention-deficit/hyperactivity disorder may augment stimulant medication and improve engagement with specific treatment strategies and homework tasks involving decision making, categorization, and discarding [78]. Psychological treatments for attention-deficit/hyperactivity disorder involve direct education and the implementation of compensatory strategies and some cognitive restructuring for unhelpful beliefs about coping with stress. The compensatory strategies may include better planning and organization, removal of distractions, memory aids, and breaking up complex tasks into simpler, manageable chunks [72]. Treatment for compulsive hoarders with symptoms of adult attention-deficit/hyperactivity disorder may thus incorporate such strategies and modify delivery of treatment.

Conclusions

In summary, it is useful to view hoarding from an addictions perspective in order to gain new insight into this complex phenomenon. First, this framework encourages us to shift our focus to the positively reinforcing aspects of hoarding behavior, rather than focusing solely on its anxiety-related features. Second, comparing hoarding with other types of behavioral addictions may shed light on some of the underlying neural mechanisms of hoarding, as well some of the cognitive and self-regulation deficits that may be associated with this disorder. Third, some of the challenges encountered in the treatment of hoarding, such as lack of insight or motivation, are common in substance abuse and behavioral addictions. We may be able to turn to this empirical literature for specific clinical strategies, such as motivational interviewing, that have been efficacious in treating addictive disorders.

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Part VI
Treatment and Application: Behavioral Treatments

Motivational Interviewing: Emerging Theory, Research, and Practice

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Contents

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What Is Motivational Interviewing?

Motivational Interviewing is a counseling approach used to explore and resolve ambivalence about behavior change. There is a strong evidence base that it reduces substance use problems and a growing evidence base for other problems. It has been defined as "a client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence" [25]. The directive aspect of the approach refers to the therapist's intentional pursuit of the resolution of ambivalence and initiation of positive change as central goals. The client-centered aspect of the approach refers to the consistent focus on the client's concerns, perceptions, hopes, and goals rather than those of the therapist. It also refers to Motivational Interviewing's reliance on client-centered techniques such as reflective listening and client-centered attitudes such as unconditional positive regard and accurate empathy. Thus, while focusing on and eliciting the client's perceptions, the Motivational Interviewing therapist explores areas of unresolved ambivalence and guides the client to resolve them to improve the client's life.

Motivational Interviewing was first described as a way to work with people having problems with drinking [19]. People with substance use problems and disorders often have mixed feelings and thoughts about their drug and alcohol use. While they may perceive some negative consequences of drinking or using, they also enjoy positive experiences such as intoxication,

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_35,

disinhibition, socialization, and pleasure. They may remain in a conflicted or ambivalent state about changing unless their perception shifts about the balance of these costs and benefits. Understanding and resolving this ambivalence is a central goal of Motivational Interviewing, and is accomplished through elicitation rather than persuasion. Therapists elicit the client's ideas and feelings about the current behavior, how the behavior fits in with hopes and values, and whether there might be more optimal choices from the client's perspective [43]. The therapist elicits the client's own reasons and rationale for possible change, referred to in Motivational Interviewing research as "change talk." In essence, Motivational Interviewing is focused more on the *whether* and *why* to change than on the *how*.

The counseling style used in Motivational Interviewing is "quiet and eliciting" and the "therapeutic relationship is more like a partnership. . .than expert/recipient roles" [36]. The spirit of Motivational Interviewing may be more important than techniques per se. The Motivational Interviewing spirit is one of collaboration between two experts, one with intimate knowledge of the self (the client) and one with skill in managing a constructive conversation about change (the therapist). The spirit of Motivational Interviewing is based on a respect and admiration for the client's autonomy, which is manifested as direct and indirect support for the client's ability and authority to make choices, consider options, and take actions. Finally, the spirit of Motivational Interviewing is evocative. Therapists ask questions and reflect the client's perceptions in such a way that a new understanding or commitment is evoked through the conversation. The therapist elicits the client's perspective on defining which behaviors might be problems, explores the client's own concerns, and elicits from the client intention to change or optimism about change.

Although the therapist has a goal of facilitating the exploration and resolution of ambivalence, the therapist is not attached to any particular outcome. By remaining focused on the client's concerns and ideas about change, therapists can assess the client's current readiness to change, and tailor the strategies they use. A growth metaphor has been used to describe readiness for change [41]. For a client not ready to make a change, the Motivational Interviewing therapist prepares the ground for planting by exploring the client's own perspectives, values, and hopes for the future. When a client is unsure about making a change, the Motivational Interviewing therapist plants seeds but understands that the soil has not been watered, maintaining a neutral but helpful stance. When a client is ready to make changes, the Motivational Interviewing therapist witnesses the plant breaking through the soil and reflects these observations. When the client is actively making changes, the Motivational Interviewing therapist understands that the plant may soon be ready for harvesting and provides support as needed.

The relational stance in Motivational Interviewing is one of respect and collaboration. Motivational Interviewing therapists believe that clients have expertise on themselves that can be used to make healthy changes. Using this approach, therapists elicit more information than they provide. The client may do more of the talking, explaining, exploring, and considering. Complementing the client's effort, the therapist offers reflections, questions, and summaries, while affirming the client's work. Therapists using the Motivational Interviewing approach tend to ask rather than tell, and to listen rather than advise. Motivational Interviewing therapists show curiosity rather than content expertise, even when they have substantial expertise in the area of the client's concern. It is more important that the Motivational Interviewing therapist develops an understanding of the client instead of providing information, education, or persuasion, all of which may provoke resistance or reluctance. This style can be seen as guiding rather than using a directing style, in which a therapist directs a client to absorb information, take advice, or follow instructions. Additionally, the eliciting, guiding, collaborative style in Motivational Interviewing tracks the client's experiences and perceptions, but differs from following in that the therapist maintains a

deliberate focus on the goal of exploring and resolving ambivalence.

Motivational Interviewing practice builds upon this collaborative relationship with a basic communication style that is used throughout consultation or counseling sessions. The style is summarized with the acronym OARS—*O*pen questions that encourage further elaboration and consideration, *A*ffirmations that foster positive feelings in the consultation, *R*eflections that indicate that the therapist has heard and accurately understood the client, and *S*ummaries that extend the basic reflections to include a sense of momentum or build interest in changing direction. These techniques are used to build rapport and gain understanding of a client's issues, to mend rifts in the treatment relationship, to redirect clients to more useful areas of consideration, and to solidify commitment to change in an established relationship where therapeutic alliance is strongly present.

In addition to the emphasis on using OARS as a basic communication style, the Motivational Interviewing therapist uses broader strategies that are consistent with the four principles of Motivational Interviewing. The four principles are Expressing Empathy, Developing Discrepancy, Rolling with Resistance, and Supporting Self-Efficacy [25]. Expressing Empathy is a principle that guides the therapist to seek understanding of the client, and to make comments that convey the accuracy and depth of this understanding. Developing Discrepancy is a principle that reminds the therapist that change is not typically sought or made until a person is at least somewhat uncomfortable with the status quo, or can envision a better, brighter opportunity sufficient to overcome the entropy of the familiar. Rolling with Resistance is a principle that reminds the therapist to avoid arguing for change when the client argues in favor of the status quo, and to acknowledge then sidestep resistance rather than identifying it as a problem, making it the focus of therapy, or confronting it in any way. Supporting Self-Efficacy is a principle that reminds the therapist to elicit client confidence about accomplishing tasks involved in making major lifestyle change. These principles lead naturally to specific strategies that are often used in Motivational Interviewing to achieve therapeutic gains.

Common Motivational Interviewing strategies and some *examples* of how the therapist might begin to use them include:

1. *Agenda setting*. How would you like to spend our time together today? Or Which of these issues would you like to discuss first? Or What's your top priority right now?
2. *Negotiation of focus*. Given your diagnosis with asthma and your doctor's advice to quit smoking, there may be a number of concerns you have. Which is most pressing to you now? Or It sounds like alcohol and drugs have been causing you some difficulties. What other issues should we put on the table for consideration? Or Of the three areas you just discussed, drinking, arguing with your wife, and spending too much money, which is the one you'd like to start with today?
3. *Scaling importance, confidence, and readiness*. I'd like to understand more about how you view your drinking. On a scale of 0–10, with 0 being not at all important, and 10 being extremely important, how important is it for you to change your drinking now? Or Given that you'd like to make these changes to your cocaine use, how confident do you feel that you can do it? Or While you believe it is quite important to quit smoking, and you feel a bit of confidence you could do it, how ready are you to quit smoking now?
4. *Providing information*. I have some information about maintaining a healthy weight while quitting smoking if you are interested. Or You talked about wanting to get some more information about managing your drinking We offer several options here including meeting with a therapist to do a kind of "check up" about drinking, enrolling in our drinkers' support group, or discussing your health further with the nurse or with me. There are additional resources I can point you to, including written materials and interactive programs on the internet. What would you like to try?

5. *Exploring strengths*. What are some personal qualities that you are proud of? OR Which strengths did you use when you overcame that challenge?
6. *Looking backward*. Let's talk about a time before you started using. What were you doing then? And then, when you began using? And later, as time went on? What do you notice, thinking about the time since you started using?
7. *Looking forward*. Where do you think you're going with this eating and exercise pattern if you look ahead a few years? What will likely happen if you maintain your current habits? What might happen if you made some small changes?
8. *Remembering successes*. You were successful in changing your heroin use. Tell me more about how you were able to stay quit. . .what parts of that change might be relevant now, as you consider quitting smoking weed?
9. *Considering hypothetical changes*. If you were to make a commitment to begin writing down what you are drinking each day, how might you remind yourself to do it? What would be challenging? What would be rewarding?

In addition to defining what Motivational Interviewing includes, it is also useful to define what it does not include. For example, while occasional advice may be given to clients who are seeking it, unsolicited advice is not offered without first securing client permission. Similarly, therapists do not confront or warn clients, engage in domineering or controlling interactions, or express their own concerns about clients or client choices (except in extenuating circumstances where clients may be in immediate danger). Motivational Interviewing strategies or techniques are not simply added into interactions that are hierarchical in nature; rather, the Motivational Interviewing style prescribes that the therapist-client relationship is inherently non-hierarchical.

In summary, Motivational Interviewing is a counseling approach in which therapists use a client-centered stance paired with eliciting techniques to help clients explore and resolve their ambivalences about changing behaviors that are not optimally healthy. It is characterized by a collaborative, autonomy-supporting, and evocative style in which therapists seek to understand clients' perspectives, while directing clients towards considering changing one or more behaviors by building a sense of discrepancy between the current and hoped-for self, avoiding confrontation, and supporting clients' optimism about the possibility and methods for change. Table 1 summarizes common characteristics of Motivational Interviewing and shows their relationships to Motivational Interviewing principles.

A Brief History of Motivational Interviewing

Although it has strong roots in client-centered counseling, Motivational Interviewing developed more out of practical experience than theoretical conviction, and can be considered atheoretical or theoretically eclectic. Bill Miller's exploration with Norwegian colleagues of his intuitive practice guided him to elucidate the principles underpinning his approach, which integrated cognitive and behavioral elements into a broadly client-centered style. Miller's original principles were supplemented by collaborator Steve Rollnick's observation that ambivalence was a central aspect of change, and that Motivational Interviewing specifically targeted ambivalence. Working together, Miller and Rollnick developed the clinical methods and described them in their 1991 book [24]. They anchored their discussion of the rationale for elements of the clinical methods on discussion of the theories to which the elements were logically linked. The first related theory was Carl Rogers' theory of the necessary and sufficient conditions for therapeutic change, such as genuineness, congruence, and accurate empathy [35]. A second related theory was cognitive dissonance theory, in which Festinger posited that people would work to reduce thoughts that were strongly

Table 1 Principles of Motivational Interviewing and relationships to common techniques and strategies

	Principles			
Techniques and strategies	Express empathy	Develop discrepancy	Roll with resistance	Support self-efficacy
Seek and accept the client's perspectives	x		x	x
Listen more than speak	x		x	
Ask open questions	x	x	x	
Set agenda collaboratively				x
Reflect your understanding	x		x	
Affirm the client's efforts				x
Summarize your understanding	x		x	
Ask key questions that build momentum		x	x	x
Explore ambivalence by examining pros and cons of changing	x	x	x	
Brainstorm broad array of options for change			x	x
Envision a different way		x		
Consider values		x		
Elicit and reflect change talk		x		x
Set goals collaboratively				x
Recall successes	x	x		x
Encourage small steps toward change	x			x
Ask for commitment or emphasize it when it emerges	x		x	x

Note: We show here a list of common Motivational Interviewing techniques and strategies, rather than a comprehensive list, and show the most likely relationship to each principle. In any particular clinical situation, it is possible that a specific technique may relate to more than one principle

dissonant with their behaviors by altering either their attitudes/thoughts or their behaviors [9]. While cognitive dissonance theory as a whole is no longer part of the model of Motivational Interviewing, recent versions of Motivational Interviewing have retained the idea of the related concept of discrepancy). A third related theory was Bem's self-perception theory, in which people observed themselves, their behaviors, and their statements, and inferred from those actions what they believed and valued [3].

Studies of Motivational Interviewing and Miller's Drinker's Check-up showed early positive findings in that brief 1–4 session interventions had a clear impact on drinking behaviors up to a year later. A four-session adaptation of Motivational Interviewing that included personalized feedback, Motivational Enhancement Therapy, demonstrated its efficacy as a treatment approach for problem drinking in the large U.S. clinical trial, Project MATCH. Interest grew in using Motivational Interviewing, originally conceptualized as preparing people for changing addictive behaviors, with problems beyond substance abuse. It is fair to say that there has been an explosion of interest and studies of Motivational Interviewing in the past 15 years, including approximately 200 clinical trials.

While the scientific literature on Motivational Interviewing helped to increase its popularity, a significant factor in its dissemination was the development of a network of skilled trainers who trained therapists in Motivational Interviewing across settings and in many countries across the globe. Rather than disseminating Motivational Interviewing through writing only, Bill Miller and Steve Rollnick personally trained the first generation of Motivational Interviewing Trainers. This group began meeting regularly at the time of the (then annual) Training of New Trainers conducted by Miller and Rollnick and was initially a loose collaboration of volunteers. As new trainers were trained, the group outgrew its original small format and added online support for its growing community. With technical assistance from the Mid-Atlantic Addiction Technology Transfer Center, the Motivational Interviewing Network of Trainers has grown into

an active international community of many hundred trainers who interact via listservs, annual meetings, an online journal, and collaborative commercial and charitable training projects around the world. The Motivational Interviewing Network of Trainers is now an independent entity that counts many of the most active Motivational Interviewing researchers among its members, thus developing a strong communication loop between researchers, practitioners, administrators in a wide variety of cultures and professional settings.

Theoretical Concepts and Emerging Models of Motivational Interviewing

Although Motivational Interviewing was derived from practice-based evidence, there are ongoing attempts to understand it theoretically. Currently, there is no comprehensive theory of Motivational Interviewing that explains its actions or drives its development, although there are several threads. In this section, we consider how an emerging model of Motivational Interviewing might be woven from the threads of self-determination theory, the transtheoretical model of behavior change, emotions theory, interpersonal theory and psychotherapy, and data on Motivational Interviewing and some of its potential mechanisms.

Motivational Interviewing as an Activator of Intrinsic Motivations and Growth

Motivational Interviewing seeks to build internal motivation to change, even in the context of clients seeking to change due to some duress or external situation. Individuals with higher levels of internal motivation for change may be more likely to succeed in achieving and maintaining the desired change. Motivational Interviewing seeks to elicit the person's healthy aspirations and propensity for positive growth. These aspirations and growth experiences are often internally motivating, rather than resulting from external reinforcement alone. These goals of activating intrinsic motivations overlap somewhat with self-determination theory. Self-determination theory posits an alternative to some views of human motivation as originating in physiological needs, or as a drive state seeking to amend deficits. Instead, self-determination theory proposes that growth-oriented activity is the central source of motivation [6]. Self-determination theory states that people have innate needs for competence, relatedness, and autonomy, and that these needs can explain intrinsic motivation. Self-determination theory proposes that motivation becomes internalized naturally because humans are ready to internalize ambient values and regulations. Individuals come to grasp the importance of social values as children. Over time, they transform observed social mores into personal values and self-regulation. Self-determination theory proposes that internal motivation is most likely when a person has a sense of efficacy, control, or self-regulation about the required behavior. Self-determination theory outlines a continuum of motivations ranging from externally regulated to truly intrinsic. Markland and colleagues propose that Motivational Interviewing is not focused on truly intrinsic motivations (defined by self-determination theory as engaging in behaviors because they are inherently interesting or enjoyable) [16]. Rather, Motivational Interviewing focuses on a broader range of autonomous motivations regarding behaviors that lead toward desired outcomes for the person. These outcomes may involve extrinsic gain or increased coordination with one's values and self-identity.

Motivational Interviewing as a Method to Move People Through Stages of Change

Motivational Interviewing is a counseling style concerned with encouraging behavior change. The transtheoretical model [7, 34] is a model

of how people make deliberate changes, especially eliminating problem behaviors and beginning new, healthier behaviors. The most well-known aspect of the transtheoretical model is the "Stages of Change" model, in which behavior change is seen as a process that progresses from low awareness and no intention to change through high awareness and active efforts to initiate or maintain change. The five stages of change are pre-contemplation, in which people may not recognize their behavior as problematic and are not planning to change; contemplation, in which people are considering change but remain ambivalent because there are also benefits resulting from their current behavior; preparation, in which people have decided to make a change and are making plans to change; action, in which people are actively taking steps to change, and maintenance, in which people are integrating the new behaviors into their ongoing lifestyle.

While distinct, the transtheoretical model and model of stages of change and Motivational Interviewing "grew up together" and complement one another [8]. Specifically, Motivational Interviewing is a valuable approach to use when people are in the early stages of change, to build interest and motivation for change. The concept of stages may be better as a heuristic than as a reflection of reality. In clinical encounters, readiness for change can fluctuate within a single discussion about change. By maintaining a client-centered perspective and eliciting client readiness to change rather than attempting to use pressure to motivate change, the therapist using Motivational Interviewing can avoid evoking resistance by "getting ahead" of the client.

Motivational Interviewing as an Activator of Emotions and Openness

Most descriptions of Motivational Interviewing and its work with ambivalence have focused on cognitive rather than emotional elements. The resolution of ambivalence is seen as a cognitive task, as in reaching a decision about which choice to make. Motivational Interviewing techniques have been described in cognitive and behavioral terms, as means to positively resolve tension created by unresolved ambivalence about change. Wagner and Ingersoll presented an alternative conceptualization of Motivational Interviewing [42]. Elicitation of negative emotions (e.g., by developing discrepancy) helps clients by narrowing their focus to areas in which they feel discontent, which leads toward them wanting to escape from the current unsatisfactory situation or avoid a future unsatisfactory situation. In contrast, the concept of positive reinforcement involves seeking positive states through behaviors that lead toward more satisfying conditions. From this perspective, motivation involves a desire to experience positive emotions. A positive emotions model encourages a view of motivation that emphasizes opening up to new experiences and actively seeking to build resources to support change and is consistent with the Broaden and Build model of positive emotions in motivation [10, 11]. Elicitation of the positive emotion of interest may lead to greater openness to experiencing. When a client experiences interest (or related emotions such as wonder or curiosity), his or her cognitive focus broadens to consider options that previously had been overlooked or rejected. This increased flexibility in conceptualizing situations may then facilitate resolution of ambivalence and increased openness to engage in activities that lead toward change. As the person acts in the newly considered direction, he or she may improve certain skills and increase the likelihood of achieving a desired outcome. Movement in this positive direction may increase confidence, sense of accomplishment, self-esteem and mood, thus establishing these increased resources for the person to draw upon in service of even more profound changes. After analyzing common Motivational Interviewing techniques and strategies through the lens of the broaden-and-build model, Wagner and Ingersoll concluded that Motivational Interviewing elicits positive emotions of interest, hope, contentment

and inspiration by inviting clients to envision a better future, to remember past successes, and to gain confidence in their abilities to improve their lives.

Motivational Interviewing as an Interpersonal Intervention

Interpersonal theory and research suggest that interpersonal interactions can be represented by two orthogonal dimensions: control and affiliation [15]. The control dimension ranges from Dominance to Submission, while the affiliation dimension ranges from Warmth/Friendliness to Coldness/Hostility. When plotted, they form a circle that represents how controlling and affiliative a person is in interactions with others. Considerable evidence exists that a friendly interpersonal style elicits reciprocal friendly responses from others and a hostile interpersonal style also elicits a reciprocal, hostile response [14]. Interpersonal theory also suggests that a dominant interpersonal style pulls for complementary submissive behavior, while submission pulls for complementary dominant behavior. However, although dominant behavior may pull for submissive behavior, it often elicits reciprocal dominant behavior as interactants struggle for the upper hand in a relationship.

Interpersonal theory has psychotherapeutic implications. While submissive and friendly-submissive clients may pull for and respond well to dominant and friendly-dominant therapists, clients having other baseline styles may not react as well to such a therapeutic stance. Clients presenting with hostile-dominance, who may be angry and lashing out, are unlikely to respond well to a therapist who attempts to assert control or dominance over the interactions even in a friendly-dominant manner, even though this is a logical stance to take if the therapist believes that the client's aggression must stop. Although being friendly and easy-going may be difficult to do in this situation, it is more likely to pull the client toward a friendly stance himself, which is likely to be more productive in moving forward. In contrast, with a client who is clinging and submissive, therapists may be pulled to provide reassurance, structure and direction, yet this is likely to reinforce the client's needy behavior. Instead, a therapist may take an interpersonal stance that pulls for the client to become more assertive and assume greater ownership of his life, even though the client may be pulling for the therapist to take a dominant stance. Figure 1 shows an interpersonal circumplex with hypothetical Motivational Interviewing-congruent therapist behavior and client responsive behavior.

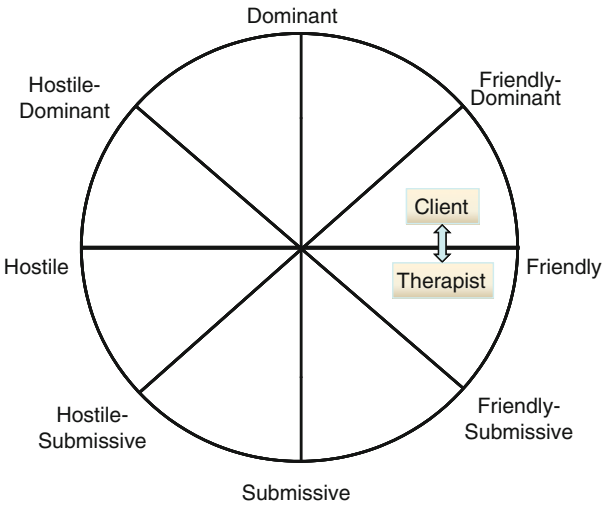

Fig. 1 Interpersonal circumplex with hypothesized Motivational Interviewing-consistent therapist characteristics and responsive client characteristics

By definition, Motivational Interviewing therapists attempt to be both client-centered and directive. Regarding the client-centered aspect, it is useful to consider a continuum of therapist centered and client centered responses. We first present the continuum in a linear fashion, with therapist-centered behaviors that are hostile and controlling on the left and friendly but controlling to the right. Client-centered responses are in the center, ranging from deflecting on the hostile side to affirming on the warm side (see Fig. 2).

On both ends of the continuum is the behavior "direct," because directing can be done in a hostile or warm manner. In our view, this behavior anchors the continuum up and around to the interpersonal circle to the top, which is dominance on the control dimension. Dominance is associated with being right, with being in authority, and with exerting authority or attempts to control others. These behaviors reflect the therapist's perceptions and needs in a moment, and tend to indicate that the therapist has moved away from being client-centered. Such therapist-centered responses are more likely to elicit reactance, whether negative or positive, because they encroach upon the client's being by establishing a hierarchy in which the therapist is above the client.

How might we classify particular therapist statements to better understand how interpersonal interactions work in Motivational Interviewing? A therapist responding to a client's reduction in drinking may say "I am proud of you." Upon first consideration, this appears to be a positive response, falling on the warm side of the affiliation dimension. However, this kind of statement is more likely to be perceived as approval, specifically praise, because it contains a dominant, judgmental element. Another example is "You worked really hard on that," which would be considered an affirmation, because it is an observation that notices the client's effort, rather than evaluating or praising the outcome. Motivational Interviewing primarily uses the middle range of responses from deflection (occasionally, shifting focus) to affirmation. Responses near to these are also used in Motivational Interviewing, but less often. On one demonstration video, Bill Miller agrees with a client angered by previous treatment staff telling him he must accept a label: "It doesn't make any sense to me! It's natural to push back when people push against you." Considering this continuum of possible therapist statements, it appears that Motivational Interviewing draws nearly exclusively from the client-centered range of responses.

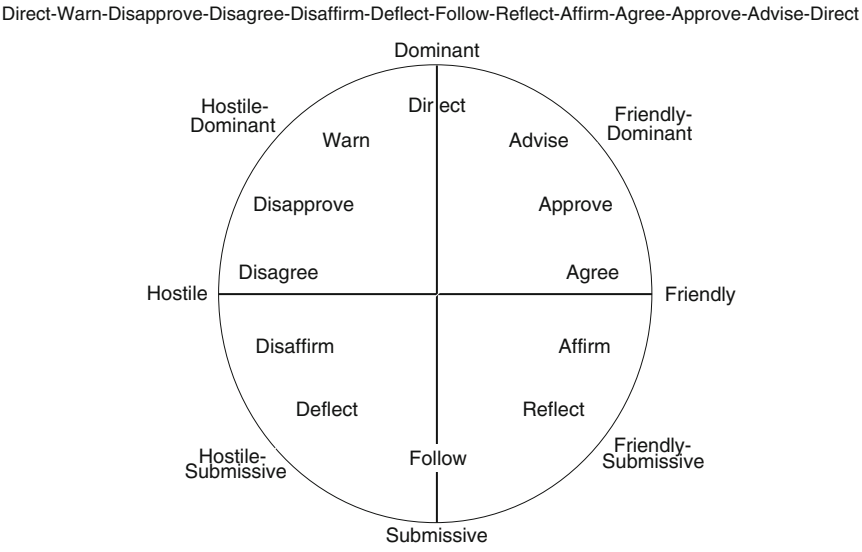

Fig. 2 Linear and circumplex depictions of therapist-centered and client-centered therapist behaviors in Motivational Interviewing

Interpersonal theory has the potential to explain some mechanisms of action in Motivational Interviewing. Interpersonally, Motivational Interviewing therapists tend to be friendly, which elicits a friendly, cooperative stance from most clients. While Motivational Interviewing has a directive component, in that the therapist leads the client to explore and resolve ambivalence and initiate change, this directive process is not necessarily dominant interpersonally. For many people in a leadership role, it is natural to default to a more dominant style to lead, using either warm dominance by being outgoing, encouraging, praising, suggesting, etc., or cold-dominance by directing, warning, confronting, or disapproving. Rather, the Motivational Interviewing therapist leads through affirmation, reflection, listening, and deflecting, all considered submissive behaviors. From the framework of interpersonal theory, these behaviors are less likely to elicit reactance, and are predicted instead to elicit reactions of more outgoing, spontaneous, confident and self-reliant behaviors from clients. Thus, clients take responsibility for deciding on and enacting steps toward change, increase their self-efficacy for specific challenging behaviors, and build momentum and excitement about change. Motivational Interviewing is thus almost entirely anchored in a friendly to friendly-submissive therapist stance. This interpersonal stance in Motivational Interviewing is paired with a leading/guiding/directing intent, and this unusual combination may contribute to the success of the Motivational Interviewing approach.

Motivational Interviewing as a Method to Reduce Resistance and Increase Change Talk

Miller discussed the evidence for different hypotheses about Motivational Interviewing and their possible implications and later elaborated these ideas [21, 26]. In his earlier presentation, he posited a model of Motivational Interviewing in which four hypotheses were considered as potential explanations for the behavior change observed following Motivational Interviewing treatment. Specifically, he hypothesized that Motivational Interviewing would increase client change talk, that Motivational Interviewing would reduce client resistance, that defense of the status quo by clients would relate negatively to change, and that change talk would relate positively to change. Using data from a previous study comparing Motivational Interviewing to a confrontational approach, he found that Motivational Interviewing yielded 111% more change talk and that therapist confront responses predicted client resistance in the form of arguing, interrupting, negative responses, or off-task responses [22]. A psycholinguistic analysis of Motivational Interviewing showed increases in change talk, especially related to therapist listening and reframing behavior and decreases in commitment to drug use [1]. He argued that these data support the hypothesis that Motivational Interviewing increases client change talk and reduces resistance talk. Resistance during counseling was correlated with no change in drinking [1] and commitment to continued drug use during Motivational Interviewing predicted continued drug use [1]; thus, he argued that the hypothesis that client resistance predicts lack of change was supported. Additionally, he concluded while there is some evidence that an increasing slope of change talk in sessions is related to positive outcomes, there is not yet evidence that this is a causal relationship. He also drew from counseling studies with some conceptual or technique similarities to Motivational Interviewing and posited that the resolution of ambivalence is promoted by accurate empathy. Therefore, Miller's model of how Motivational Interviewing may be working is that in an empathic relationship, where there is low confrontational behavior by the therapist, listening and reframing relate to more change talk, which related to better outcomes. Additionally, he asserted that as change talk is observed by the client, the client takes action, consistent with the assertion in self-perception

theory that people observing their own speech draw conclusions about their interest or motivation to take actions based on their speech. That is, they infer motivation to change and a desire to take action when they hear themselves speak in favor of changing. Alternatively, change talk could be interpreted as *implementation intentions*, which have been shown to relate to initiation of action across behavioral domains [12] and specifically, to reduction of substance abuse behavior following verbal commitments to change [1, 17]. In essence, many models using different terms assert that when a client talks about doing something, or making a specific change, they are more likely to do so.

Summary: Emerging Components in a Model or Theory of Motivational Interviewing

In a more recent elaboration, Miller and Rose summarize Miller's early work, and propose that two active components in combination lead to the efficacy of Motivational Interviewing: a relational component that includes empathizing, collaborating, evoking client talk about their perspectives, and supporting client autonomy, and a technical component that includes evoking and reinforcing change talk [26]. Miller's emerging model presents some pieces of the puzzle, but these pieces may or may not be unique to Motivational Interviewing and might be common factors, shared by other psychotherapies. Further, while Miller's recent work may provide a working model of Motivational Interviewing in describing what happens, it is not an encompassing theory that attempts to explain why clients make changes after such interactions. An eventual model of Motivational Interviewing would elucidate elements unique to Motivational Interviewing and elements shared with other psychotherapies, and would demonstrate how the relational, technical, and interpersonal components work to produce client changes in beliefs, perspectives, emotions and actions.

Evidence About Motivational Interviewing

Evidence About Efficacy

What is the evidence base for Motivational Interviewing? The literature on Motivational Interviewing has been on an exponential growth curve. There were 161 grants funded by the U.S. National Institutes of Health that test some aspect of Motivational Interviewing active as of June 2009. Motivational Interviewing and its most common adaptation, motivational enhancement therapy, have been listed as an evidence-based practice in two prominent compendia of evidence-based treatments for substance use disorders [31, 32]. There have been three meta-analyses of Motivational Interviewing since the 2002 book was published. Because Motivational Interviewing is a general counseling approach of unspecified duration, researchers are required to make specific adaptations to individual populations and settings. Thirty randomized controlled trials of adaptations of Motivational Interviewing were subjected to meta-analysis [5]. Most commonly, adaptations of Motivational Interviewing targeted drinking ($n = 15$, 50%), while 2 targeted smoking cessation, 5 targeted drug use, 4 targeted diet and/or exercise, 1 targeted psychiatric treatment adherence, and 1 targeted disordered eating. These studies were conducted in a variety of settings, with the most common setting a substance abuse treatment center ($n = 11$), while 9 were in hospitals. The mean dose of the intervention ranged from 15 to 240 min, and averaged 99 min. The authors found variable effect sizes depending on the target behavior. There were medium effects in drug use and diet/exercise areas, small to medium effects in drinking, and no effects on smoking cessation or HIV risk behaviors. Adaptations of Motivational Interviewing improved client success rates, with one-third making the desired change without the adaptation of Motivational Interviewing and one-half making the desired change with the adaptation of Motivational Interviewing.

In the substance use areas, adaptations of Motivational Interviewing doubled abstinence rates from 1 in 5 to 2 in 5. The observed effects were durable, diminishing only slightly from 20 to 67 weeks of follow-up. In addition to effects on a single target behavior, adaptations of Motivational Interviewing also demonstrated medium social impact effect sizes that were not correlated with the target symptom. In a test of the "file drawer problem," in which insignificant results are unlikely to be published, the authors found that 1181 unpublished studies finding a null result would be needed to reduce the effect size of the published studies to non-significant. There is an investigator effect, with Miller's studies yielding a 0.51 (moderate) effect size, compared to studies conducted elsewhere, 0.21 (small). Adaptations of Motivational Interviewing are efficient; they produce similar results in 2 sessions that are achieved by other psychotherapy studies in 8 sessions for a variety of target behaviors.

The next meta-analysis of extant studies of Motivational Interviewing included a variety of target behaviors [13]. These investigators included studies with at least a pre-post design as well as randomized controlled trials, so included a broader spectrum of designs. They rated the methodological quality of the 72 studies and found that their characteristics did not differ from the larger literature on alcohol treatment outcome studies. The target behaviors included: alcohol (31), drug abuse (14), smoking (6), HIV risk (5), treatment compliance (5), water purification (4), diet and exercise (4), and one each on gambling, relationships, and eating disorders. Across all studies, the total n of participants was 14,267, while the n of each study ranged from 21 to 952, with a mean of 198. Men represented 54.8% of the total sample, with a mean age of 34. 43% of participants in the studies were ethnic minorities. The number of Motivational Interviewing characteristics ascribed to the treatment by study authors showed no relationship to effects, but those studies using a treatment manual showed lower effects than those without. Hettema and colleagues found that similar to other behavioral treatments, effects of Motivational Interviewing appear early and tend to diminish somewhat over time, except in additive studies, where they remain stable. They found that the average effect size of Motivational Interviewing was $d = 0.77$ at post-treatment, $d = 0.31$ at 4–6 months, and $d = 0.30$ at 6–12 months. They concluded that Motivational Interviewing is effective but that a number of process variables may affect outcomes, including therapist behaviors.

Another meta-analysis of Motivational Interviewing evaluated its impact on a number of health behaviors compared to the impact of brief advice [37]. Seventy-two trials published from 1991 to 2004 were found that compared Motivational Interviewing to brief advice across medical and psychological settings. There was a significant effect of Motivational Interviewing on a number of diverse target behavior indicators including body mass index, total blood cholesterol, systolic blood pressure, blood alcohol concentration, and standard ethanol content, but not on cigarettes per day or hemoglobin A1C. Motivational Interviewing demonstrated an effect in 74% of the randomized controlled trials assessed regardless of the interventionist's profession (psychologist, physician, nurse, etc.), and likelihood of an effect increased with increases in the number of minutes per session and the number of encounters per client. The authors concluded that Motivational Interviewing is more beneficial than brief advice for a broad range of target behaviors.

Evidence About Motivational Interviewing Processes and Their Relationships with Outcomes

The connection between process and outcome has not been established in Motivational Interviewing. However, there are therapist and client processes that are presumed to relate to change in Motivational Interviewing based on Miller and Rollnick's description of Motivational Interviewing. Motivational Interviewing therapists maintain the collaborative,

evocative, autonomy-supporting stance known as Motivational Interviewing spirit across sessions, and demonstrate empathy for the client. Therefore, it is hypothesized that when Motivational Interviewing therapists display Motivational Interviewing spirit and empathy, clients will show higher engagement and lower resistance. A corollary hypothesis is that clients with lower resistance and higher change talk in Motivational Interviewing sessions should have better outcomes. Additionally, Motivational Interviewing therapists use open questions, reflections, affirmations, and summaries as primary techniques, while employing strategies such as emphasizing choice and control, reframing, and rolling with resistance. Therefore, it is hypothesized that Motivational Interviewing performed with more open than closed questions, more reflections than questions, and more Motivational Interviewing-consistent strategies should result in better client outcomes. While the literature addressing this area is limited, it is growing and is providing some consistent answers about how Motivational Interviewing may be working.

Therapist interpersonal skills include acceptance, egalitarianism, empathy, warmth, and spirit. When therapists display a high degree of these qualities, they may facilitate the formation of a helpful therapeutic alliance and the engagement of clients in the process. This hypothesis was tested in a secondary analysis of therapists undergoing training to refine their Motivational Interviewing skills, in which therapists generated audiotapes of themselves working with a client with a substance abuse problem [30]. Tapes were rated with the Motivational Interviewing Skill Code to assess therapist global characteristics and provide frequency counts of therapist Motivational Interviewing consistent and Motivational Interviewing-inconsistent behaviors. Client affect, cooperation, engagement and disclosure were also rated using the Motivational Interviewing Skill Code. Using a structural equation model, they found that the latent construct of therapist interpersonal skills composed of acceptance, egalitarianism, empathy, warmth, and spirit were positively related to client involvement and that the correlation between therapist interpersonal skills and Motivational Interviewing-inconsistent behaviors was negative. They concluded that therapist interpersonal skills directly facilitated client collaboration, and that therapists with these skills did not undermine client engagement even when they displayed some Motivational Interviewing-inconsistent behaviors.

In a study of Motivational Interviewing treatment fidelity to a semi-structured, scripted Motivational Interviewing intervention targeting HIV medication adherence, investigators rated audiotaped sessions of about 30 min in length using the Motivational Interviewing Skill Code [20], a 3-pass system that generates global scores, behavior counts, and client global scores [39]. They found that interviewers achieved behavior counts consistent with the Motivational Interviewing style, while their global scores did not quite reach the benchmark. They found that a higher ratio of reflections to questions and the number of affirmations were associated with higher antiretroviral therapy adherence at study exit, while closed-ended questions were negatively associated with better adherence.

Similarly, Boardman et al. [4] assessed initial counseling sessions targeting smoking among inner-city African-Americans using the Motivational Interviewing Skill Code. They used a mixed linear models approach to control for therapist effects in all models, and found that an averaged Motivational Interviewing global score composed of acceptance, egalitarianism, warmth, genuineness, empathy, and Motivational Interviewing spirit and behavior counts of higher Motivational Interviewing consistency (including advice with permission, affirming, emphasizing choice and control, reframing, supporting, and using open questions and reflections), were related to greater frequency of client change talk (statements about recognizing problems, expressing concern, desire, intention, or optimism for change) and to a higher averaged global score of client expression of affect, cooperation, self-disclosure, and engagement. Behavior counts indicating Motivational Interviewing-inconsistent behaviors (giving advice without permission, confronting, directing, raising

concern without permission, and warning) were unrelated to client change talk or global scores. However, specific behaviors were related to some outcomes. Behavior counts of affirm, open questions, reflect, and support were positively related to a therapist-client interaction global score composed of averaged ratings of collaboration and benefit. Behavior counts of advice without permission showed a negative correlation with change talk. They found no predictors of client resistance statements.

In a study of Motivational Interviewing skills of peers conducting Brief Alcohol Screening and Intervention for College Students sessions targeting college drinking, investigators used the Motivational Interviewing Treatment Integrity scale [29] to assess the relationship between facilitator skills and drinking-related outcomes [40]. Participants in Brief Alcohol Screening and Intervention for College Students sessions showed increases in contemplation and decreases in drinking from baseline to 3-month follow-up. Peer therapists providing the Brief Alcohol Screening and Intervention for College Students intervention achieved beginning proficiency levels on global ratings of Empathy, percent Motivational Interviewing-adherent behaviors, and percent open questions, while they fell below beginning proficiency on Motivational Interviewing Spirit, reflections to questions ratio, and percent complex reflections. Regression analyses showed that closed questions were associated with decreased contemplation and open questions were associated with increased contemplation. More simple reflections were associated with increased drinking, but this relationship was attenuated when therapists attained a greater proportion of complex reflections.

Several studies have assessed client resistance and its relationships to therapist behaviors and to outcome. Although not directly examining Motivational Interviewing, an early study exploring the relationship of therapist behavior to client resistance found that resistance varied depending on therapist behaviors, with educational or confrontational behaviors eliciting more resistance, and client-centered behaviors eliciting less resistance [33]. The more time the client showed resistance in the session, the poorer the drinking outcome [22]. The reverse was also true; clients who showed little resistance manifested improved drinking outcomes up to 12 months later.

Amrhein and colleagues rated client speech across deciles of Motivational Interviewing sessions in a single-session intervention and examined the relationships of client change talk and commitment talk to outcomes [1]. They found that those who changed and maintained change in drug use evidenced increasing commitment language across a Motivational Interviewing session. In contrast, those who were categorized as strugglers showed decreasing change talk and a reduction in commitment language by the end of the session, and had poorer drug use outcomes. Further, Strang and McCambridge rated client speech for change talk and found that action-oriented change talk, presumably representing either commitment or a stronger implementation intention, was related to subsequent marijuana use at three month follow-up [18].

The association between client speech, therapist behaviors, and outcomes has been investigated in a line of ongoing research with one unpublished and three published studies to date. Moyers and colleagues found that client change talk and counter-change talk were related to substance abuse outcomes in the expected directions [18]. They found that the more the therapist affirmed, emphasized control, asked permission before raising concerns, and made reflections, the more clients engaged in total change talk in the session [27]. Going beyond simple correlational analysis, Moyers further studied the conditional probabilities of certain classes of client speech following various forms of therapist speech in Project MATCH's motivational enhancement therapy sessions [27]. They used an instrument designed for the study, the Sequential Code for Observing Process Exchanges, which consisted of 46 behavior counts (30 therapist and 16 client) derived from the Motivational Interviewing Skill Code. They combined client speech about the target behavior into positive (indicating change talk),

negative (indicating counter change talk) or other. Therapist behaviors were combined into Motivational Interviewing-inconsistent, Motivational Interviewing-consistent, or other categories. Motivational Interviewing-consistent behaviors included specific strategies such as emphasizing choice and control. They found that when therapists performed in a Motivational Interviewing-consistent manner, there was an immediate increase in the probability that clients would produce change talk in the next utterance. In contrast, therapists displaying Motivational Interviewing-inconsistent behaviors (such as warning or advising without permission) increased the immediate probability of clients producing counter change talk. Additionally, change talk sometimes followed "other" therapist behaviors that are part of the basic Motivational Interviewing style such as questions, and reflections, as well as other strategies such as giving information, providing feedback, providing opinions, and conversational fillers.

Lastly, these investigators investigated whether client change talk during three types of substance abuse treatment sessions predicted drinking outcomes [28]. They rated sessions from 12-step facilitation, cognitive-behavioral therapy, and motivational enhancement therapy from Project MATCH using the Motivational Interviewing Skill Code. Using the outcome definitions from Project MATCH, they considered the impact of client change talk and counter change talk on percent days abstinent and drinks per drinking day, taking into account baseline values on both these drinking variables. They found that adding change talk and counter change talk improved the model of outcome percent days abstinent, with counter change talk being a significant predictor. Adding change talk and counter change talk also improved the model of outcome drinks per drinking day, with both change talk and counter change talk acting as significant predictors in the expected directions. They concluded that the causal chain tested in their series of studies demonstrate that therapist behaviors evoke change talk, that counter change talk and change talk are different constructs, and that both are simultaneous predictors of outcome.

While the literature on how Motivational Interviewing works is still small, there are some common findings emerging from the studies to date. Empathy and Motivational Interviewing Spirit (collaboration, evocation, autonomy-support) both relate to engaging clients and building therapeutic alliances. Several studies found that open questions, reflections, and affirmations encouraged change talk, while closed questions did not. In addition, those behaviors considered to be Motivational Interviewing-consistent, such as asking permission to give advice, affirming, emphasizing client choice and control, and support, have been related to more change talk, as well as to more positive substance abuse outcomes in several studies. Some aspects of a model of how Motivational Interviewing works are emerging already, although many questions remain about the directionality and causality of current hypotheses. Table 2 presents a summary of tests of mechanisms of action of Motivational Interviewing published to date.

The evidence base and the summary from these meta-analytic and process-outcome studies indicate a number of important findings. First, nearly all studies have been adaptations of Motivational Interviewing, with most including both the counseling style and some form of personalized feedback rather than tests of it as a "pure" clinical method. Second, Motivational Interviewing is superior to no treatment and is equivalent to other active treatments despite its relative brevity, thus there may be cost effectiveness advantages to Motivational Interviewing. Third, the measurement of intervention fidelity needs to be expanded among clinical trials, many of which claim to use Motivational Interviewing but do not present evidence of its competent use or fidelity to its spirit and methods. Fourth, the study of process-outcome relationships in Motivational Interviewing is in early stages, and will require time to demonstrate which components of Motivational Interviewing are necessary and sufficient, and whether these are unique to Motivational Interviewing or might occur in

Table 2 Summary of evidence regarding mechanisms of action of Motivational Interviewing

Study	Rating system	Global bench-marks	Beh. counts bench-marks	R:Q	OQ	CQ	SR	CR	MI global	MICO	MIIN	Client CT	Client CCT
Miller et al. [22]	Modiified Patterson and Forgatch [33] structured behavior checklist	N/A	N/A	N/A	N/A	NA	N/A	N/A	NA	Listening correlated w/ positive or following client behaviors; restructuring correlated w/ positive client behaviors	Therapist confrontation related to more resistance		Resistance related to more drinking at 12 month outcome
Amrhein et al. [1]	Client commitment language	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Related to commitment talk which was related to outcome	
Strang & McCambridge [38]	Practitioner checklist	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	NA	NA	Action-oriented CT related to cannabis outcomes	N/A
Moyers and Martin [27]	MISC						Related to more change talk	Related to more change talk		Affirm, emphasize control, asking permission all related to more change talk	N/A		
Moyers and Martin [27]	SCOPE	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Produced immediate increase in probability of change talk	Produced immediate increase in probability of counter change talk	N/A	N/A
Boardman et al. [4]	MISC	No	Not reported	N/A	Related to collaboration and benefit	N/A	Related to collaboration and benefit	N/A	Averaged global score related to change talk and client participation	Related to change talk and client participation			

Table 2 (continued)

Study	Rating system	Global bench-marks	Beh. counts bench-marks	R:Q	OQ	CQ	SR	CR	MI global	MICO	MIIN	Client CT	Client CCT
Thrasher et al. [39]	MISC	No	Yes	Associated with better HIV medication adherence		Negatively associated with better HIV medication adherence	N/A	N/A	Related to better adherence among subset with focus on adherence	Affirm was related to adherence	N/A	N/A	N/A
Moyers et al. [30]	MISC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Related positively to substance use outcomes	Related negatively to substance use outcomes
Tollison et al. [40]	MITI	Yes Empathy No spirit	Yes % MI Adherent Yes % OQ No R:Q ratio No % CR	N/A	Associated with increased contemplation	Associated with decreased contemplation	Associated with increased drinking	Associated with a lower increase in drinking	N/A	N/A	N/A	N/A	N/A
Moyers et al. [28]	SCOPE	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Significantly predicted DDD and decreased probability of poor outcome	Significantly predicted PDA and DDD and increased probability of poor outcome

MI Motivational Interviewing, *MISC* Motivational Interviewing Skill Code, *Global* a measure that estimates a quality across a whole session or section of a session, *Beh. Counts* behavior counts, a measure that counts specific behaviors across a session or section of a session, *R:Q* reflection to question ratio, the number of reflections compared to the number of questions, *OQ*: open questions: the number of questions with infinite possible answers, *CQ* closed questions: the number of questions with limited or defined answers such as yes/no or A, B, C, or D, *MICO* Motivational Interviewing-consistent behavior as coded on the Motivational Interviewing Skill Code, *MIIN* Motivational Interviewing-inconsistent behavior as coded on the Motivational Interviewing Skill Code, *CT*: change talk, or talk in which the client speaks about changing, *CCT* counter change talk, or talk in which the client speaks about not changing, *MITI* Motivational Interviewing Treatment Integrity scale, *SCOPE* Sequential Code for Observing Process Exchanges, *PDA* percent days abstinent, *DDD* drinks per drinking day

other psychotherapy approaches as in a common factors model. As more information about process-outcome relationships in Motivational Interviewing accumulates, it will inform the development of an empirically based model of Motivational Interviewing, and perhaps, of related psychotherapies.

Populations, Settings, and Applications of Motivational Interviewing

When Miller and Rollnick first described a complete version of Motivational Interviewing, its basis was work with drinkers. The current status of Motivational Interviewing is vastly different. There are at least six broad domains of concern that have been addressed by Motivational Interviewing, but within these domains, there are many potential populations of people and even more potential behavioral targets that could be addressed by Motivational Interviewing. We will review some of these briefly (see www.motivationalinterviewing.org for an expansive bibliography).

In the domain of substance abuse, common populations treated with Motivational Interviewing in clinical and research settings have included people with symptoms of problem drinking or drug use, ranging from youth experimenting with drinking for whom drinking is a statutory offense, through adolescents and adults with alcohol abuse disorders, through adults with severe alcohol and drug dependence problems, including those whose addiction problems have resulted in involvement in the criminal justice system. Studies have been published showing the efficacy of Motivational Interviewing to reduce drinking, increase abstinence from drinking, reduce heavy drinking days, reduce smoking, increase abstinence from tobacco, reduce gambling problems, facilitate harm reduction as in using needle exchange programs, and reduce drug use.

In the domain of medical disorders, Motivational Interviewing has been used to help patients with a number of medical diagnoses and related health conditions, some of which have obvious or less obvious relationships with substance abuse. At the high end of the severity of illness spectrum, some Motivational Interviewing practitioners and researchers have explored helping people with traumatic brain injury to increase healthy habits to assist in their brain injury rehabilitation, and increasing motivation among patients with heart disease to undergo cardiac rehabilitation including making changes in diet, exercise, and medication use. At the moderate level of medical acuity, Motivational Interviewing has addressed chronic pain management as well as diabetes risk reduction and diabetes management. Others have used Motivational Interviewing for prevention of disease or illness, for example, by targeting obesity before medical consequences develop. Consistent with prevention are a number of Motivational Interviewing applications toward health promotion that seek to increase healthy eating habits, physical activity, safer sexual practices, mammography screening, medication adherence, oral health care, and osteoporosis prevention and treatment.

In the domain of mental health, there is much growth in applications of Motivational Interviewing, resulting recently in a book with chapters ranging the gamut of psychological problems [2]. Relating to substance use problems, Motivational Interviewing has been used clinically and tested in research as a dual disorder intervention, targeting both substance use and mental illness. It has also been adapted to target behaviors that are often problematic in mental health treatment for anxiety, bipolar disorder, depression, post traumatic stress disorder, and schizophrenia, such as keeping appointments, taking psychoactive medications, and attending support groups. Motivational Interviewing methods have also been adapted in marital counseling for problems that may be related to substance abuse, including dysfunctional relationships.

The United States Department of Justice has adopted Motivational Interviewing as a preferred best practice in the area of criminal justice, including imprisoned inmates and those supervised in community correctional settings. Many

of those who are in criminal justice settings have substance abuse issues. Related to these settings are child protective services and domestic violence prevention and treatment services, which provide care to those involved in the legal system.

A domain that is just beginning to use Motivational Interviewing is education. So far, efforts to use or test Motivational Interviewing have focused on literacy acquisition and employment readiness, which are often found to be life problems among those with a significant substance abuse history.

Lastly, there is another domain that overlaps but does not neatly fit into any of the others. Motivational Interviewing is being used increasingly to target simultaneous health risk behaviors across a number of settings beyond the typical medical consultation room, including public health and media-accessed settings. Promising projects have shown the benefit of Motivational Interviewing to reduce the risk of alcohol-exposed pregnancy by targeting both drinking and contraception, sexual behavior-change including safer sex behaviors often in the context of drug or alcohol use as an additional target, and drug and alcohol use that overlap with criminal behavior.

The list of possible applications and behavioral targets of Motivational Interviewing is dauntingly long, and there is also increasing diversity in the settings in which Motivational Interviewing is delivered. Motivational Interviewing began as an outpatient psychotherapy for alcohol problems, with the model of an individual person seeking counseling coming in to a therapist's office and sitting for 45 min or an hour to discuss a troubling issue. It then expanded into medical consultation, where brief versions of Motivational Interviewing were developed and tested that could be managed in the much shorter visit times expected in the setting. Common practices include using Motivational Interviewing for all individual substance abuse treatment sessions, or adding Motivational Interviewing as a prelude to treatment entry where treatment follows a different model. Some therapists combine Motivational Interviewing with personalized feedback, employing a strategy based on motivational enhancement therapy, to begin considering the issue of change with a client. Other therapists combine Motivational Interviewing spirit, techniques, or strategies with other clinical methods, such as cognitive-behavioral therapy or values clarification methods. In the public sector, both in the community mental health system in the U.S. and the criminal justice system, Motivational Interviewing is commonly provided in a group format, because these services often offer groups as the primary treatment modality.

New Directions in Motivational Interviewing

Studying Motivational Interviewing

Most of the research on Motivational Interviewing to date has shown that Motivational Interviewing has strong main effects. There are now enough studies showing that Motivational Interviewing is efficacious in research settings applied to many challenging behavior change situations. An understanding of Motivational Interviewing should now progress toward identifying how Motivational Interviewing can be made effective in routine clinical care across a number of settings. This will require not only research on the dissemination process itself, but consistent evaluation of the fidelity of various Motivational Interviewing-informed interventions. The field has produced nearly a dozen instruments to measure Motivational Interviewing behaviors and processes that could be used to demonstrate whether and when Motivational Interviewing was delivered competently. Identifying the key components of Motivational Interviewing and how it works will allow it to be transformed into new methods of service delivery. Several teams are already working on computerized or web-based delivery of Motivational Interviewing that could allow the method to be delivered independent of the

availability of a competent Motivational Interviewing therapist. Identifying salient components of Motivational Interviewing will also inform efforts to disseminate it and make it work in various settings outside of the tight control of a research study.

Preparing Therapists to Use Motivational Interviewing

Therapists prepare themselves to use Motivational Interviewing by diverse methods. A decade ago, therapists may have read the original Miller and Rollnick book, and possibly attended a workshop offering a one or two-day introduction to Motivational Interviewing practice, and began to use Motivational Interviewing in their practice. With the emergence of studies showing that workshops often do not produce many competent Motivational Interviewing therapists in the absence of additional training, supervision, and coaching about specific Motivational Interviewing behaviors, the expectations for training have changed. Reading and introductory workshops are ways to increase interest in learning Motivational Interviewing. Monitoring or coding sessions provides additional data for therapists to use to improve practice by identifying areas of competence and areas that need attention to achieve competence. It is unclear whether therapists can do this themselves and achieve competence, or whether additional supervision and coaching of Motivational Interviewing practice is needed. Many therapists now enroll in introductory, intermediate, and advanced clinical workshops, while others seek supervision or evaluation of practice samples to improve their competence in Motivational Interviewing.

In addition to individual therapists becoming trained in Motivational Interviewing, it is now common for agencies to request training for many of their staff in Motivational Interviewing, or to seek to become a Motivational Interviewing-competent organization. This goal would seem to require several steps, such as exploring therapist and management perspectives about current services and competencies, broadening perspectives to build curiosity or interest in adding skills to the therapists' and agency's repertoires, and taking action to procure training, supervision, and organizational consultation. It is still relatively rare for an agency to take all of these steps, and to evaluate progress in a systematic way.

Some therapists and teachers provide training for others in Motivational Interviewing. Some of them are self-trained and others undergo a series of training experiences intended to increase their competency in training others in Motivational Interviewing. These experiences may include learning Motivational Interviewing and providing it clinically, seeking consultation on Motivational Interviewing practice, providing basic training on Motivational Interviewing, seeking consultation on Motivational Interviewing training skills or co-training with a more experienced trainer, obtaining training on the various methods to code Motivational Interviewing practice and/or to provide supervision using various systems, training agency-based supervisors or trainers on how to provide Motivational Interviewing supervision or training within an agency, and participating in a formal training for trainers such as that offered by the Motivational Interviewing Network of Trainers.

Improving the competence of Motivational Interviewing therapists, organizations, and trainers is an emerging area. Miller has compared learning Motivational Interviewing to learning to play the piano. While a brief workshop to teach fingering methods or specific compositions may help, more is needed to create a competent pianist. Similarly, a Motivational Interviewing workshop may pique the interest and increase some skills of a therapist, but training in theory, specific methods, timing, self-monitoring, and much actual practice may be required to achieve competence, and later, fluency in Motivational Interviewing. How to train or produce Motivational Interviewing-skillful organizations is a challenge already being addressed in some large scale projects, especially in the area of criminal justice. However, there is

little current evidence about preferred methods in this area, and similarly, little evidence about best practices in training trainers. All of these areas await further development as the demand for training therapists and organizations continues.

Defining Motivational Interviewing

As practice evolves and new evidence about effectiveness and process-outcome relationships emerges, it is likely that definitions of Motivational Interviewing will change. In some ways, this has already happened. There are at least four perspectives on defining Motivational Interviewing. One is that Motivational Interviewing *is a creation of and defined by its original developers*. Motivational Interviewing was described initially by Miller [19, 23] and then by Miller and Rollnick [24, 25] and these founders of the approach may continually revise and update it as their own experiences and thoughts develop. Therefore principles, goals, techniques, strategies, and terms of Motivational Interviewing follow from the founders' decisions, which may be influenced by data or practice or even whim. If the founders are the sole arbiters in defining Motivational Interviewing, it is whatever they say it is, and elements may be added or deleted based on their preferences.

From the clinical research perspective, Motivational Interviewing may be viewed instead as *a set of attitudes, techniques, and strategies that can be described in a manual and can be evaluated with measures of treatment fidelity*. This clinical research perspective focuses on sharp boundaries, specified timeframes, clearly defined strategies and techniques to address specific target behaviors, and attempts to isolate the unique elements of Motivational Interviewing. The clinical research definition of Motivational Interviewing results in a binary decision in that either Motivational Interviewing is being done or Motivational Interviewing is not being done. From this perspective, that Motivational Interviewing is a specific definable intervention, a therapist could be seen as "doing Motivational Interviewing" in some sessions and not others, or possibly during some moments and not others.

Yet another perspective is the practitioner's angle. Practitioners might view Motivational Interviewing *as an overarching counseling style*, a general way of working with clients. The practitioner using this style weaves whatever strands are most useful in the moment, no matter where those elements might have originated (in Motivational Interviewing, in adaptations of Motivational Interviewing, or in similar or complementary therapeutic approaches, disciplines, or experiences). From this perspective, practitioners may see themselves as doing Motivational Interviewing even when a video sample of a discrete moment in therapy might show them to be providing a cognitive-behavioral therapy-derived intervention, albeit in a Motivational Interviewing-consistent style. In such practice, a decision rule might be "can one smoothly transition in and out of elements borrowed from elsewhere?" The therapist may be exploring ambivalence with a client and notice a bit of distorted thinking, slip unnoticed into working with the client on exploring the background of that thinking, or its fit with reality or rationality, then slip back out and back to exploring ambivalence again. To the practitioner, this whole session may be defined as Motivational Interviewing if Motivational Interviewing spirit and techniques are present, and if the client's responses indicate that the therapeutic alliance is steady.

A fourth perspective is that Motivational Interviewing is a set of ideas or concepts that originated with Miller and Rollnick, but are now independent from them. A conceptual perspective might define Motivational Interviewing as *a set of specific ideas that fit into a nomological net, a framework of logically coherent and connected constructs into which empirical and practice findings are placed and interrelated*. A conceptual perspective on defining Motivational Interviewing may be based less on either need for clear definition and fidelity to that definition

as in the clinical research perspective, or need for pragmatism and devotion to doing what works best in the moment as in the practice perspective.

In summary, Motivational Interviewing is an efficacious method to facilitate behavior change that has strong evidence for its positive impact on addictive behavior. It often achieves good outcomes with fewer sessions and less time than other substance abuse treatment methods. It has become a popular approach and is utilized around the world for the treatment of substance abuse as well as other behavior change challenges. While the clinical methods have been detailed thoroughly, assessing practice and exploring process-outcome relationships are areas getting more attention recently. Additionally, models of Motivational Interviewing are being proposed and tested using old and new data. As Motivational Interviewing expands into new areas of application beyond its individual substance abuse counseling roots, there is a need to develop innovative methods of delivery, and to provide effective training for therapists, agencies, and trainers. Lastly, the very definition of Motivational Interviewing may be changing. It could become a clinical method that retains a distinct identity and is used in specific situations. Alternatively, Motivational Interviewing may become incorporated into practice and eventually lose its individual identity or become one of several specific approaches that focus on client motivation as a central component in fostering behavior change.

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Cognitive Behavioral Therapy for Addiction

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Contents

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Introduction

Cognitive behavioral therapy has proven to be an effective psychotherapeutic treatment for psychiatric disorders such as mood and anxiety spectrum disorders, as well as substance use disorders, including abuse and dependence. It is an individualized, collaborative approach to psychotherapy that emphasizes the importance of thoughts, feelings, and expectancies and also incorporates more traditional behavioral approaches that utilize counter-conditioning and contingency management in addressing the problem of addiction. Cognitive behavioral therapy is based, in part, on social learning theory. Thus, an underlying assumption of cognitive behavioral therapy is that learning processes play an important role in the development and continuation of substance abuse and dependence. These same learning processes can be used to help individuals reduce their drug and alcohol use through modification and substitution of existing patterns. Cognitive behavioral therapy also is based on stress and coping theory. These theories promote that life stressors are likely to trigger the use of avoidance or emotion-focused coping strategies such as substance use among individuals who have low self-efficacy and poor problem-solving coping skills in an attempt to avoid experiencing distress. As such, cognitive behavioral therapy focuses on challenging individuals' positive expectancies about substance use, enhancing their self-confidence and self-efficacy to resist substance misuse, and

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_36,

improving their overall and specific skills for coping with life stress.

When applied to the addicted population, cognitive behavioral therapy helps a client change his/her drug or alcohol use as well as risky attitudes and beliefs. Cognitive behavioral therapy combines two very effective kinds of psychotherapy—cognitive therapy and behavioral therapy. Cognitive behavioral therapy for substance use disorders focuses on helping clients in two major behavioral ways. The first is to help reduce the intensity and frequency of their urges to use, by undermining their underlying beliefs or cognitions about using. The second is to teach the clients specific techniques for controlling or managing their urges to use or drink. In other words, the basic goals are to reduce the pressure to use and increase control. When a client's addiction is determined to be related to a co-occurring disorder, the psychiatric disorder also needs to be addressed by the mental health care provider.

Cognitive therapy focuses on how certain thinking patterns or beliefs cause symptoms. Distorted or unproductive thoughts or cognitions can produce negative moods such as anxiety and depression, which can ultimately provoke more maladaptive thinking and/or behaviors that do not help facilitate positive change or affect. Cognitive therapy strategies focus on thought processes, recognizing that emotions and behaviors are best addressed by considering the faulty thought processes that precede such feelings and acts. Specifically, cognitive therapists collaborate with clients to define problems, explore beliefs, re-examine appraisals and thoughts about their use of substances, and modify these thoughts to promote more favorable and adaptive cognitions, which, in turn, impact positively both behaviors and mood. In addition, coping skills training expands this emphasis on thought processes by focusing clients on accepting stressors in their lives and constructively pursuing strategies to change their valence and tendency to pursue substances to escape and/or avoid situations [3]. While researchers/clinicians affirm the practicality of this approach as well, cognitive therapy cannot comprehensively address all aspects of substance abuse without addressing the destructive behavioral inclinations common to substance users.

Behavioral therapy focuses on weakening the connections between troublesome situations and habitual behavioral reactions to them. Strategies included in behavioral therapy include repeated behavioral practice of techniques such as distraction and relaxation, and exploring consequences and reinforcement. A major goal of the behavioral component is to weaken the learned association between triggers such as the environment, situation, people, or moods and the response of drug or alcohol use and replace it with a more appropriate response. In time, the healthy response will become more familiar and replace the old response of using. Thus, in many ways, the behavioral strategies employed are similar to those used for habit reversal or compulsive behaviors. These include teaching relaxation strategies such as deep breathing and progressive muscle relaxation, learning alternative responses such as drinking juice instead of alcohol, employing behavioral distraction, and avoiding triggers or risky situations. Two subtypes of this approach include contingency management (a positive-reinforcement treatment method in which clients are given rewards for constructive actions taken toward their recovery) and community reinforcement (a set of procedures that systematically reinforce treatment retention and substance reduction/abstinence). Clients may be rewarded for specific positive behaviors, such as producing drug-negative urine, returning to therapy, specific lifestyle changes, etc. [1]. These effective behavioral strategies frequently are incorporated into cognitive behavioral therapy for substance use disorders.

Cognitive behavioral therapy integrates both methods into a logical series of cognitive and behavioral strategies that can identify maladaptive thoughts and resultant actions (via decisional matrix and functional analysis), disrupt automatic patterns of functioning (through coping skills training and practice), reduce the impact of—and harmful response to—stress, and adopt more pro-social learning and interactions.

The goal of cognitive behavioral therapy can be either abstinence or moderate/controlled drinking or drug use (i.e., harm reduction), and is employed routinely for relapse prevention in abstinent individuals. Cognitive behavioral therapy helps the client identify his/her own unique high-risk situations for use. Then, the client may develop plans and skills that are alternatives to using in these situations. Cognitive behavioral therapy also increases the client's confidence about his/her ability to resist using. Because substance use disorders have high rates of return to using, cognitive behavioral therapy includes effective relapse-prevention components of treatment.

Overview of Cognitive Behavioral Therapy

Cognitive behavioral therapy combines two effective kinds of psychotherapy—cognitive therapy and behavior therapy—to help clients change their drinking or drug use behavior and related risky attitudes and beliefs. Cognitive therapy teaches individuals how certain thinking patterns contribute to their symptoms—by giving them a distorted picture of events and interpersonal interactions in their lives, thus directly contributing to feelings of anxiety, depression, or anger that may provoke them into ill-chosen actions. Behavior therapy helps individuals weaken the learned connections between troublesome situations and their habitual behavioral reactions to them.

Following the work of the more radical behaviorists (i.e., Skinner, Watson), Albert Ellis applied behavioral concepts to his work on human emotions. Ellis drew attention to the relationship between events (the "activating event"), personal beliefs, and resultant emotional responses. This model (a main component of rational emotive therapy) came to be known as ABC (A: activating event, B: beliefs, and C: emotional response), highlighting how a personal belief (B) about an activating event (A) could impact emotions (C). Ellis demonstrated that changing maladaptive beliefs (termed "irrational beliefs") regarding a client's perceptions of activating events to more rational and practical personal beliefs would lead to more desired emotional self-management. This model is used frequently in cognitive behavioral therapy and has been shown to be very effective in altering negative emotional states that predispose a person to seek unhealthy substances [12].

Similarly, Aaron Beck extended Ellis's work to address irrational beliefs in primarily depressed clients. Since negative mood states have a high concordance rate with substance abuse and dependence (13–30%), Beck's strategies can be very helpful in addressing the myriad of irrational beliefs held by individuals with substance abuse or dependence disorders [4]. Specifically, Beck identified several common irrational beliefs held by these individuals that serve to reinforce their desires to use substances. These thought patterns include thoughts of helplessness, ideas that drugs improve their functioning, all-or-none thinking, self-criticism, assuming need for perfection, and mind reading. Failure to question the rationality of these thoughts relegates substance-abusing clients to repeat continuously the ABC cycle with the addition of behaviorally acting on "C" in a way that further discourages the clients and reinforces the hopelessness that they feel through substance use. Through cognitive behavioral therapy, however, these irrational thoughts are explored extensively while supplanting drug behavior with healthy coping strategies. The goal of cognitive behavioral therapy can be to attain either no drinking/drug use (abstinence) or moderate/controlled drinking/use (i.e., harm reduction).

When utilizing cognitive behavioral therapy, the client identifies his/her own unique high-risk situations for heavy drinking or drug use with the help of the therapist. Then, using cognitive behavioral therapy techniques, the therapist helps the client to develop plans and skills that are alternatives to using alcohol or drugs in these situations. Thus, using cognitive behavioral therapy also increases the client's confidence about

his/her ability to resist using alcohol or drugs. As people who are addicted typically demonstrate high rates of return to using, cognitive behavioral therapy also includes relapse-prevention training and strategies to employ when lapses occur.

Therapists who provide cognitive behavioral therapy typically possess at least a master's-level degree plus specific training in this area, and more typically possess a Ph.D. in clinical or counseling psychology or an M.D. and advanced training in psychotherapy. Cognitive behavioral therapy has been used within both inpatient and outpatient settings. Longabaugh and Morgenstern [23] recommended at least 12 sessions for substance abuse clients. In this way, cognitive behavioral therapy not only is clinically effective for substance abuse treatment, but it is also efficient, time-limited, and cost-effective. Prior to initiating a cognitive behavioral therapy course of treatment, however, it is helpful for the therapist to assess the client across a number of functional areas in order to customize therapy to the client's specific needs. Specifically, a thorough evaluation of readiness to change, mood, anxiety, and other emotional difficulties can be very helpful in defining the content of therapy. Information regarding the most recent negative consequences precipitated by substance abuse and the client's current stage of change can be particularly helpful in determining how the therapist should interact with the client initially.

Prochaska et al.'s transtheoretical model is a useful conceptualization of a client's stage of change that can be used to motivate a client and better inform subsequent psychotherapy [34]. The transtheoretical model of behavior change, or stages of change model, describes a series of six behavioral stages that an individual experiences in modifying a negative behavior in his/her life. These stages include precontemplation, contemplation, preparation, action, and maintenance. Precontemplation is the first stage in this model and refers to individuals who do not consider their current behavior to be problematic and have not thought about stopping/changing their behavior within the past 6 months. As individuals begin to recognize the negative consequences of their behaviors, they move into the contemplation stage, where they begin to think about changing their behavior over the next 1–6 months. In the preparation stage, the individual begins to implement changes in drinking or drug use behaviors. In this stage, the individual is attempting changes and practicing new behaviors. In the action stage, the individual has successfully changed his/her behavior and has been able to sustain these changes for up to 6 months. In the maintenance stage, the individual has successfully changed his/her behavior and maintained these behavioral changes for 6 months or longer. By identifying a client's current stage of change, the cognitive behavioral therapist can better tailor the initial dialog of therapy to address related barriers to the client's desire to change and level of progress with respect to making changes. Clients at less advanced stages of change (precontemplation, contemplation, and preparation) have been known to express more resistance to change or deny the impact of substance abuse [34].

Using the collaborative encouragement of motivational interviewing in conjunction with cognitive behavioral therapy, clients can begin to resolve feelings of ambivalence that interfere with their desire to change. Motivational enhancement can begin to reveal a client's maladaptive thought patterns that can be explored in more detail as the cognitive behavioral therapy sessions progress. Strategies such as using open-ended questions, affirming client thoughts, reflecting client statements, and summarizing client messages can be helpful in resolving clients' confusion and resistance to change.

Clients in more advanced stages of change (action and maintenance) can begin cognitive behavioral therapy immediately. In such cases, exercises such as the decisional matrix, which involves having the client list the pros and cons of using and not using substances, can be employed to clarify further any remaining ambivalence and reinforce motivation to change.

Cognitive Model of Addiction

Multiple interrelated cognitive models of addiction have been developed and evaluated since Bandura's classic presentations of social learning theory in the late 1960s and 1970s [2]. For example, Marlatt [25] described four cognitive processes related to addictions that reflect the cognitive models: self-efficacy, outcome expectancies, attributions of causality, and decision-making processes. According to Beck et al. [4], people try drugs initially to get pleasure, to experience the exhilaration of being high, and to share the excitement of using with others. In addition, often additional positive expectations are associated with use of the drug. For example, with cocaine, individuals expect greater energy, fluency, and creativity. They might desire reduced appetite that can lead to weight loss and greater productivity. For alcohol abusers, greater sociability, reduced anxiety, and relief from boredom are often prime motivations for early use. These positive consequences often mask the negative consequences of drug use. While these desired states may be based partly on real drug effects, substance users begin to distort the valence and importance of these effects over time. Cognitive distortions, in combination with life stressors (which ultimately increase as the person begins to neglect or avoid problems or responsibilities), lead to increased drug and alcohol use in pursuit of greater relief and/or pleasure, or a desire just to feel "normal." Such problem-distracting behaviors have been described as self-medicating, whereby the person seeks to reduce the distress and problems associated with using through avoidance behavior and by increasing the use. This increased drug and alcohol use leads to greater problems in the person's life and greater problem avoidance through greater and/or more frequent substance use.

In addition to the distorted thoughts that substances users hold regarding the positive effects of using, users have been found to have a significantly greater tendency to ruminate on irrational or automatic cognitive thoughts. These thoughts include beliefs such as: "I can't settle down without a few drinks," "I can't stand this feeling," and "people don't like me unless I am intoxicated." Such thoughts often relate to feelings of depression and anxiety, and the substance users seek the substance to reduce the distress of such thoughts. Drugs initially act as a distraction against these automatic and distressing thoughts and allow the person to forget the unpleasant ruminations. In this way, drugs appear to serve an adaptive function by allowing the person to "turn off" the ruminations temporarily. Unfortunately, this distraction is maladaptive over the long term, in that it prevents the individual from facing and dealing with problems in a healthy manner and creates more functional life problems. As the person becomes physiologically and psychologically dependent (addicted) upon the substance, the ability to change cognitive distortions without assistance becomes less and less likely. The goal of the cognitive therapist, then, becomes helping the client to recognize these distortions and to develop self-efficacy to actively address such thoughts in a more adaptive manner.

In Beck et al.'s [4] words, "self-efficacy refers to one's judgment about one's ability to deal competently with challenging or high-risk situations." Marlatt [25] explained that low levels of self-efficacy are associated with relapse, and high levels are associated with abstinence, with levels of self-efficacy increasing as a function of success. Outcome expectancies refer to an individual's anticipation about the effects of an addictive substance or activity. To the extent that a person expects a greater positive than negative outcome from drinking or using drugs, the person is likely to continue using. Attributions of causality refer to an individual's belief that drug use is attributable to internal or external factors. External attributions typically result in continued substance use since the individual perceives his/her use to be predestined and out of his/her control [25]. Finally, Marlatt [25] described the process of alcohol abuse, dependence, and relapse as a cognitive decision-making process, and proposed that substance use is a result of multiple decisions,

which may or may not lead to further substance use. He explained that although some decisions initially appear to be irrelevant to substance use, they nonetheless may result ultimately in an increased likelihood of relapse because of their incremental push toward higher-risk situations.

Persons with substance abuse problems remain very vulnerable to high-risk stimuli for a variety of reasons. Specifically, as people accommodate their drinking and drug habits, they begin to establish behavioral patterns in a variety of environmental contexts, which reinforce their intention to use as well as their experiential expectations. These environmental contexts become associated with the positive experiences of the drug over time and evolve into "triggers" that stimulate the user's desire for the drug. These triggers include both internal and external cues. Internal cues may include positive or negative emotions, pain, and/or frustration. External cues can include time of day (evening, night, etc.), place (at a friend's house, at a bar, etc.), or even other persons (friend, family, etc.). External cues also can include situations such as getting paid or working in an environment where alcohol is served (waitresses, bartenders, etc.). These triggers often activate clients' erroneous or irrational beliefs and lead them to make risky decisions that bring them closer to using. Such triggers must be identified and explored for underlying beliefs that shape physiological sensations linked to craving.

Beck found that underlying addictive beliefs result from dysfunctional core schemas in three areas: personal survival, autonomy, and freedom [4]. These addictive and dysfunctional thought patterns are experienced as taking over the individual's life, goals, and values, thereby leaving one's job and families as secondary priorities. The short-term gain of a "high" or reduction of internal tension is followed by long-term negative consequences and problems [4]. To break this pattern, clients need to learn to cope directly with problems associated with substance dependence, as well as to confront problems of everyday life in a more active and problem-solving manner.

The obstacle, unfortunately, in eliminating the substance use is the dysfunctional beliefs that the individual holds about the substance [4]. These beliefs range from the fear of the side effects of withdrawal to the belief that he/she cannot function without the substance. In addition, permission beliefs are common in addicted individuals. These are conceptualized as thoughts that allow or give permission to the individual to go ahead and use. These thoughts include such self-statements as "Just one drink won't hurt anything. Go ahead and have one." Changing these schemas, maladaptive beliefs, thought patterns, and associations with common triggers is at the core of the cognitive approach. Thoughts must be altered to achieve long-term behavioral change.

From this perspective, the primary tasks of treatment are to identify and challenge the maladaptive cognitions surrounding alcohol and drug use and replace them with more realistic and adaptive thoughts and beliefs in order to facilitate more adaptive behaviors of reduced use or abstinence. When more adaptive cognitive thinking has been restored, behavioral changes consistent with constructive thinking will follow. Figure 1 portrays the cognitive behavioral conceptualization of addiction.

Behavioral Model of Addiction

From the perspective of cognitive behavior theory, alcohol and drug dependence is viewed as learned behavior that is modeled, acquired, and reinforced through experience and learning. If alcohol or drugs provide or are perceived to provide certain desired results (e.g., good feelings, reduced tension, etc.) on repeated occasions, the person may learn that the substance leads to the desired outcome. In other words, the substances and positive feelings become strongly associated with each other. People typically begin using drugs or alcohol as a positive reinforcer in their lives—to celebrate a special occasion, as a reward, to reduce inhibitions, and/or to promote relaxation. In other words, initial use of drugs

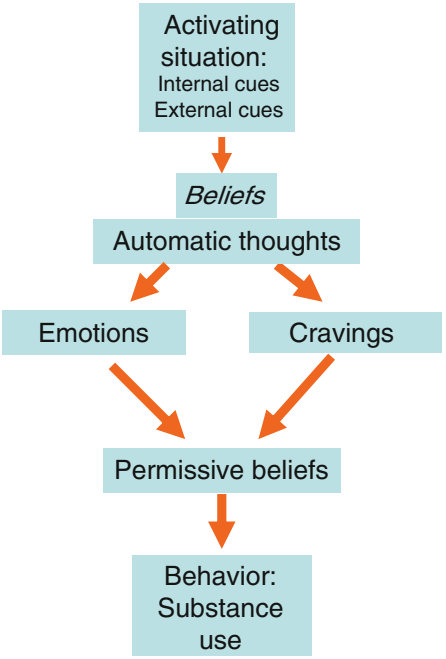

Fig. 1 Cognitive behavioral conceptualization of addiction

or alcohol is associated with its positive consequences, becoming the preferred way of achieving those results, particularly in the absence of other ways of meeting those desired ends. For some individuals, chronic use of drugs or alcohol can become a problem in cases where the substance is no longer used to feel good, but to avoid negative thoughts/feelings or to "feel normal" by reducing withdrawal symptoms. When this happens, substance use becomes a negative reinforcer instead of a positive reinforcer. From this perspective, the primary tasks of treatment are to: (1) identify the specific needs that alcohol and drugs are being used to meet, and (2) develop skills that provide alternative ways of meeting those needs. In so doing, this breaks the learned associations between using drugs and alcohol and both the positive and negative reinforcers.

Case Conceptualization

As is the case in the treatment of other disorders, cognitive behavioral therapy for substance use disorders involves a unique case conceptualization for each individual. This forms the basis for a strong collaborative relationship between client and therapist and effectively guides the content of the sessions. Through such collaboration, the client and therapist proceed to utilize specific, goal-oriented techniques tailored to the client's individualized needs and goals [15] while simultaneously enhancing the therapeutic alliance and collaborative nature of the work. Individuals also are taught to address and resolve naturally arising ambivalence about treatment to develop their motivation and progress toward their treatment goals. During therapy sessions, as well as through the use of self-help homework assignments, clients pursue solution-focused strategies that address the realities of recovery from addictive disorders. Psychotherapeutic innovations in relapse prevention often are implemented over the course of cognitive behavioral therapy for alcohol and other drug use disorders through identifying and reducing or learning to cope with high-risk use situations.

Case Example

> Jared is a 47-year-old man with a history of using alcohol since adolescence. He initially began using alcohol to reduce anxiety and facilitate dating experiences after he divorced his wife in his thirties. He began using alcohol as a way to enhance his ability to generate conversations in social situations. He works as an accountant and believes that others are very critical of him and see him as "stuffy" and "boring". He uses the alcohol mainly in the evenings when he goes out with business associates after work, although on weekends he has noticed that his drinking often starts early and continues all day long when he is visiting with friends or family.

When Jared first divorced, he was quite anxious about becoming more social and going out with peers again. He started consuming a few alcoholic beverages as a way to reduce his anxiety and lower his inhibitions about making interesting conversation. In this way, Jared's behavior was positively reinforced and he would later remember the situation as enjoyable and without anxiety. Over time, however, his

tolerance for alcohol increased and he required more drinks to achieve his perceived degree of calmness required to make good conversation. He started feeling more anxious, and even depressed, if he could not consume alcohol, particularly when meeting with others.

Figure 2 shows a cognitive behavioral case conceptualization of Jared's alcohol use.

Fig. 2 Cognitive behavioral conceptualization of Jared's case presentation

By understanding the relationships between Jared's dysfunctional thoughts and behavioral patterns, insight regarding the nature of his alcohol problems can be gained and an individualized treatment program can be developed to address his unique needs. Since cognitive behavioral therapy has evidence-based techniques as its foundation, techniques such as recognizing and challenging maladaptive automatic thoughts, cue exposure, drug refusal training, and methods for coping with craving are used to help an individual break his/her pattern of addiction. Furthermore, as addictive disorders often involve deficits in areas such as social skills, management of emotions, and tolerance of difficult emotions, individuals often pursue progress in these areas within cognitive behavioral therapy. For example:

> Jared was encouraged to keep a diary of his thoughts and behaviors to help him understand and recognize the connection between his maladaptive thoughts and subsequent emotions and behaviors. With this information, Jared and his therapist were able to challenge the veracity of his anxiety-provoking thoughts and substitute his critical interpretations with more rational views of his reality. In addition, Jared was taught relaxation techniques (progressive muscle relaxation and imagery) to help manage his anxiety, as well as learning to tolerate some anxiety in his interactions with others. Finally, Jared learned social skills regarding interactions with others, particularly in regard to his unrealistic expectation that he should always be the entertainer in a conversation. Through these interventions, Jared began to expose himself to social situations without reaching for a drink.

The rationale of cognitive behavioral therapy holds that substance abuse is learned and, therefore, it can be unlearned over time through the use of cognitive behavioral techniques. Understandably, a person with a substance use disorder faces many challenges and, potentially, many serious consequences. However, through cognitive behavioral therapy, such individuals can take part in an effective, flexible, and evidence-based therapy specifically tailored to the challenges involved in overcoming substance abuse or dependence and their individual needs. In doing so, they can avail themselves of a solution-focused approach to treatment embedded within a respectful and collaborative therapeutic relationship to facilitate recovery from addiction and the overall lifestyle change that they need.

Application of Cognitive Behavioral Therapy for Addiction

Understanding the theoretical underpinnings of cognitive and behavioral conceptualizations of addiction helps the therapist identify logical cognitive and behavioral targets for therapeutic intervention. This allows the therapist to individualize treatment for each client while remaining consistent with the general theoretical approach.

Therapy typically begins with an introduction to cognitive behavioral therapy and an opportunity for the client to disclose information about himself/herself. This is an important time for

self-disclosure and building of the therapeutic alliance, as well as the beginning of the process of case conceptualization of the client and his/her presenting issues. During these early meetings, initial treatment goals are discussed. These goals are set collaboratively, with the client having the final say in the establishment of his/her goals. Abstinence is encouraged but may not be an absolute requirement. Treatment goals may involve substance use behaviors as well as other aspects of clients' lives, such as improved relationships, mood states, and level of functioning. Therapists work with clients to ensure that these goals are attainable (the client can produce them), realistic (the environment can produce them), and appropriate (they are related to the designated work to be done in therapy). Goals are revisited and revised as needed throughout treatment, based primarily upon the client's progress, which is assessed regularly.

The therapeutic process itself includes meeting regularly (usually for an hour weekly) for at least 3–6 months or longer if necessitated by continuation of symptoms or development of additional problems. Within each session, material is presented and reviewed regarding specific areas of concentration that relate to substance use disorders as well as more general issues related to emotional dysfunction. Session material may be presented orally and in writing (e.g., using written materials, flip charts, or a wipe-off board), and clients are encouraged to take notes, as visual learning significantly augments oral presentation of material and helps clients retain more information and stay involved in the session. There are issues that must be covered for the majority of clients receiving cognitive behavioral therapy, including: coping with cravings, thinking about using, problem solving, refusal skills, dealing with lapses, and relapse prevention. In addition, there often are additional issues that need to be addressed, such as assertiveness training, anger management, and recognizing and managing negative moods. These issues are addressed on an individual basis, but in a standardized cognitive behavioral conceptualization. Thus, evidence-based treatment is tailored to the individual and provided in a consistent manner.

Weekly assignments or "homework" are assigned at each session and reviewed at the following session. The homework is a major part of cognitive behavioral therapy and ensures that clients are actively incorporating skills and techniques presented and reviewed in sessions in real life. Clients are encouraged to complete the homework, preferably in writing, and always through real-world practice. Research demonstrates that those who complete homework assignments more regularly and consistently attain a better outcome from therapy, particularly for those higher in readiness to change [7, 11]. Therefore, homework completion is strongly encouraged. Compliance with homework can be increased in many ways: (1) through explaining the reasoning for the assignment and why and how it is theorized to help the client; (2) reviewing in session how to complete the homework; (3) assessing the client's motivation and ability to complete the homework by asking the client how likely he/she is to complete it and identifying any potential obstacles for completion, and then (4) clarifying ambivalence about homework and planning for obstacles, as well as (5) setting realistic expectations for the length of time and level of difficulty of the homework.

If a client is regularly non-compliant with homework, efforts are made to explore and change this therapy-interfering behavior. Specific techniques are employed to improve homework compliance, including making homework assignments specific and clear and explaining the rationale of the homework as well as the potential benefits of completing the assignment. As stated, setting realistic expectations for the homework is also important. Most assignments take less than 15 min to complete, and this needs to be made explicit to the client or else the client may overestimate the time needed to complete the assignment and may not even attempt it. Behavioral experiments need to be clearly defined and a rationale provided for their use, along with expected benefits. In addition, the client's level of motivation and commitment

to completing the assignments can be assessed prior to the end of the session, so that realistic expectations are made regarding the homework. For instance, if a client understands the rationale of the homework and knows how to complete it and how long it will take, but still states that he/she does not want to do it and does not think that he/she is likely to complete it, then both the therapist and client understand that the homework will most likely not be completed unless the client's motivation changes. Some authors argue that homework non-compliance, to some degree, is an inevitable feature of cognitive behavioral therapy and, when effectively addressed, can yield some of the greatest opportunities for therapeutic change [18]. To that end, it is an expected and important component of cognitive behavioral therapy, and both clients and clinicians are wise to anticipate and prepare effectively for non-compliance issues.

General Components of Manualized Cognitive Behavioral Therapy for Addiction

Cognitive behavioral therapy is often provided in a standard, manualized format for conceptualizing drinking and drug abuse problems and designing interventions that focus on developing healthier coping skills. It is delivered in a collaborative motivational interviewing style, which facilitates the individual's progress through stages of change and therapeutic recovery. Manualized cognitive behavioral therapy is based on the early works of Beck et al. [4], Ellis and Velten [10], and the later works of Marlatt et al. [25, 26]. These works eventually were condensed into the National Institute on Alcohol Abuse and Alcoholism's treatment protocol used in multi-site national addiction studies, including MATCH and COMBINE [16]. While there have been many variations and therapy subtypes that fall under the collective umbrella of cognitive behavioral therapy, this protocol specifically outlines standardized session themes and activities that have been shown to bring about positive outcomes (reductions in drinking or drug use) and ensures systematic, effective, reliable, and replicable administration of treatment to individuals. The structure of cognitive behavioral therapy discussion topics and session activities for substance abuse has been useful in promoting effective management of session time, focus on client thoughts, and development of more effective coping strategies [44]. It should be noted, however, that while this manualized approach has proven helpful and represents one of the most common cognitive behavioral frameworks for treating substance abuse and dependence, therapists have considerable flexibility in matching unique client strengths and weaknesses to specific cognitive behavioral interventions within the weekly theme (such as role plays, review of take-home assignments, construction of agenda, etc.). As such, the session is approached in a collaborative manner that tolerates modifications to planned activities as necessary. Yet, even with these potential changes and exploration of therapy-related themes, an overall commitment to therapeutic setting and following a set agenda is recommended to provide useful structure to the client problem-solving and coping resolution process [44].

The following recommendations are based on results from the University of Virginia Center for Addiction Research and Education clinic, which is part of the Department of Psychiatry and Neurobehavioral Sciences. Like the National Institute on Alcohol Abuse and Alcoholism's cognitive behavioral therapy manual, our clinic also administers cognitive behavioral therapy over 12 sessions in either group or individual format. There are seven core sessions, four elective sessions, and a termination session. Specific material is covered in each session as tolerated and has been designed and studied for optimum effectiveness.

Contraindications

There are some contraindications for use of cognitive behavioral therapy in populations

with substance use disorders. First of all, this approach requires a minimum level of cognitive functioning. Specifically, abstract reasoning is deemed necessary for clients to understand and process session material and apply this knowledge to changing their behavior patterns and coping skills. Clients with serious psychopathology (such as manic episodes, psychosis, or acute intoxication) or low IQ/cognitive impairment [28] are likely to have great difficulty understanding concepts such as cues or automatic thoughts and/or systematically adopting new coping skills. Furthermore, clients with a diffuse set of maladaptive thoughts and behaviors may require a greater number of sessions to achieve abstinence in comparison with those with specific, more circumscribed maladaptive symptoms. Finally, cognitive behavioral therapy, although person-centered, is also directive in nature, with the therapist playing a major role in directing the focus and content of each session. As such, some clients may respond with resistance to this approach or demonstrate slow progress in therapy. Thus, it is important to be aware of the stage of change for your client and consider integrating a motivational interviewing style into your work if it is clear that the client is unwilling to admit that they have an addiction problem or if your client loses motivation at any time during treatment. If clients report that they do not wish to change their behavior, cognitive behavioral strategies, such as listing the pros and cons of using and quitting in the form of a decisional matrix (see Fig. 3), clarifying values, examining consequences of use, and challenging expectancy beliefs about use can successfully be utilized to clarify ambivalence and help refocus the therapeutic work on change.

BOX 1: Good things about drinking:	BOX 4: Good things about changing my drinking:
BOX 2: Bad things about drinking:	BOX 3: Bad things about changing my drinking:

Fig. 3 Decisional matrix or advantages-disadvantages analysis

Format/Length/Setting

Clients are seen either one-on-one or in a small group setting (2–5 individuals per group) in a private, confidential clinic for 12 sessions. Each individual session lasts approximately 60 min, and group sessions last approximately 90 min, although some sessions can be extended or reduced based on client needs. During the first session, the therapist devotes the time to develop a strong therapeutic alliance with the client, approaching the client in a friendly and neutral (i.e., not extremely dominant, not extremely submissive) interpersonal manner. In our clinic, clients are given a questionnaire every three sessions that assesses their interpersonal impression of the therapist and their working relationship. Research has shown that therapists who are able to maintain friendly and neutral interactions best facilitate client outcomes [16]. During each session, the therapist checks in with the client and reviews his/her progress over the preceding week. Then, the therapist reviews the take-home assignment from the previous week, highlights achievements, and determines the cause of skill failures. Next, the therapist and the client create an agenda for the session duration that includes exploration of the weekly theme (see list of themes below). The remainder of the session explores new skill acquisition, and, together, the therapist and the client determine new practice activities and goals for the subsequent week.

Expectations of Therapist for Client

It is important for the therapist to discuss treatment expectations on the first day of therapy.

Clients are expected to attend therapy regularly, on time, and sober. They are expected to report about their addiction honestly and to complete practice assignments before returning to therapy.

Functional Analysis

At the beginning, as well as throughout addiction treatment, clients and therapists should use monitoring records and functional analysis tools as a way to conceptualize clients' use and problems. In Table 1, clients are asked to notice and record the situations in which they crave alcohol or drugs and record the severity of the craving and their subsequent behavior. By doing so, people increasingly become aware of the specific triggers in their environment and the variations in their cravings, as well as when they give in to their cravings. In Table 2, a functional analysis table, clients are asked to track the triggers (What set me up to use?), thoughts and feelings (What was I thinking and feeling?), behavior (What did I do?), and positive (What positive thing happened?) and negative (What negative thing happened?) consequences of their substance use. Clients should be instructed to write down every time they think about drinking or using a drug. It is important that clients record the time and day whenever they record an entry in this log to help with understanding behavioral patterns. In the "Triggers" column, clients should record who they are with, what they are doing, details about the situation, etc., to give a full picture of what was happening at the time a craving or urge to use or drink began. In the next column, they are to record specific thoughts and feelings that provoked the urge to use. In the middle "Behavior" column, clients should record how they were responding to the situations. Did they call a friend? Watch TV? Or pop open a can of beer? They should record all of this information here. In the last two columns, they should record the consequences, both positive and negative, of their behavior. Clients should bring this record with them to their next appointment for further review. These exercises should continue throughout treatment, particularly as clients become more skilled at choosing more adaptive coping strategies.

Table 1 Self-monitoring of cravings

Event/situation	Intensity of cravings (0–100)	Behavior

Skills Training

Clients also are taught pro-social adaptive coping skills to substitute maladaptive ways of coping. Specifically, clients are taught to set realistic self-goals, self-monitor thoughts and behaviors, challenge irrational thoughts, delay reacting to cravings, pursue distractions, confront problems directly, problem-solve actively, talk to others, avoid triggers, and reduce stress. These skills are assessed at baseline and tracked throughout treatment. Clients are taught to practice strategies between therapy sessions and to treat drinking opportunities as "experiments" for learning to implement new skills in the face of triggers to use.

Manualized Sessions—Sequence of Therapy Topics

Session 1: Introduction—Set goals, review therapy expectations, and teach self-monitoring of triggers, thoughts, feelings, behaviors, and positive and negative consequences; also determine clients' drinking/using patterns. Clients are given a manual to reinforce weekly topics.

Session 2: Coping with Cravings—Explore a variety of active coping strategies to reduce cravings, such as: distraction, delaying use, pursuing social support, avoiding triggers, deep breathing/progressive muscle relaxation, imagery/urge surfing, and recalling negative consequences/planning ahead.

Session 3: Thinking about Using—Review thoughts common to persons with addiction

Table 2 Functional analysis: self-monitoring record

Event/ Situation (Day & time) –What was I doing? –Who was I with? –Where was I?	*TRIGGERS (antecedents) What set me up to drink/use?*			*STOP for a second!!!!*		*(Consequences of behavior)*	
	Thoughts/images	*Feelings*	*Intensity of cravings, desire to drink/use (0–100)*	*Alternative thoughts* (try to challenge your automatic thoughts about drinking)	*Behavior*	*Positive consequences (short-term)*	*Negative consequences (long-term)*
3/3/08, 9 P.M. At home with girlfriend, arguing	I can't stand this; I need a drink	Frustrated, upset, angry	95	I might want a drink, but I do not really need it; drinking is not really going to make any difference	Got away, drank 4 beers	Calmed down	Girlfriend got even more mad

problems, such as: nostalgia, disillusionment, frustration, all-or-none thinking, self-doubt, feeling uncomfortable, helplessness, wanting to escape, crisis response, and testing control. Also consider how clients' expectations regarding how substance impacts thoughts/feelings affect behavior.

Session 4: Problem Solving—Present a model for solving problems in an active way that considers generating a list of alternatives and evaluating pros and cons and the likelihood of positive outcomes, given the potential to resolve.

Session 5: Drink Refusal Skills—Consider ways to avoid giving in to requests by peers to use. Teach client to avoid these high-risk situations to the extent possible and, when unexpectedly exposed to triggers, to rely upon a predetermined plan to avoid use.

Session 6: Dealing with a Lapse—Describe how clients can lapse from time to time and how such lapses need not derail progress. Give strategies to help client return to recovery and refocus on treatment goals.

Session 7: Seemingly Irrelevant Decisions—Examine how small, seemingly irrelevant decisions that do not appear to affect drinking/use decisions can put a person at risk for relapse. Examine ways to prevent relapse through the deliberate choice of low-risk behavioral choices.

Termination/Maintenance/Relapse Prevention—Review client progress over the course of therapy, re-examine client goals, review briefly all material, determine client skill achievements, recommend further practice with some skills, and make recommendations for follow-up.

Example of Skill Acquisition

Jared completed a coping strategy questionnaire at baseline, indicating that he was relatively passive in dealing with his stress and anxiety and that he generally gave in to cravings when they developed. To collect more information about Jared's coping skills and to help Jared see a connection between his coping strategies and behaviors, he was assigned to complete a functional analysis diary. Jared was initially reluctant to keep a diary regarding his daily drinking habits because he felt that he did not have any triggers and that he "just liked the taste" and "enjoyed a few drinks" with others. However, after reviewing his first week with his therapist and attempting to complete the diary retrospectively, Jared became aware that much of his drinking related to feelings of inadequacy and loneliness. Jared found that these feelings were reinforced each night with different people in that he was able to stop his feelings of anxiety by drinking "a few" beers. Unfortunately, the next day Jared would always feel tired and disappointed by how many beers he had in fact drunk. He also worried about what he may have said in his "entertaining" conversations, as he often could not even remember much of the night beyond his second drink. In this way, the therapist was able to challenge his expectation that drinking made him entertaining and also help him to realize that drinking did not cure his anxiety over the long term; it only served to blunt temporarily all feelings. It also was determined by reviewing the diary that Jared was going to nightly events that all involved opportunities to consume alcohol. With his therapist, he was able to recall healthier activities such as playing tennis or volunteering with a local charity. These activities helped to remove some of Jared's temptation to drink, as well as distracting him for several hours in the evening, a time when his cravings were the most intense. Through the activities, Jared learned how to cultivate a few new friendships without alcohol, which helped provide support for Jared when he was feeling stressed. Over time, Jared was able to look forward to not going to the bars with his old friends; he then felt encouraged that he could tolerate some anxiety around others and developed pride that he did not need alcohol to endure his stress. Jared continued to keep a journal of his thoughts and behaviors throughout therapy and became more aware of the great importance of monitoring his triggers, particularly when his problem seemed too overwhelming to overcome. Jared completed a post-therapy coping skills questionnaire and was able to identify several strategies that he found to be helpful and effective for dealing with his cravings.

Research Support for Cognitive Behavioral Therapy in Addiction Literature

Cognitive behavioral therapy has been demonstrated to facilitate effectively improvement for

a number of mainstream substance abuse disorders. Reductions in drinking and drug use were seen mostly when clients were motivated to change and possessed at least a low average intelligence level needed to process and relate thought patterns with behavioral reactions [27]. Treatment gains with respect to stimulant use have been well established, with evidence that gains persist and grow over periods of 6–12 months [5, 37].

Review of Cognitive Behavioral Therapy for Stimulant Drugs

Cocaine

Approximately 1.5 million adults use cocaine in the United States, often leading to problems in daily functioning and, ultimately, cocaine dependence. Cognitive behavioral therapy has been demonstrated to be useful for managing and resolving the problems associated with drug abuse and dependence. Marlatt and Gordon [26] introduced cognitive behavioral interventions as an effective approach that can alleviate psychological distress associated with repetitive physical and psychological habits arising from specific, reinforcing cognitive and behavioral patterns. Additional work by Carroll et al. [5] extended Marlatt and Gordon's work to include a specific, manualized protocol (see the National Institute on Drug Abuse–endorsed format for cognitive behavioral therapy sessions above) for treating cocaine disorders. Subsequent researchers studying the effectiveness of cognitive behavioral therapy protocols typically have adopted this manual.

A group of clients receiving cognitive behavioral therapy for cocaine dependence was compared with a similar group receiving contingency management treatment (in which the client gets a "reward" contingent on reduced drug use) [37]. Individuals in this study received three sessions of 90-min group cognitive behavioral therapy weekly, or three 2- to 5-min contingency management sessions (including receipt of voucher, if warranted), for a total of 16 weeks. Individuals demonstrated efficacious results 1 year after treatment was terminated, although these differences did not emerge until after treatment had ended [5, 37]. Although contingency management clients reported less use during the study, those who had received cognitive behavioral therapy did significantly better than contingency management clients at distant follow-up (6 months and 1 year later) [37]. In another comparison study of cognitive behavioral therapy versus interpersonal therapy and/or disulfiram administration, cognitive behavioral therapy was found to be at least as effective as these other therapies [6, 7].

Trujols et al. [43] undertook the painstaking task of evaluating specific cognitive behavioral therapy styles and techniques to determine the best practices within this model. These cognitive and/or behavioral therapy interventions included contingency management with vouchers, cue exposure treatment, relapse prevention therapy, and motivational interviewing. This review highlighted several strengths and weaknesses within these interventions. Contingency management interventions were found to present economic limitations, with questionable results regarding the maintenance of drug reduction outcomes. In contrast, cue exposure treatment (exposing individuals to cognitive cues that promoted drug use) resulted in definite treatment gains, including greater client retention and increased negative urine drug screens [7], although Carroll et al. [7] noted that cravings initiated by cues outside the scope of clinical practice tended to perpetuate drug use. Researchers examined the role of at-home practice of cue exposure over 12 weeks of cognitive behavioral therapy and found that these reinforcing assignments resulted in higher program retention rates and thus kept clients committed to treatment [7, 11].

Schneider and Khantzian [39] further evaluated specific beneficial cognitive behavioral therapy mechanisms in an attempt to identify cocaine-dependent populations that could best benefit from cognitive behavioral therapy. They found that individuals' level of readiness for change differentiated treatment outcomes. They cautioned therapists to elicit and consider a

client's stage of change prior to initiating any cognitive behavioral therapy technique, as some techniques can be contraindicated depending on where the client is in the cognitive process of making a change in his/her drug-use behavior [24]. Trujols et al. [43] concluded by noting that careful tailoring of cognitive behavioral therapy to the cocaine-dependent individual's needs in conjunction with other empirically derived biological approaches (i.e., pharmacotherapy) may ultimately equip these individuals with the best tools to overcome their addictive behaviors. The ability to choose appropriate homework tasks, therefore, may represent an important mechanism by which cocaine dependence might be attenuated. Additionally, affective functioning (i.e., history of depression or anxiety) and deficits in abstract reasoning have been cited as important mediators in promoting superior cognitive behavioral therapy outcomes [28].

Knapp et al. [19] evaluated specific components of various substance abuse therapies to identify best-practice strategies in counseling substance-abusing or substance-dependent individuals. They identified five components as integral to the cognitive behavioral therapy process: (1) client-therapist collaboration, (2) case conceptualization, (3) structure, (4) socialization to the cognitive model, and (5) the use of cognitive and behavioral techniques [19]. They also described a number of supplementary methods involved in cognitive behavioral approaches including "Socratic questioning", analysis of advantages and disadvantages of use, monitoring of drug-related beliefs, activity monitoring and scheduling, behavioral experiments, and role playing. When 26 comparison studies (i.e., cognitive behavioral therapy versus another psychosocial modality) were examined, mixed outcomes were reported. Although cognitive behavioral therapy emerged as a better therapy in approximately one-third of these studies, the loose conceptualizations and definitions used to characterize the cognitive behavioral therapy studies in this review likely obscured true differentiation of cognitive behavioral therapy versus other therapy effects. While additional research is warranted to understand better the precise mechanisms of action for effective cognitive behavioral therapy, available research to date confirms its potential value as an effective treatment approach for substance disorders.

Methamphetamines

The National Survey on Drug Use and Health reports that an estimated 10.4 million people are afflicted with problems associated with methamphetamine abuse or dependence. Despite multiple efforts to reduce access and prevent experimentation, methamphetamine abuse and dependence remain increasingly difficult to treat once an individual is introduced to this drug. While several psychosocial approaches have been explored and evaluated, cognitive behavioral therapy has emerged as a superior option in reducing or arresting drug consumption [36].

Specifically, Rawson et al. [36] looked at several components of a "Matrix model" approach that was developed to impact the use of methamphetamines in dependent individuals. These components were derived from the cognitive behavioral therapy literature and included detailed information about the effects of stimulants, family education, 12-step program participation, and positive reinforcement for behavioral change and treatment compliance. Clients received 16 weeks (36 sessions) of cognitive behavioral therapy in a group format along with family education, social support, and individual counseling. While it is difficult to tease out the effect that additional therapies may have had on clients, Rawson et al. [36] concluded that cognitive behavioral therapy techniques produced greater treatment adherence and greater abstinence than did various community treatment protocols.

In a randomized controlled trial of cognitive behavioral therapy for regular amphetamine users, Baker et al. [1] reported on the feasibility of a brief (four-session) dose of cognitive behavioral therapy. They found that cognitive behavioral therapy was moderately effective among regular methamphetamine users in promoting abstinence, but cautioned that their

results were preliminary and more research was needed. Baker et al. replicated these findings by examining the role of motivational interviewing with cognitive behavioral therapy and found that those clients who received at least two treatment sessions were most likely to increase abstinence compared with controls [1]. In addition, reductions in depression also were reported among cognitive behavioral therapy treatment groups. Further, these reductions in methamphetamine use and depression symptomatology extended beyond predicted outcomes and were associated with stage of change, polydrug use, injection use, risk-taking behavior, criminal activity level, and psychiatric distress.

Baker et al. [1] recommended use of a "stepped-care" approach whereby the intervention starts with a structured assessment session and self-help material, followed by regular cognitive behavioral therapy sessions. The amount and dose of cognitive behavioral therapy is commensurate with the presentation of the clients' level of pathology (e.g., two sessions for regular users and additional sessions for those with moderate-to-severe levels of depression). Pharmacotherapy and/or longer-term cognitive behavioral therapy was recommended for non-responders [1]. Lee and Rawson [20], however, emphasized the limited effectiveness of medications for methamphetamine users and acknowledged psychological interventions as the treatment of choice. These researchers reviewed randomized trials of cognitive behavioral therapy and found reductions in methamphetamine abuse, as well as other positive changes, even when treatment was limited to 2–4 sessions. The longevity of these effects, however, is not yet known. As such, cognitive behavioral therapy, even in its briefer adaptations, appears to be effective in reducing methamphetamine use.

Caffeine

Despite the widespread availability and cultural norm for caffeinated beverage consumption, little research exists examining the negative consequences of excessive and harmful caffeine consumption as well as consideration of potential interventions that might reduce these behaviors. Ogawa and Ueki [33] advocated that caffeine manufacturers should clearly indicate caffeine content, specify a low-risk and safe amount of caffeine consumption, and state clearly that large quantities lead to long-term health risks. Through case studies, Ogawa and Ueki [33] revealed the nature of caffeine dependence and requested further study for interventions that can impact the nature of these behaviors. As caffeine dependence resembles other psychostimulant addiction (although it is notably less risky), cognitive behavioral therapy represents a promising psychosocial approach by which to reduce excessive caffeine consumption. More research is needed to confirm this possibility.

Nicotine

Cognitive behavioral therapy has been used to help smokers reduce or quit smoking with mixed success. In a study of outpatient smokers receiving cognitive behavioral therapy plus nicotine replacement therapy or placebo for 2 h weekly for 5 weeks, 28% of those clients receiving cognitive behavioral therapy became abstinent from smoking and maintained that abstinence at 12 months [38]. In a group of cancer patients, although cognitive behavioral therapy reduced smoking behavior, it did no better than a basic health education condition in achieving smoking abstinence [40]. Sykes and Marks [41] developed a self-help cognitive behavioral therapy program for disadvantaged smokers and reported abstinence or reduced consumption in clients who were provided with cognitive behavioral therapy tools.

Recent trends in cognitive behavioral therapy research and smoking have considered the role of depression in maintaining smoking abstinence. Hall et al. [13] randomized individuals in a $2 \times 2 \times 2$ design whereby recently quitting smokers had a chance to receive cognitive behavioral therapy or no cognitive behavioral therapy and an antidepressant (nortriptyline or

placebo). Analysis of the resultant data demonstrated that cognitive behavioral therapy was superior to other treatments for those reporting depressed mood but not for those with normal mood [13]. There was a non-significant trend favoring cognitive behavioral therapy in achieving abstinence, but cognitive behavioral therapy did not enhance smokers' compensatory coping skills. Discussion focuses currently on the need to examine a wide range of possible mediating variables in future research on cognitive behavioral therapy for smoking cessation [42]. Several clinical trials have tested whether cognitive behavioral therapy for smoking cessation would especially benefit depression-vulnerable smokers, with mixed results [12].

Review of Treatment for Depressant Drugs

Alcohol

Cognitive behavioral therapy for the treatment of alcohol dependence likely represents one of the most studied treatments for the reduction or cessation of compulsive alcohol drinking. These cognitive behavioral therapy treatments have varied in length, modality (groups, individuals, or couples), content, treatment setting, and the addition of coping skills training [31]. Despite these differences, all cognitive behavioral therapy approaches focus on deficits in coping with stress and alcohol cues that maintain excessive drinking. Within these approaches, several strategies are explained: identification of situations likely to elicit inadequate coping, the use of instruction, therapist modeling, role playing, and behavioral rehearsal to enhance coping skills. Through repeated instruction and therapist support, clients begin to manage exposure to alcohol-related stimuli and handle stressful situations in more adaptive ways. Across 21 studies using cognitive behavioral therapy as a component of a larger treatment program, Longabaugh and Morgenstern [23] found that this treatment approach was more effective in reducing drinking than comparison treatment 71% of the time. Indeed, Miller and Wilbourne [31] documented significant and maintained improvements for alcohol-dependent individuals receiving cognitive behavioral therapy. Subsequent study replication by Kavanagh et al. [17] that compared additional cue exposure strategies with traditional cognitive behavioral therapy techniques (listed above), while demonstrating efficacy, did not further enhance the strength of these findings. In comparing cognitive behavioral strategies with other treatments with strong theoretical underpinnings, Longabaugh and Morgenstern [23] found equal effectiveness in 80% of cases.

In a more comprehensive review of behavioral and cognitive behavioral treatments for alcoholism, Kadden [15] explored several topics used within a cognitive behavioral therapy framework in an effort to identify inconsistencies in the literature and target research needs. In this paper, Kadden considered cue exposure, contingency management, community reinforcement, coping skills training, behavioral marital therapy, and client-treatment matching. Following an extensive review of the literature, Kadden [15] reported that coping skills training was ranked highest for effectiveness in treating alcoholism. The other approaches revealed mixed evidence in terms of efficacy and clear mechanism of action. Although coping skills training raised some concerns and limitations compared with other treatments, it increased consistently treatment effectiveness when used in conjunction with other cognitive behavioral therapy strategies. Kadden concluded by suggesting that treatment matching to individuals' characteristics may maximize the effectiveness of these interventions despite the lack of robust matching effects (in the absence of severe psychopathology) reported in previous publications of Project MATCH [15, 35].

In an attempt to understand better how mechanisms of action within cognitive behavioral therapy account for favorable outcomes, Long et al. [21] identified five promising variables in predicting treatment success: higher self-efficacy

in positive social situations, greater treatment program involvement, a lower perception of staff control, a greater perception of treatment as helpful, and a reduction in psychological symptoms during treatment. As such, the authors suggested promoting clients' confidence and the perception of helpfulness in conjunction with skill-based relapse prevention strategies [21]. Furthermore, social exchange models of intimate relationships also play a role in recovery, and therapy targeting the social functioning in an alcohol-dependent individual leads to improved relationship satisfaction, marital stability, and decreased domestic violence [32]. These cognitive behavioral therapy strategies promote better drinking outcomes associated with partner reinforcement of abstinence. Longabaugh et al. [22] cautioned, however, that more research is needed to confirm these preliminary findings.

Finally, in a more basic focus on social interactions, Meier et al. [30] considered the role of the therapeutic alliance in treating alcohol dependence. The research thus far has indicated mixed results. While Meier et al. found that early therapeutic alliance predicts engagement and retention in drug treatment, Dundon et al. [9] could only confirm these findings with non-cognitive behavioral therapy interventions. In Dundon et al.'s study, three groups were examined (a medication-only group, a medication plus medication-adherence focus group, and a medication plus cognitive behavioral therapy group); yet only the medication-only and medication plus adherence groups were associated with positive outcomes (number of sessions attended and/or days abstinent). It should be noted, however, that Dundon et al. [9] studied individuals interested in receiving pharmacotherapy, which may select for a different subject population from those who might benefit from the therapeutic alliance developed through psychotherapy alone. Also, Dundon et al. [9] did not follow the role of changes in the therapeutic alliance over time, which can take time to develop and is likely to affect client behavior. More research is needed in this area to better inform cognitive behavioral therapy for alcohol dependence [9].

Benzodiazepines

A paucity of literature exists regarding benzodiazepine abuse or dependence and cognitive behavioral therapy. The majority of publications focus on pharmacotherapeutic dosing or medication changes with close monitoring as a means of reducing benzodiazepine misuse problems. Future research should consider how psychosocial interventions can enhance these efforts. Given the success of cognitive behavioral therapy with similar substances in this class, cognitive behavioral therapy would likely provide additional means by which to ameliorate benzodiazepine dependence.

Barbiturates

The current state of barbiturate dependence and cognitive behavioral therapy has not been studied. Most people with barbiturate abuse or dependence problems are treated with pharmacotherapeutic dosing and medication strategies without psychosocial approaches. Cognitive behavioral therapy would likely add benefits to these treatments.

Hypnotics

A review of hypnotics and cognitive behavioral therapy revealed a lack of cognitive behavioral therapy interventions in altering hypnotic abuse or dependence behaviors. As cognitive behavioral therapy has been found to be efficacious in treating other depressant drug dependence, additional research in this area is warranted.

Future Directions

In our clinic, our primary goals are to keep our clients safe and to keep them returning for therapy. If these goals cannot be met, no other goals can be achieved. As such, there are

times when a cognitive behavioral therapy protocol must be adapted to meet these specific goals. Anecdotally, we have found that some sessions must run longer or shorter than stated in the protocol to maintain these goals. In addition, there are times when one session must be reviewed a second time, or when a scheduled session's content must be truncated to address other issues that are more pressing in the client's life. Further research that tracks these cognitive behavioral therapy modifications and how they impact clients' outcomes is needed.

Additionally, future research needs to focus on the development of an effective working alliance between therapist and client. While past research has considered the working alliance at the first session, more information is needed regarding how the therapist/client relationship changes over time, how to augment these changes, and how best to achieve an effective relationship that promotes changes in clients' substance use.

Another area of research potential is treating substance-abusing individuals with co-occurring disorders (depression, anxiety, etc.). Thus far, cognitive behavioral therapy emerges as an effective adjunct for reducing addictive behaviors in depressed individuals when depression is targeted; yet additional research is needed to apply best these findings to the diverse populations who suffer from drug dependence. To begin with, additional research is needed to determine the specific mechanisms of action at play in cognitive behavioral therapy that best promote the reduction of drug-seeking and drug-using behaviors. With the finding that individuals with substance abuse problems also report high rates of depression, cognitive behavioral therapy strategies that specifically identify and target the unique thought patterns and behaviors of these individuals hold much promise. In fact, research that considers and targets all *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition disorders in substance-abusing individuals should be examined using cognitive behavioral therapy as a potential therapeutic tool that can likely address both disorders in a way that medications and/or educational sessions cannot. Research that considers matching specific cognitive behavioral therapy strategies with specific Axis I disorders will likely prove very promising in addressing the unique experiences of substance abusers and comorbid disorders.

Another area of promising research considers the role of computers and electronic devices in promoting reduced addictive behaviors and/or reinforcing abstinence. Multiple Web sites have emerged that provide education and a chance to network with other addicts or specialists who can provide help during non-work hours when cravings and high-risk behaviors are more likely to take place. Carroll et al. [8] recently explored the use of a computer-assisted delivery of cognitive behavioral therapy for addiction and noted this agent to be an effective adjunct to standardized outpatient treatment for substance dependence. More research is needed to expand on this likely successful variation of traditional cognitive behavioral therapy. Through exploration of these potential adjuncts to traditional cognitive behavioral therapy, treatment of substance dependence will continue to improve and impact the lives of those who struggle with substance dependence.

Despite the demonstrated effectiveness of cognitive behavioral therapy for the treatment of substance abuse or dependence, there is still much about this therapy that remains unknown. Researchers continue to try to define specific dose-effect relationships by condensing treatment durations and identifying clients who are most suitable to benefit from fewer sessions. Research efforts need to compare directly the standard cognitive behavioral therapy with these briefer truncated cognitive behavioral interventions. In addition, the specific therapeutic mechanism(s) of change or action for cognitive behavioral therapy must still be identified [23]. Greater understanding of the impact of therapist variables on identified mechanism(s) of change also may be helpful in facilitating the development of efficacious, condensed forms of cognitive behavioral therapy [14].

Kadden [15] has suggested that the study of cognitive behavioral therapy for relapse prevention may be advanced by identifying the most

efficacious approaches to cognitive behavioral therapy, exploration of mediating factors, and identifying clients who are most likely to benefit from specific cognitive behavioral therapy strategies. Important elements of cognitive behavioral therapy selected for further investigation include cue exposure (i.e., factors that mediate or moderate cue reactivity), contingency management (i.e., optimal schedules for reinforcing abstinence and other supportive behaviors), community reinforcement (i.e., elements that are critical to maintaining outcomes), coping skills training (i.e., relative effectiveness of the various skills-training components, optimal combinations of them for different types of clients, and the optimal number and duration of treatment), the role of personality, interpersonal and environmental factors, and a re-examination of client-treatment matching. McKee et al. [29] has questioned further how future treatment might better motivate clients for successful cognitive behavioral therapy. Through greater understanding of the components of cognitive behavioral therapy and the interactions among client, therapist, and intervention factors in substance abuse treatment, best-practice strategies can be developed to provide briefer, more effective cognitive behavioral therapy to clients with limited resources and/or need, for more immediate outcomes.

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Community Reinforcement Approach and Contingency Management Therapies

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Contents

Introduction

This chapter first describes the rationale behind and evidence in support of the efficacy of community reinforcement approach therapy. This treatment is most often applied to alcohol-dependent individuals, but there have also been a few studies examining its effects among individuals with illicit drug use disorders. Most typically, when applied to illicit substance abusers, community reinforcement approach therapy is combined with another behavioral therapy—contingency management. The second section of this chapter details the theoretical basis and evidence of efficacy for contingency management interventions. The chapter concludes by discussing issues related to the cost-effectiveness of these interventions and their adoption in practice settings.

Community Reinforcement Approach Therapy

Community reinforcement approach therapy was first developed over 30 years ago by Hunt and Azrin [21]. They described the community reinforcement approach as a comprehensive bio-psychosocial treatment for alcohol dependence. It is based on the theoretical view that individuals use substances for their positive, reinforcing effects and that the relative lack of alternative, non-drug reinforcers maintains dependence. The development of alternative reinforcing activities that are incompatible with drug use is central to the community reinforcement approach.

The community reinforcement approach begins with a detailed functional analysis concerning the triggers and consequences of drug use behaviors. An example of a functional analysis is presented in Table 1. The treatment package itself includes a number of aspects: sobriety sampling, monitored disulfiram consumption (when appropriate), behavioral skills training, social and recreational counseling, behavioral

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_37,

Table 1 Sample functional analysis form for use in community reinforcement approach therapy

Day/time	Situation	Thoughts/ feelings	Substance use? What and how much?	Positive consequences	Negative consequences
Mon pm	Argument with neighbor	Angry!	Alcohol 9–10 beers	Forgot about neighbor for a while	Neighbor called cops because of noise.
Tues pm	Friend offered me a hit.	Terrible craving, really wanted to use.	Cocaine. 1/2 gram	Fun to be with old friend. Felt good.	Went home and drank more that night, even though I wasn't planning on drinking. Felt guilty next day.

Adapted from Budney and Higgins [5]

marital therapy, problem solving, and drink refusal skills. Thus, some of the components of the community reinforcement approach are similar to cognitive behavioral therapy (see Chapter "Cognitive Behavioral Therapy for Addiction").

The difference between the two types of therapies is that the community reinforcement approach is more directive, community based, and behavioral than cognitive behavioral therapy. In the community reinforcement approach, the therapist places a great deal of emphasis on changing environmental contingencies in the client's life. Employment, recreation, and family systems are all addressed to promote a lifestyle that is more reinforcing than substance use. Rather than being entirely office-based, the community reinforcement approach is typically performed, at least in part, in the community. If clients do not attend treatment or do not follow through with an employment or recreational goal, the therapist may go to their homes, take them to job interviews, or help them try a new recreational activity. The purpose of expanding the treatment beyond the office setting is to increase the positive reinforcing effects of non-substance-using activities by direct exposure.

Initial reports of the efficacy of the community reinforcement approach for the treatment of alcohol dependence were promising. Hunt and Azrin [21] and Azrin [2] described two early studies in which 16 and 18 alcohol-dependent individuals, respectively, were randomized to usual psychosocial therapy plus disulfiram or to the community reinforcement approach plus disulfiram. In both studies, the community reinforcement approach-treated individuals spent significantly fewer days drinking than did those receiving usual care. The latter study had a long-term follow-up, which found that 90% of those who had received the community reinforcement approach remained abstinent up to 2 years later.

Additional studies in alcohol-dependent individuals have found the community reinforcement approach to be of therapeutic benefit to alcohol-dependent individuals. For example, Azrin and colleagues [3] noted a therapeutic benefit of the community reinforcement approach, and Smith et al. [51] also reported that this approach led to greater abstinence during treatment than did usual care plus disulfiram treatment. Miller et al. [28, 29] examined the various components of the community reinforcement approach and likewise found the community reinforcement approach to improve the treatment outcomes of those who received concomitant disulfiram treatment.

Several independent reviews and meta-analyses have concluded that the community reinforcement approach is an important, established, and effective treatment for alcohol use disorders [10, 19, 20, 27]. Furthermore, in a recent review of the community reinforcement approach's effectiveness, Roozen et al. [48] concluded that the community reinforcement approach, alone or with disulfiram, is efficacious for the treatment of alcohol dependence. However, the use of the community reinforcement approach alone in the treatment of other illicit drug use disorders has not been examined

extensively. Most studies that have examined the community reinforcement approach have done so in conjunction with another behavioral therapy, contingency management.

Contingency Management Interventions

Contingency management, similarly to the community reinforcement approach, is based on the principles of behavioral therapy. The primary difference between the two interventions is that contingency management provides *tangible* reinforcers for achieving target behaviors to increase the likelihood of those behaviors reoccurring, while the community reinforcement approach exposes clients to reinforcing activities and experiences. Typically, contingency management interventions identify an appropriate target behavior (e.g., abstinence as verified by a negative urine toxicology test) and provide tangible reinforcers each time the target behavior occurs. The reinforcers are most often monetary-based vouchers exchangeable for retail goods and services or the chance to win prizes of varying magnitudes. If the target behavior does not occur, the reinforcers are removed [13, 33].

Contingency management is generally not provided as a stand-alone treatment for substance use disorders, but instead it is added to another treatment to improve outcomes. Contingency management is often combined with the community reinforcement approach in attempts to improve further the efficacy of the community reinforcement approach alone. An early study of voucher-based contingency management by Higgins et al. [15] offered the community reinforcement approach along with contingency management to 13 consecutively admitted cocaine-dependent outpatients and offered 12-step-based drug counseling to the next 15 consecutively admitted cocaine-dependent outpatients. In the contingency management condition, vouchers worth a specific amount of money were provided whenever individuals submitted cocaine-negative urine samples. Significant group differences emerged in the percentage of participants who remained in treatment for 12 weeks, with 85% in the community reinforcement approach plus contingency management group and 42% in the 12-step group remaining in treatment for the entire period. Participants in the community reinforcement approach plus contingency management group also achieved significantly longer periods of objectively verified continuous cocaine abstinence, with 77% vs. 25%, respectively, achieving a month or more of continuous abstinence.

Higgins et al. [14] next conducted a 24-week randomized study comparing the same two treatments in a sample of 38 individuals, with half of them assigned to community reinforcement approach plus contingency management and the other half assigned to 12-step counseling. Fifty-eight percent of the participants in the community reinforcement approach plus contingency management group completed treatment versus 11% of those in 12-step counseling. The groups also differed significantly on rates of continuous abstinence. Sixty-eight percent of participants receiving community reinforcement approach plus contingency management achieved 8 weeks of continuous abstinence compared with 11% in the 12-step counseling group. Group differences remained at 6-, 9-, and 12-month follow-up interviews [12]. Participants who received community reinforcement approach plus contingency management were more likely to self-report cocaine abstinence over the past 30 days and to submit cocaine-negative urine samples compared with those who received 12-step counseling.

To isolate the specific contribution of contingency management to these beneficial outcomes, Higgins and colleagues [13] next randomized 40 cocaine-dependent individuals to the community reinforcement approach alone or community reinforcement approach plus contingency management. Significantly more participants in the combined condition remained engaged in treatment for 24 weeks (75%) than in the community reinforcement approach-alone condition (40%). Longest duration of continuous abstinence

differed between groups as well. Participants in the community reinforcement approach plus contingency management condition achieved an average of 11.7 (± 2.0) weeks of continuous abstinence from cocaine, while those in the community reinforcement approach-alone condition achieved an average of 6.0 (± 1.5) weeks. These studies demonstrate that community reinforcement approach plus contingency management is more effective than the community reinforcement approach alone for increasing the duration of abstinence. Further, the benefits of community reinforcement approach plus contingency management persist up to a year beyond the end of the period during which vouchers are available [11, 18].

While contingency management adds to the benefits of the community reinforcement approach, the converse is also true: including the community reinforcement approach improves the benefits associated with contingency management alone. Higgins et al. [17] assigned 100 cocaine-dependent individuals in a random fashion to either the combination of contingency management plus the community reinforcement approach or contingency management alone. Participants who received the combined treatment remained in therapy longer, used cocaine less frequently during treatment, and reported a lower frequency of drinking to intoxication than did those who received contingency management alone. Individuals treated with community reinforcement approach plus contingency management also evidenced improvements on other domains relative to those who received contingency management only. These included higher days of employment, reduced depressive symptoms, and fewer hospitalizations and legal problems. Thus, contingency management is an efficacious intervention for cocaine dependence, but it is most effective when administered in conjunction with the community reinforcement approach in this population.

Other studies have extended these benefits of community reinforcement approach plus contingency management to other substance-abusing populations. Bickel et al. [4] randomized 39 opioid-dependent individuals to a usual-care condition or community reinforcement approach plus contingency management. During treatment, abstinence rates were significantly higher among those who received contingency management. Using a non-randomized design, Schottenfeld et al. [49] compared 117 opioid-maintained, cocaine- and opioid-dependent individuals who received either drug counseling or community reinforcement approach plus contingency management. Although retention and drug use did not differ between those receiving different forms of therapy in this report, engagement in community activities unrelated to drug use (e.g., parenting activities, employment, or planned recreational activities) was significantly associated with abstinence.

In the treatment of other drug use disorders such as nicotine, marijuana, or benzodiazepines, contingency management is typically applied as an adjunct to usual-care psychotherapies, rather than in conjunction with the community reinforcement approach. A variety of studies demonstrate that contingency management improves the treatment outcomes of marijuana-dependent individuals when added to motivational enhancement therapy or cognitive behavioral therapy [6, 7, 23]. Contingency management is also efficacious in the treatment of nicotine dependence [9, 16, 46, 47] and benzodiazepine use [54].

Two recent meta-analyses have demonstrated the therapeutic efficacy of contingency management in treating different substance use disorders [26, 44]. Across 30 studies comparing treatments with and without the addition of voucher-based contingency management, Lussier et al. [26] found medium-sized group differences in length of abstinence from cocaine, opiates, tobacco, alcohol, and marijuana, with no significant difference in outcomes across specific drugs. More immediate delivery of reinforcement and higher reinforcement magnitude were associated with greater therapeutic benefit [26]. In an independent analysis of 47 contingency management trials that used vouchers as well as other forms of reinforcement (e.g., cash and privileges such as take-home methadone doses), Prendergast et al. [44] found that contingency management was most effective in reducing cocaine

and opiate use. Smaller effects were noted with respect to reducing tobacco and polydrug abuse. While both of these meta-analyses found benefits of contingency management, they included many studies that did not incorporate appropriate behavioral principles in the design of the reinforcement structure, such as frequent monitoring and reinforcement and escalating reinforcers with sustained behavioral change [33]. The benefits of contingency management are greater in studies that utilize appropriate behavioral principles.

Issues Hindering the Implementation of the Community Reinforcement Approach in Practice

Despite the strong research evidence that supports the efficacy of community reinforcement approach and contingency management in substance-abusing populations, these interventions are rarely implemented in clinical practice. The primary reason for lack of use relates to costs. The community reinforcement approach is labor intensive and difficult to employ in practice settings, most of which are understaffed and underfunded. In its traditional sense, the community reinforcement approach is individually based and quite labor intensive in nature. Typically, one therapist will manage a small caseload of 10 or fewer clients.

In an attempt to make the community reinforcement approach less labor intensive for therapists and more practical to implement in busy clinical practice settings, some studies have examined a modification of the approach by providing contingency management for completing goal-related activities. Rather than the therapist going out into the community with the client to ensure exposure to non-drug-related activities, the therapist will contract with the client each week to complete up to three goal-related activities. If the client engages in the activities and provides objective verification of completion, the client will earn tangible reinforcers such as vouchers. Table 2 provides an example of a typical activity contract.

This approach has been studied in several clinical trials. In a sample of polydrug-using individuals on methadone, Iguchi et al. [22] found that an intervention that provided tangible reinforcers for completion of goal-related activities resulted in lower drug use both during the treatment period and throughout the follow-up period than a usual contingency management approach that only reinforced drug abstinence. However, a subsequent study with cocaine-abusing individuals from psychosocial (non-methadone) clinics failed to show a significant benefit of the contingency management for activity condition relative to usual care [34]. In that study, contingency management for submission of negative urine samples did significantly improve outcomes relative to standard care. Thus, there is inconsistent evidence that this modified contingency management approach is sufficient to improve drug use outcomes in clinical settings.

Importantly, contingent activity contracting is important for engaging individuals in drug-free recreational and other activities. If activity contracting procedures are employed without contingent reinforcement, these activities are completed less than one-third of the time [40]. In contrast, when tangible reinforcers are provided in a contingent manner, these activities are completed about two-thirds of the time [40, 43]. Furthermore, completion of these activities was typically associated with a reduction in drug use and improvements in psychosocial functioning. Individuals who completed family activities compared with those who did not reported a greater reduction as well as improvements in family functioning [25]. Also, the completion of exercise-related activities appeared to decrease drug use [55]. Another popular contingent activity that can be targeted is engagement in religion. For instance, individuals who became involved in religious activities (going to church or mosques or attending Bible studies), compared with those who did not, remained in treatment longer, had longer periods of drug abstinence, and submitted more drug-negative

Table 2 Sample activity contract

Specific activity	Goal area	Projected date/ time of completion	Things that could go wrong	Problem solve	Verification	Completed and verified?
1. Complete draft of resume	Employment	Wed pm	Don't feel like it, No blank paper in house	Do on Thurs if not Wed, Bring blank paper from clinic	Bring in draft	
2. Go to 3 AA meetings	Sobriety	Wed pm, Fri pm, and Sat afternoon	Don't feel like going, car won't start	Make plans will Sally to go together and for coffee after meeting, ask Sally to drive	Signed attendance slip and coffee receipts	
3. Go to church	Recreation/ spirituality	Sunday 10 A.M.	Oversleep, no transportation	Set alarm Sat night, make plans to go with John	Bring back dated bulletin	

Adapted from Petry et al. [43]

urine samples [38]. In sum, the reinforcement of salient non-drug-related activities through the use of tangible reinforcers has appeared to be an important method for decreasing drug use and should be more cost-effective than having therapists attend community events with their clients.

Issues Associated with Implementation of Contingency Management in Practice

While contingency management can be used to reinforce engagement in non-drug-related activities, it is most often applied to encourage abstinence from using substances. Irrespective of the target behavior reinforced, contingency management has been criticized for being costly to implement, especially the voucher-based version.

An important component of contingency management is that the value of vouchers earned increases with each consecutive instance of a desired behavior. Thus, the first negative specimen (or activity completed) may result in a $2.50 voucher, the second a $3.25 voucher, the third a $4 voucher, and so on [45, 46]. Thus, by the end of a 12-week treatment period, individuals may be earning in excess of $40 for each negative sample or activity completed, and most effective voucher-based contingency management programs arrange for about $1000 in vouchers over the course of a 12-week treatment period (see Table 3). Hence, the costs of voucher-based contingency management are prohibitive for most community-based settings.

Studies that have attempted to reduce the amounts of vouchers available show that the procedure is less effective in decreasing drug use. Stitzer and Bigelow [52, 53] found that nicotine abstinence increased as a function of the magnitude of the reinforcer, ranging from $0 to $12 per day. Dallery et al. [8] noted a direct relationship between voucher amounts and abstinence in another study of individuals receiving methadone maintenance treatment. These studies all suggest that the larger the magnitude of the reinforcer, the greater the improvement in treatment outcomes. Hence, reducing the value of the vouchers decreases their efficacy in promoting abstinence from substances.

Table 3 Sample voucher-based contingency management schedule

Week	Sample	Points	Dollars	Bonus	Cumulative earnings
1	Mon	10	$2.50		$2.50
	Wed	15	$3.75		$6.25
	Fri	20	$5.00	$10.00	$21.25
2	Mon	25	$6.25		$27.50
	Wed	30	$7.50		$35.00
	Fri	35	$8.75	$10.00	$53.75
3	Mon	40	$10.00		$63.75
	Wed	45	$11.25		$75.00
	Fri	50	$12.50	$10.00	$97.50
4	Mon	55	$13.75		$111.25
	Wed	60	$15.00		$126.25
	Fri	65	$16.25	$10.00	$152.50
5	Mon	70	$17.50		$170.00
	Wed	75	$18.75		$188.75
	Fri	80	$20.00	$10.00	$218.75
6	Mon	85	$21.25		$240.00
	Wed	90	$22.50		$262.50
	Fri	95	$23.75	$10.00	$296.25
7	Mon	100	$25.00		$321.25
	Wed	105	$26.25		$347.50
	Fri	110	$27.50	$10.00	$385.00
8	Mon	115	$28.75		$413.75
	Wed	120	$30.00		$443.75
	Fri	125	$31.25	$10.00	$485.00
9	Mon	130	$32.50		$517.50
	Wed	135	$33.75		$551.25
	Fri	140	$35.00	$10.00	$596.25
10	Mon	145	$36.25		$632.50
	Wed	150	$37.50		$670.00
	Fri	155	$38.75	$10.00	$718.75
11	Mon	160	$40.00		$758.75
	Wed	165	$41.25		$800.00
	Fri	170	$42.50	$10.00	$852.50
12	Mon	175	$43.75		$896.25
	Wed	180	$45.00		$941.25
	Fri	185	$46.25	$10.00	$997.50

Adapted from Budney and Higgins [5]

Prize-Based Contingency Management

To address the issue of cost in contingency management interventions, Petry et al. [39]

developed a prize-based contingency management intervention that provided tangible reinforcement on a variable ratio schedule. Individuals who provided objective evidence of abstinence or other target behaviors earned the opportunity to draw slips of paper that could be redeemed as prizes. The number of draws earned, similar to the voucher-based approach, increased with each consecutive negative sample, such that the first negative sample or completed activity resulted in one draw, the second in two draws, and so forth. Typically, the drawing of prizes was capped (e.g., at a maximum of 8 draws per activity completed or negative sample submitted) after about 1 month of sustained behavioral change (see Table 4).

In most prize-based contingency management programs, clients draw from a bowl containing 500 slips of paper. Half the slips have encouraging messages but do not result in prizes, and half the slips result in a prize. There are typically three prize magnitudes, "small" (worth about $1), "large" (worth about $20), and "jumbo" (worth about $100). The majority of the slips (e.g., 209) are associated with small prizes, and when clients draw a small slip they select from items such as bus tokens, fast food gift certificates, food items, and toiletries. Fewer slips (e.g., 40) are exchangeable for large prizes such as portable CD players, telephones, telephone minutes, pot and pan sets, and $20 gift cards to stores and restaurants. One slip corresponds to a jumbo prize such a DVD player, stereo, or television. With this system, there is always an opportunity to earn something of high value, but overall earnings are expected to be relatively modest. On average, the maximal arranged reinforcement for a 12-week treatment period is about $250 to $400, and typically clients earn about half the programmed reinforcement.

Table 4 Sample drawing schedule for prize-based contingency management

Week	Sample	Draws
1	Mon	1
	Fri	2
2	Mon	3
	Fri	4
3	Mon	5
	Fri	6
4	Mon	7
	Fri	8
5	Mon	8
	Fri	8
6	Mon	8
	Fri	8
7	Mon	8
	Fri	8
8	Mon	8
	Fri	8
9	Mon	8
	Fri	8
10	Mon	8
	Fri	8
11	Mon	8
	Fri	8
12	Mon	8
	Fri	8
Total		173

Adapted from Petry et al. [35]

Prize-based contingency management was first evaluated in a sample of 42 alcohol-dependent men participating in a Veterans Affairs outpatient substance abuse treatment program [39]. Twenty-three participants were assigned to standard care, a 4-week intensive outpatient program that included 12-step meetings, relapse prevention, coping skills training, and AIDS education followed by 4 weeks of less intensive aftercare. Nineteen individuals received the same standard care plus contingency management for abstinence and for compliance with treatment goals (a modification of the community reinforcement approach). All participants submitted Breathalyzer samples at each daily visit to the treatment program, and those in the contingency management group who tested negative for alcohol earned the opportunity to draw for prizes. Contingency management participants also earned additional draws for completing activities related to their treatment goals, such as attending an Alcoholics Anonymous meeting, filling out a job application, or participating in planned recreational activities with non-drug-using family members. Individuals who received contingency management in addition to standard care were significantly more likely than those receiving standard

care alone to remain in treatment for the 8 weeks of the study (84% vs. 22%) and to remain abstinent from alcohol for the duration of the study (69% vs. 39%). Individuals who received contingency management compared with those who got standard care were less likely to relapse to heavy alcohol use by the end of the study (26% vs. 61%). The average value of prizes earned by each participant in the contingency management condition was $200.

A direct comparison of voucher- and prize-based contingency management interventions for cocaine-abusing individuals entering a community-based outpatient drug-free treatment program found both approaches to contingency management to be more effective than standard care alone [36]. Both contingency management interventions compared with standard care increased retention in treatment and the duration of continuous abstinence from drugs significantly. Individuals in standard care, voucher-based contingency management, and prize-based contingency management remained in the program for 5.5 (± 3.6) weeks, 8.2 (± 3.8) weeks, and 9.3 (± 3.7) weeks, respectively. While there was no statistically significant difference between the two contingency management groups, the trend toward longer retention in treatment in the prize-based contingency management group was notable. Individuals who received standard care achieved 4.6 (± 3.4) weeks of continuous abstinence compared with 7.0 (± 4.2) weeks in voucher-based contingency management and 7.8 (± 4.2) weeks in prize-based contingency management.

Petry and colleagues did a follow-up study to examine the relative efficacy of two contingency management approaches plus standard care vs. standard care alone among cocaine-dependent individuals who were receiving methadone [35]. Participants were assigned in a random fashion to standard care, standard care plus prize-based contingency management, or standard care plus voucher-based contingency management. The amount of arranged reinforcement was twice as high in the voucher-based vs. the prize-based contingency management condition. Both contingency management conditions increased the duration of abstinence and the proportion of cocaine-negative samples submitted; hence, even the prize-based contingency management approach of lower cost was efficacious.

Since the low-cost prize-based contingency management approach had similar therapeutic benefit to the voucher-based contingency management program, the extent to which prize values could be reduced and still reduce drug use was examined in another study of cocaine-abusing outpatients [42]. In that study, one group received standard care at community-based drug-free clinics, and two groups received prize-based contingency management plus standard care. One contingency management group offered the opportunity to earn up to an average of $240 in prizes, whereas the other offered the chance to earn up to an average of $80 in prizes. Both contingency management conditions offered a similar number of opportunities to draw for prizes; however, compared with the $240 group, the prizes available in the $80 group were less valuable. While contingency management with $240 available for prizes was significantly more efficacious than standard care, there was no difference between standard care and contingency management with $80 available for prizes. Therefore, although the prize-based version of contingency management does offer some cost advantage over its voucher-based counterpart, even within the prize-based version there appeared to be a lower bound or threshold in monetary value for it to be of greater therapeutic benefit than standard care.

Prize-based contingency management was selected by the National Institute on Drug Abuse Clinical Trials Network for more extensive evaluation in community treatment settings [41] based upon the encouraging results from controlled clinical studies. The goal of the Clinical Trials Network is to evaluate the effectiveness of treatments found to be efficacious in controlled studies done at specialized research centers in community-based clinical settings, where most individuals receive treatment for substance use disorders. In the largest studies of contingency management to date [32, 41], over 800 stimulant (cocaine, methamphetamine, or amphetamine)

abusers were recruited from community clinics throughout the United States. About half of the participants were recruited from psychosocial (drug-free) clinics ($N = 415$) [41] and half from methadone clinics ($N = 388$) [32]. The clinics were located primarily in urban settings, but suburban and rural settings were represented as well. The duration of the combined studies was 12 weeks. As in other contingency management studies, participants were assigned to one of two groups, standard care or standard care plus prize-based contingency management using a system of escalating draws for consecutive stimulant-free urine samples. The maximum number of draws available was 204, with average maximal expected earnings of about $400 in prizes. In the psychosocial programs [41], individuals who received contingency management plus standard care were significantly more likely than those receiving standard care alone to remain in treatment for the entire 12 weeks of the study (49% vs. 35%). Contingency management participants also attended more counseling sessions during the study period (19.2 ± 16.8) than did those receiving standard care (15.7 ± 14.4). The longest duration of continuous verified abstinence from stimulants was significantly greater in the contingency management group compared with the standard care group (8.6 ± 9.2 weeks vs. 5.2 ± 6.9 weeks), and contingency management participants were more likely than those receiving standard care to achieve 4 (40% vs. 21%), 8 (26% vs. 12%), or 12 (19% vs. 5%) weeks of continuous abstinence from stimulants. Similar results were noted for stimulant abusers maintained on methadone [32]. Individuals who were assigned in a random fashion to the contingency management condition were significantly more likely to achieve long durations of abstinence and to submit higher proportions of stimulant-negative urine samples. The average amount of reinforcement earned in the methadone programs was $120 per individual, and in the psychosocial programs it was $203 per individual. Thus, the costs of reinforcers in prize-based contingency management are relatively low, and the procedure is widely efficacious across settings and substance-abusing populations.

Cost-Effectiveness

Investigators have begun to examine the cost-effectiveness of contingency management. Using data from the Clinical Trials Network studies, Olmstead et al. [31] estimated resource utilization (treatment services including counseling sessions attended, urine and Breathalyzer tests, counselors' time associated with drawings, and value of prizes won) of individuals receiving standard care or standard care with contingency management at community-based outpatient psychosocial drug abuse treatment clinics. Unit costs of services were estimated via surveys administered at the 8 participating clinics. Participant outcomes (primarily duration of continuous abstinence) were also obtained from the trials. The incremental cost to lengthen abstinence by 1 week was $258 (95% confidence interval, $191–$401) in psychosocial clinics [31]. In a follow-up analysis of the same data, Olmstead et al. [30] sought to determine by how much the cost-effectiveness of contingency management varied across the 8 psychosocial clinics in the Clinical Trials Network trial. Incremental costs, incremental outcomes, and incremental cost-effectiveness ratios of contingency management versus standard care were calculated for each clinic. The incremental cost of contingency management ranged across the clinics from an additional $306 to an additional $582 per individual. The effect of contingency management on abstinence ranged from an additional 0.5 weeks to an additional 4 weeks across the clinics. Incremental cost-effectiveness ratios for abstinence ranged from $145 to $666 per individual across the clinics. Thus, the cost-effectiveness of contingency management did vary widely among clinics in the Clinical Trials Network trial, and future work is needed to focus on identifying sources of this variation, perhaps by identifying clinic-level best practices or identifying subgroups of individuals who respond the most cost-effectively, with the ultimate goal of improving the cost-effectiveness of contingency management overall.

Sindelar et al. [50] evaluated the incremental cost-effectiveness of contingency management in a study in which different magnitudes of the prize in the prize-based contingency management were compared. They found that the $240 prize-based contingency management condition produced outcomes at a lower per-unit cost than the $80 contingency management condition. This finding suggests that sometimes increasing up-front costs is more cost-effective overall. These results may be particularly relevant for substance-abusing populations who utilize high-cost resources such as inpatient medical and criminal justice services.

Challenges to Dissemination

While the efficacy of the community reinforcement approach and contingency management for the treatment of substance use disorders in controlled settings is established, the adoption of these procedures by treatment providers in clinical practice has been limited. As noted earlier, the costs of the reinforcers and of staff time for administration of the procedures are some obstacles to implementation.

The costs associated with contingency management can be decreased by providing contingency management in a group context. While typically implemented individually, prize-based contingency management can also be administered in a group format [1, 24, 40], perhaps facilitating its adoption, as group therapy predominates in practice. Witnessing others winning prizes appears to lead to a camaraderie among clients, and group- and prize-based contingency management has been implemented at a fairly low cost (e.g., $15–$20 per week in direct costs) [24].

Cost is not the only barrier to implementation of these evidence-based practices. Implementation also depends on familiarity with and proficiency in techniques and principles of behavior modification. These include behavioral therapy and behavioral contracting and—in the case of contingency management—consistently applying contingencies, frequently monitoring and reinforcing behaviors, integrating escalating or bonus reinforcers, and providing adequate reinforcement magnitude [33]. Developing comprehensive training procedures for the community reinforcement approach and contingency management for community-based treatment staff is a large undertaking, but efforts toward dissemination are under way. Budney and Higgins [5] provided a treatment manual for the combination of the community reinforcement approach and voucher-based contingency management, and a training manual and video are also available for prize-based contingency management at http://info.med.yale.edu/psych/research/psychotherapy/orderform.doc.

Other implementation concerns relate explicitly to prize-based contingency management. Because this procedure contains an element of chance, concerns have arisen that it might promote pathological gambling. However, gambling by definition involves risking something of value, which is not the case with contingency management. Examination of gambling behaviors among 803 individuals participating in the Clinical Trials Network prize-based contingency management studies found no evidence of increases in gambling behavior over time [37].

The ability of treatment systems that are under tight fiscal restraints and understaffed to absorb the additional costs of community reinforcement approach and contingency management is understandably met with skepticism. In the case of contingency management explicitly, reducing reinforcement magnitudes to under $240 for prize-based contingency management will compromise efficacy [42], but it may be possible to offset costs in part or in full via fundraising or other strategies including the use of clinic privileges for some prizes. Moreover, the immediate costs of contingency management and the community reinforcement approach may pale in comparison with the societal and individual costs of continued drug abuse. Comprehensive cost-effectiveness analyses are needed to evaluate more clearly contingency management and the community reinforcement approach, when delivered either alone or together, relative to other modalities for treating substance abuse.

Conclusion

The community reinforcement approach and contingency management are efficacious interventions for the treatment of substance use disorders. The community reinforcement approach addresses the multiple bio-psychosocial factors that contribute to substance abuse and provides intensive intervention to help individuals develop alternative forms of reinforcement to compete with substance use. Contingency management enhances the outcomes of the community reinforcement approach by providing tangible reinforcers for drug abstinence and other positive behaviors as clients learn self-reinforcement strategies, engage in new adaptive behaviors, and adopt a drug-free lifestyle. Numerous studies demonstrate the efficacy of these interventions as treatments for alcohol, cocaine, opiate, and marijuana use disorders.

Despite their efficacy, community reinforcement approach and contingency management have rarely been implemented in community settings. Many factors contribute to the implementation and sustainability of treatments, including the soundness of forged research-treatment partnerships, the readiness of communities to accept an innovation, and financial resources for training and implementation. Future adoption of these interventions for perhaps the most seriously impaired substance abusers may ultimately prove to be efficacious and cost-effective. Recent innovations such as using contingency management to reinforce community reinforcement approach activities (reducing the burden on counselors) and administering contingency management in group settings may facilitate wider adoption of these empirically validated treatments in practice.

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Relapse Prevention and Recycling in Addiction

Carlo C. DiClemente, Meredith A. Holmgren, and Daniel Rounsaville

Contents

Introduction

In the struggle to be free from Addiction, repeated attempts are required for most individuals to stop the addictive behavior. Multiple attempts to change and multiple treatment events are the norm rather than the exception in recovery from addiction [28]. There seems to be a predictable cycle in the path to recovery. Once addicted individuals become convinced that they need to change problematic addictive behaviors (illegal or nonprescription drug use, excessive alcohol consumption, tobacco use, or gambling), they will attempt either to quit completely or to significantly modify these behaviors (e.g., cutting down or using methadone or buprenorphine instead of heroin). The majority of these individuals who make an attempt to change, however, are unsuccessful. In any cohort of individuals that enters treatment and makes a bona fide attempt to change, the majority, between 60 and 80%, return to the problematic behavior after some period of success [9, 28]. This event, though defined in various ways, has been labeled a "relapse".

Understanding the Concept of Relapse and Its Role in Recovery

The definition of what constitutes a relapse varies depending on the definition of success and failure in changing an addictive behavior. The most stringent definitions define

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_38,

success as complete abstinence from the behavior and identify relapse as any engagement in the addictive behavior (any consumption of alcohol, use of cocaine, etc.) [58]. Other clinicians and researchers make a distinction between a slip or lapse and a full blown relapse [39]. Slips and lapses have been defined variably as a single use, a single period of use, minimal amounts of use, or use without any consequences. Relapse is then a more significant engagement in the behavior than a single event or a brief period of use. Lapses could extend into what has been defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision as "partial remission", indicating that there are some vestiges of the behavior present, but that there is an absence of the negative consequences and the physiological and psychological dependence that marked the problematic period of use [19].

Making a distinction between a lapse and a relapse can be clinically useful because the very strict definition of complete abstinence or failure can have unintended consequences, as will be described later. It is important first to note some common misconceptions about the phenomenon of relapse. Relapse is often viewed as a unique problem of substance abusers by practitioners and the public. However, relapse and lapsing back to unhealthy behaviors occurs in all types of health behavior change and is not limited to addictions. Many health behaviors, such as dietary change, diabetes management, regular physical activity, and medication adherence have a similar course with large numbers of individuals lapsing and relapsing [9, 42]. Relapse is not merely a function of physiological addiction; it is a function of the process of behavior change when individuals attempt to change difficult-to-modify patterns of behavior [20, 43].

Another misconception is that relapse is often viewed as failure since the desired behavior change is not sustained. However, although it does not represent complete success, relapse is an integral part of learning during the recovery process. Individuals do not become addicted, nor do they recover from an addiction, with a single learning event [20]. Within the stages of change model, relapse represents an event that not only involves a return to a problematic behavior but also signifies a return to an earlier stage of change for that behavior [11, 63]. After relapsing, individuals can return to any of the previous stages, Precontemplation (not considering change in the near term), Contemplation (considering and decision making), Preparation (building commitment and planning), or Action (initial change lasting for 3–6 months). Individuals returning to the Precontemplation stage after relapse likely believe they cannot change or are they are no longer interested in changing the addictive behavior. Relapsers who reconsider the pros and the cons of the addiction, try to resolve the associated ambivalence and make a new decision to quit have returned to the Contemplation stage. Those who determine what went wrong during the last quit attempt and are poised to make another attempt return to the Preparation stage. Relapsers who quickly make another attempt move back into the Action stage of change. The return to earlier stages of change after relapsing from the action or maintenance stage is called "recycling" back through the stages and often leads to another attempt that is successful [21, 54]. The cyclical movement though the stages of change represents the learning process of "successive approximations" whereby an individual learns gradually through trial and error how to avoid the problems from past attempts and to make a successful change in behavior.

Relapse, considered from this perspective, is not so much a failure as an opportunity to learn what went wrong and what was missing in the unsuccessful process of change. Most individuals who enter stable recovery do so only after multiple attempts to change. This pattern is true of individuals who have changed the addictive behavior without the aid of formal treatment as well as those who have been successful after a particular course of treatment [22, 45, 49]. In any case, understanding relapse and recycling is critical to understanding successful recovery. Helping individuals avoid relapse and/or to learn how to profit from the experience and become more successful is the goal of relapse

prevention and of successful recycling. This chapter will examine relapse prevention models, highlight critical components of relapse prevention, identify key clinical strategies that can be used in the service of preventing relapse, and discuss how to promote successful recycling for those who were unable to change their behavior at any one point in time.

Relapse Prevention

As the field of addiction moved from a moral explanation of addiction to a focus on habit and disease, the challenge of maintaining change and avoiding relapse became a focus of research and theory [9, 35, 39, 61]. Interest and research activity expanded to understand what precipitates relapse and the possible interventions that would reduce the relapse rate and increase the potential for recovery from a slip or a relapse. There were several dominant theories that were developed during the 20th century not all of which were compatible with one another.

Models for Relapse Prevention

The two partially compatible models for understanding relapse came from different explanatory frameworks. The Medical Model countered the prevailing perspective at the beginning of the twentieth century that alcoholism and other addictions were moral problems that could be overcome with willpower and by observing moral standards. The view of addiction as a disease was intended to change the conversation about addiction, remove some of the stigma, and make it a medical condition that was treatable. This model was not only adopted by the medical professionals but also by the influential founders of Alcoholics Anonymous and the 12-step model for recovery [58]. At the same time in the academic community, the social and behavioral learning perspectives described addictions as over-learned behaviors that were supported by contextual forces. Interestingly, both models arrived at some similar relapse prevention strategies.

Medical and Mutual Help Model

In the Medical Model addiction is viewed in terms of the changes that are made in the neurochemistry of the addicted individual, which causes physiological dependence. The perspective is that the addiction acts as a disease and changes biological processes which, in turn, pose significant barriers for change for the addicted individual. The physiological changes that result from prolonged substance abuse manifest themselves in craving, which continually pushes the addicted individual to return to the addictive behavior [52]. For the addicted individual their "normal" biological state inherently is resistant to behavior change [14, 33]. Medical Model oriented interventions to prevent relapse include periods of hospitalization that focus on breaking the physiological and psychological connections to addiction as well as using medications that decrease cravings.

In the Medical/Mutual Help or Twelve-Step Model, addiction is also described as an illness or disease that addicted individuals are powerless to control [53]. One analogy for the disease is an "allergy" such that the individual cannot have contact with the substance without a loss of control. This perspective supports the view of relapse as any contact with addictive substance or behavior. The addicted individual is seen as someone who has a defect such that willpower can not be the solution for recovery. Preventing relapse must include an admission of powerlessness and a reliance on a higher power, whether that is seen as a spiritual power or the power of the mutual help network that is created by associating with Alcoholics Anonymous and working the 12 steps of recovery. The program includes a number of strategies (e.g., approach recovery, one day at a time, you are always an alcoholic and must always be vigilant, meeting attendance) and support systems (e.g., sponsors, fellowship of Alcoholics Anonymous) for the prevention of relapse.

Social Learning Models

In 1980, G. Alan Marlatt and Judith Gordon developed the Relapse Prevention Model, an extensive, empirically focused conceptual model that we will use as the basis of our discussion of relapse in this chapter. Their cognitive-behavioral model of the relapse process [39] is based on social cognitive and learning models of behavior and posits that addiction stems from maladaptive habit patterns. Relapse is conceptualized as resulting from a series of predictable cognitive and behavioral events that lead to a return to substance use. This relapse prevention model hypothesizes that common cognitive, behavioral, and affective mechanisms underlie the process of relapse for a variety of problem behaviors. This view of recovery is based on learning theory and differs from the disease model in many ways, though does share some theoretical precipitants of relapse.

The model assumes that a complex array of determinants is involved in the development of an addiction and the ability to successfully change the addictive behaviors. Some influential factors include genetics, environmental/situational factors, family history of addiction, peer influence, early use of substances, and expectancies of the effects of the substance. During periods of abstinence, individuals move along a continuum of engagement in cognitive and behavioral activities that lead to successful behavior change. Along the way, they are likely to face situations that put them at risk for relapse. These high-risk situations are a core component of Marlatt and Gordon's Relapse Prevention Model. Eight categories of relapse determinants were formulated from detailed, retrospective interviews of substance abusers who had experienced a return to their substance use [40]. This was done to identity the experiences that immediately preceded relapse episodes. From this investigation, a taxonomy was developed which included interpersonal and intrapersonal factors. Cummings et al. [17] found that the most frequently reported precipitants of relapse included negative emotional state (35% of relapses), social pressure (20%), interpersonal conflict (16%), and urges and temptations (9%). Factor analysis on the Reason for Drinking Questionnaire [68] expanded beyond Marlatt's taxonomy of relapse precipitants to reveal three major factors that differentiated the types of relapses people experienced: (1) negative emotions, (2) social pressure and positive emotions with others, and (3) temptation and craving.

According to the cognitive-behavioral relapse model [39], individuals with effective coping responses and high self-efficacy are less likely to elicit the problem behavior. When an individual faces a high-risk situation and has access to the appropriate coping behavior, the successful use of this coping behavior increases self-efficacy [5, 6]. This accomplishment should reduce the probability of subsequent relapse in similar high-risk situations. If an individual does not use the appropriate coping behavior, the attractiveness of substances will increase while self-efficacy to abstain decreases, escalating the likelihood that the individual will use the substance in that particular situation. Guilt and low self-esteem can occur if the substance is used during this period of abstinence. These feelings can propel an individual from the initial use of alcohol, often termed a "lapse", into a full-blown relapse.

Marlatt and Gordon [39, 40] describe the onset of guilt and lowered self-efficacy as a possible effect of a lapse from an initial goal of abstinence. They label this reaction as the Abstinence Violation Effect. This reaction is related to the individual's causal attribution for the slip. For example, when drinkers attribute the lapse to their own personal failure they tend to experience guilt and negative emotions that can lead to increased drinking in an attempt to avoid or escape those feelings. When people attribute the lapse to stable, global factors that are beyond their control, they are more likely to avoid a full-blown relapse. A subsequent relapse is more likely for those who attribute the lapse to a personal inability to cope with high-risk situations [39]. It is the individuals who are able learn from the mistake and avoid future relapses that are better able to develop effective coping skills to deal with triggers [34].

Review of Relapse Prevention and Substance Abuse Studies

Since the advent of a focus on relapse and maintenance and, in particular, the response to the detailed, conceptual perspective of the Relapse Prevention Model, interventions designed to prevent relapse have been developed as a clinical application of Marlatt and Gordon's model [39]. The conceptual foundations of this model and a review of its applications have been recently updated by Marlatt and Donovan [38]. These interventions are designed to enhance the maintenance stage of intentional behavior change and emphasize self-management and coping skills in order to withstand the challenges presented by relapse precipitants [38]. The goals of relapse prevention are twofold: to prevent an initial lapse and to provide lapse management to prevent a complete relapse if a lapse does occur. Although treatment goals based on harm reduction and decreasing substance use have also been attempted, most controlled studies that administered relapse prevention treatment measured outcome success based on the goal of abstinence [12, 30].

The effectiveness of relapse prevention as an intervention has been reviewed for a variety of different substances, as well as compared with a variety of alternative interventions. Relapse prevention programs have been designed specifically for smoking, alcohol, marijuana, cocaine, and other drug use. Although early reviews concluded that there was little evidence for differential effectiveness of relapse prevention across classes of substance abuse [12], later reviews found some support for the greater effectiveness of relapse prevention when applied to alcohol or polydrug use disorders in combination with medication treatment [30].

In terms of comparative efficacy, relapse prevention has been found to be superior to no-treatment control groups , and equally effective as other treatments, such as supportive therapy, social support groups, and interpersonal psychotherapy [12]. Another review of relapse prevention [30] found that relapse prevention has a greater impact on improving psychosocial functioning than on reducing substance use. Relapse prevention also was more effective when combined with use of prescribed medication. Although results were based on a small number of studies and should be interpreted with caution, Irvin et al. [30] concluded that individual, group, and marital modalities were equally effective in preventing relapse in cohorts of substance abusers. What follows is a brief review of the literature on the efficacy and use of relapse prevention strategies with different types of addictive behaviors. A detailed presentation of the standard elements is included on the section entitled Strategies for Relapse Prevention.

Effectiveness Studies Across Addictive Behaviors

More research has been done on the effectiveness of relapse prevention for alcoholism and nicotine addiction than in any other area of addiction. The recent second edition of *Relapse Prevention* by Marlatt and Donovan [38] provides a detailed chapter on relapse prevention for each of the addictive behaviors. For most drugs of abuse, relapse prevention constructs and strategies have been applied in clinical settings. However, there is limited literature on specific relapse prevention treatments separate from more generic cognitive-behavioral approaches, and the research consists mainly of trials focusing on the Abstinence Violation Effect or other dimensions of the model. It is disappointing that there have not been more studies of the entire model and its efficacy specifically in preventing relapse across multiple behaviors. However, since cognitive behavior therapy approaches have incorporated many aspects of the relapse prevention strategies and evaluations of the cognitive behavioral approaches in addictions have been favorable in terms of effectiveness and efficacy in trials [12], there is some empirical support for many of the constructs and the strategies that are described later in this chapter.

Relapse Prevention has been found to be most effective in treating alcohol and poly-substance use compared with other substances alone (cocaine, marijuana, cigarettes, etc.) or abusive behaviors [30]. Reviews of alcohol and drug treatment studies generally report a broad, multidimensional range of outcomes that include reductions in use, increased time before relapse, and improvement in functioning [12].

A comprehensive review of relapse prevention interventions for smoking cessation conducted by the Cochrane Collaborative found insufficient evidence to support use of interventions designed specifically to prevent smoking relapse in those who already successfully quit [27]. Nevertheless, many relapse prevention strategies have been included in standard tobacco dependence treatment (knowing personal and environmental cues for smoking, delaying and urge management, relaxation, rewards, etc.) and are incorporated into self-help, and internet-assisted programs [59]. Thus, relapse prevention has become a core component of intervention for smoking cessation, rather than a separate and independent intervention specifically designed to prevent relapse. The advent of pharmacotherapies that can be used to promote smoking cessation and enhance long-term success (Chantix®, nicotine replacement products, Zyban®) have made them part of the standard empirically supported approaches to quitting and maintaining smoking cessation.

Critical Mechanisms for Relapse Prevention

An increasing number of studies indicate that the prevention of relapse or promotion of its inverse, successful maintenance of change, involves several overarching constructs. The key dimensions are motivation, coping, and self-efficacy. These three elements are critical to the long-term success of recovery and are important components to address in any program attempting to prolong abstinence and prevent relapse.

Motivation

Motivation plays an important role in relapse prevention. There is ample evidence that motivation for change as well as treatment outcome expectancy and client goals of abstinence are related to successful treatment outcomes [55, 56]. Motivation at the beginning of treatment and the attitudes and intentions that individuals bring into treatment are related to early cessation of drinking and drug use as well as long-term success [46]. Individuals who enter treatment after making a decision to change and taking steps toward change have a better prognosis compared with those who enter treatment not have yet made a decision or taken steps [31]. Those who appear more committed to change and demonstrate this in the treatment sessions by statements that indicate a determination to change (labeled "commitment language") also have better outcomes [1]. In addition, studies have found that relapse prevention is less effective for individuals who have low initial readiness [24].

How motivation and expectancies affect successful change and prevent relapse are not completely understood. Motivation is clearly multidimensional and involves different mechanisms of change [22]. If motivation is viewed as a series of tasks outlined by the stages of change, there are multiple elements that are necessary for the success of recovery and the prevention of relapse. For example, in order to avoid relapse, addicted individuals need to have some continuing, compelling reasons to abstain, a firm decision based on realistic expectations, commitment to follow through despite difficulties, an effective set of strategies and plans on how to manage triggers, and the ability to problem solve effectively when the plan is not working. These tasks outlined in the five stages of change have to be accomplished in a "good enough" manner to be able to sustain change and overcome the difficult challenges presented to anyone stopping or modifying an addictive behavior [20]. As individuals begin to have some success at changing the addictive behavior, their motivation to make an attempt to change has to shift to motivation to sustain the change over time in the face of the multiple personal and environmental barriers

that could undermine the decision, the commitment, the determination, and the plan. Triggers have to be met successfully and the centrifugal forces that bring one back to the addictive behavior, be they physiological, behavioral, or social/environmental, must be countered.

One way to understand the function of relapse in recovery is to see it as a sign that the motivational tasks involved in the stages have not been adequately addressed or successfully mastered. So relapse serves to indicate that the process of change has not been done well enough to support success. Recycling through the stages then serves to help the addicted individual "get it right" in terms of accomplishing these tasks to a degree that enables change to be maintained and relapse to be avoided. Much of the work of relapse prevention has focused on the cues and triggers that precipitate relapse. While those precipitants are important, they do not explain relapse [59]. Looking more broadly at the entire process of change and successful completion of multiple tasks of the stages can help clinicians explore a range of challenges and topics that span the entire motivational process instead of focusing only on the moment of the slip, lapse, or relapse.

Coping

Strong support has been found for a relationship between coping and relapse prevention [51]. Those who fail to use any coping response in a crisis have been found to be more likely to relapse [18]. There are two main theoretical aspects of coping responses: (1) the focus of coping and (2) the methods of coping [51]. In both of these areas there is an important distinction between active coping and avoidant coping. In terms of focus, active coping strategies are those which are oriented toward the problem, whereas avoidant coping strategies rely on avoidance of the problem. Active strategies are most appropriate when an individual has some control over the situation; whereas avoidant coping may be more useful when dealing with situations or events in which there is little or no control [48]. Methods of coping involve strategies and coping activities that involve both cognitive and behavioral strategies.

An individual's inability to utilize an effective coping behavior when he or she is experiencing a high-risk situation results in decreased self-efficacy and increased use of a substance as a coping mechanism [39]. However, differential effects have not been found for cognitive coping skills versus behavioral coping skills. Rather, actively engaging either type of coping skills seems to facilitate positive outcomes [9, 18]. In summary, it appears that in preventing relapse there is an important role for the addicted individual's response to any threats to abstinence or recovery. However, it is not only the actual effectiveness of the response but also the sense of confidence that the individuals have in their ability to perform the behaviors critical to recovery and to sustain change.

Self-Efficacy

Confidence in one's ability to perform behaviors seems a critical mechanism in intentional behavior change. Bandura [5] defined self-efficacy as the degree to which an individual feels confident and capable of performing a certain behavior in specific situations. The self-evaluation of one's confidence to remain abstinent has been associated with lower rates of relapse for both men and women, in inpatient and outpatient settings, and for both short-term and long-term follow-ups [10, 26, 55].

Deficits in abstinence self-efficacy have been found to be a significant predictor of relapse in a number of studies [29, 65]. Moreover, the longer an individual stays abstinent, the stronger their self-efficacy and sense of personal control becomes. Higher levels of self-efficacy have been found to be predictive of improved alcohol treatment outcomes in a variety of contexts [2, 55].

In a study that investigated abstinence self-efficacy of inpatient alcoholics in predicting their ability to remain abstinent after treatment, the level of abstinence self-efficacy measured at discharge from the residential center was the strongest predictor of abstinence at 1-year

follow-up [29]. Additional support has been found for the predictive power of abstinence self-efficacy using the Alcohol Confidence Questionnaire [65]. Higher levels of confidence to resist the urge to drink in high-risk situations were associated with greater likelihood to maintain abstinence 6 months after treatment. Also, lower levels of confidence in situations related to urges and testing control were found to predict relapse to heavy drinking during a 12-week treatment period [7]. Greenfield and colleagues [26] found that those who relapsed to alcohol the year after hospitalization had lower overall confidence scores than those who did not relapse. This later relapse onset for the group with higher self-efficacy indicates a relation between efficacy to abstain and duration of abstinent behavior following treatment.

A large clinical treatment trial for matching participants to optimal alcohol treatments based on a number of client characteristics, Project MATCH, considered abstinence self-efficacy to be an important variable for determining appropriate treatment. Levels of abstinence self-efficacy were measured at the start of the study (baseline) and at the end of treatment (post-treatment). For the outpatient arm of the study, baseline abstinence self-efficacy was predictive of drinking outcomes during treatment, throughout the 1-year follow-up, and at a 3-year follow-up [23, 56]. However, for aftercare clients, baseline self-assessment of abstinence self-efficacy did not predict post-treatment drinking, suggesting that efficacy was a more powerful predictor for those individuals who were just beginning therapy, compared with those who were continuing treatment and may have already experienced changes to their levels of abstinence self-efficacy or who evaluated their self-efficacy in a residential setting.

Strategies for Relapse Prevention

The challenge of preventing relapse is one of trying to find strategies that can support and increase motivation, can teach or implement appropriate coping activities when internal or external cues trigger a desire or temptation to drink or use drugs, and can encourage and strengthen the self-efficacy of the addicted individual. Proper motivation, coping and efficacy would then support recovery and prevent relapse. Most programs and models of treatment and mutual help provide activities and support that target these variables. Alcoholics Anonymous, for example, encourages continued self-reevaluation (e.g., moral inventories, reading supportive literature), active coping both in avoiding high-risk situations, and turning to meetings and a sponsor to support sobriety, and supports efficacy with a focus on one day at a time and messages of empowerment based on support from a higher power. However, the most extensive discussion of relapse prevention strategies comes from the social learning and relapse prevention models.

Relapse prevention is best used with clients who have finished an initial detoxification round of treatment and/or may be coming to the end of initial phases of treatment since they are the ones who have been able to achieve some measure of abstinence or change. In addition, rates of relapse are highest in the initial phases of the action stage and once initial treatment has been completed. Relapse prevention would also be appropriate for individuals who have experienced a slip after a period of sustained abstinence, and as a follow-up treatment for individuals in the maintenance stage of change [42].

Relapse prevention treatment strategies have been divided into five specific categories of activities: (1) assessment, (2) increasing insight/awareness, (3) skills trainings, (4) cognitive strategies, and (5) lifestyle interventions. Each of these activities will be described in detail below. The activities are interconnected and there is a logical flow beginning with the initial strategy of behavioral assessment, which often starts with self-monitoring by the client. The goal of this behavioral assessment is to get a clear and complete picture of the circumstances surrounding potential substance use, and the client's reactions to each of those situations or cues. If the client is still actively

using substances, it is critical to obtain accurate information about the amount, environment surrounding the use, and the events that preceded and followed the use. The next step is to identify high-risk situations, coping skills, and the effectiveness of both cognitive and behavioral coping strategies being used to address the cues [32].

Once key skill deficits are identified, coping skills training can be conducted using either group or individual sessions. An advantage of the group format is that peers are natural partners for role plays, and can provide examples of coping or scenarios for group brainstorming. Including significant others in sessions can also potentially assist in cue reduction and coping training and have a comprehensive impact on a client's recovery [32]. Finally, the focus turns to the lifestyle of the individual to see how overall patterns of life activities can help of hinder continued recovery and the maintenance of change. We will review each of these components in greater detail and then discuss two newer strategies that have been added to the relapse prevention tool box: mindfulness strategies and medications.

Assessment

Behavioral assessments can be conducted using direct observation by a therapist (when cues are available or presented), role plays, interviews with family members or peers, self-report questionnaires (Alcohol or Drug Abstinence Self-Efficacy; Alcohol Confidence Questionnaire, Situational Confidence Questionnaire), and self-monitoring [34, 64, 66]. In fact, self-monitoring serves not only as a means of gathering information, but also as an intervention. While clients may initially be resistant to self-monitoring as a homework assignment, frequently after completing it, they report it is a positive experience. In addition to the insight gained though the self-assessment, monitoring often acts as a catalyst for behavior change and leads to a reduction of the monitored behavior [35]. Self-monitoring can also be an effective tool to combat denial, challenge cognitive distortions, and identify substance-related automatic processes and negative thoughts, by which a client is on "autopilot" during a sequence of behaviors that lead to using [66].

If the individual is still engaging in the addictive behavior then using self-monitoring to assess the factors surrounding use is important. If the client has been able to achieve abstinence, a self-assessment of cravings is appropriate to identify their personal high-risk situations. A frequently used type of self-assessment is assigning a drinking diary or craving diary to identify habit patterns, potential triggers, high-risk situations, consequences of use to themselves as well as others, and the physical, emotional, and financial costs of using. It is important for the individual to understand the social, situational, emotional, cognitive, and physiological precipitants of relapse that make up a high-risk situation [66].

High-risk situations are any situation that threatens an individual's abstinence self-efficacy and poses a strong potential for relapse back to the addictive behavior. High-risk situations include both intra-personal determinants as well as inter-personal determinants. The intra-personal determinants include both positive and negative emotional states as potential risk factors. Negative emotional states such as anger, depression, anxiety, boredom, and frustration can be triggering particularly if substances were used as a way of dealing with the emotional states. Clients may need additional treatment such as anger management or therapy for depression in addition to drug counseling to give them the coping skills to deal with such negative emotions [32]. Positive emotional states such as feeling good, confident, or celebrating can bolster overconfidence in being able to handle "just one" use of the substance [34]. Interpersonal determinants include conflicts with friends, spouses, family members, and co-workers. Another interpersonal determinant is social pressure that can either be overt encouragement to use, or covert pressure to conform in a situation where everyone else may be smoking, drinking, or drugging [66].

Once the self-assessment has been completed, this information can be used to create a decisional balance sheet that helps to concretely lay out the pros and cons of using in particular situations. Such a worksheet can clarify the specific reasons for maintaining abstinence and increase motivation particularly for individuals who are not fully committed to treatment or recovery. Assessments can not only identify high-risk situations but also examine the commitment, self-efficacy, and coping skills that the individual may use to address challenging situations.

Insight and Awareness

Increasing insight and awareness assists clients in understanding the processes that trigger a relapse including social pressure, physiological mechanisms, or emotion management. Understanding these mechanisms is an important part of preparing for high-risk situations and unexpected triggers and urges. This can be made more concrete by creating an ongoing road map to relapse by which clients identify upcoming high-risk situations, as well as potential unexpected risks and emergency situations. They can also identify early warning signs that predict a high-risk situation [25]. The road map can also identify ways they can refrain from using with an effective coping strategy for a particular situation [34]. The next challenge is to make sure that they have access to the types of skills and self-management strategies that would be needed to effectively address their risk situations that could provoke a return to the substance use or addictive behavior.

Behavioral Coping Skills

The behavioral skills training component involves training in a number of skills and strategies in different life domains to assist clients in resisting relapse. Skills training is designed to develop specific skills needed to cope with situations and to increase the client's sense of self-efficacy to sustain recovery and overcome risks for relapse. For example, relaxation training can be particularly helpful with clients who used substances to alleviate anxiety or to cope with stressful situations. Progressive relaxation training or mindfulness meditation can assist in decreasing anxiety in a high-risk situation enough that an alternative coping strategy can then be employed [67]. Assertiveness training can assist clients with poor social skills in navigating interpersonal pressures to use, as well as encouraging use of social support for continued abstinence. Practicing ways to refuse substances, deal with criticism, and appropriately express feelings of frustration, anger or anxiety can assist clients in building their repertoire of coping skills [66].

Cue exposure is another cognitive behavioral technique that is used to build up client's abstinence self-efficacy through gradually exposing them to substance-related cues. It is a counter conditioning procedure in which clients are progressively desensitized to the stimuli associated with the addictive behavior in controlled conditions. Clients practice using coping skills as they are gradually exposed to different high-risk situations. In order to avoid iatrogenic effects from putting clients in potentially very unsettling conditions, exposure should always end with adequate processing of the experience and debriefing such as a relaxation exercise or meditation [3, 67].

There are numerous skills that can be developed and there are manuals for various types of addictive behaviors that contain modules for specific skills training in effective communication, anger management, coping with negative emotions, depression, assertiveness, handling rejection, meditation, and managing family members who use substances. These modules can be used depending on the types of situations that are identified by the addicted individual so that the relapse prevention strategies can be personalized to the types of situations and cues that are most salient for that individual [47].

Cognitive Strategies

In addition to behavioral skills, there are also a number of cognitive strategies that can be taught and used to combat relapse. Often relapse is precipitated not just by the external cues but by the interpretations and self-statements from within the individual when confronted with a high-risk situation. Cognitive strategies are designed to challenge and change ways that individuals process information and problematic self-statements that undermine coping and efficacy. These cognitive strategies include cognitive restructuring, relapse rehearsal, labeling and detachment, and coping imagery. Cognitive restructuring is the process of correcting addiction-related cognitive distortions and frequent patterns of thinking such as seemingly irrelevant decisions and the abstinence violation effect. Seemingly irrelevant decisions are decisions which are not inherently related to the actual substance use, but can put the client in a high-risk situation. An example would be a client getting his car fixed at a mechanic one block from his favorite bar (alcohol-associated cues). Doing so could prompt him to go in to see if any friends (interpersonal pressure) were around as a way to alleviate the boredom (negative emotion) of waiting for his car to be fixed [34]. The goal of cognitive interventions is to help individuals examine and prevent such seemingly irrelevant decisions that put individuals in harm's way and can lead to relapse.

As was previously noted, the abstinence violation effect is a potential reaction to initial use or reengagement in the addictive behavior. If after a lapse clients feel they failed and experience a significant decrease in abstinence self-efficacy, they are more likely to go back to using as much as they used to rather than attempt to regain abstinence. It is important to put a lapse into proper perspective so that clients can return to the recovery process rather than returning to their prior habits. Recovery from a slip seems to require an interpretation and attribution of the lapse as caused by external or environmental factors, a continuing commitment to the change goal, a confidence in the ability to recover from a lapse, and a reactivation of active coping to avoid or manage the triggering situations or cues [34].

Relapse rehearsal and relapse fantasies are a means of associating the coping skills learned in treatment with a crisis situation. By imagining a high-risk situation and using an effective coping skill to avoid substance use, the client is able to prepare for a variety of high-risk situations and evaluate the expected effectiveness of different coping strategies. Labeling and detachment are coping strategies aimed at helping clients experience urges and cravings without succumbing to them. This strategy reframes cravings as temporary sensations of desire as opposed to unending compulsions that dictate a client's behavior. Helping clients view cravings as coming from environmental cues, and not coming from within themselves, can assist in decreasing the subjective strength of the cravings [66].

Other coping strategies to deal with urges include challenging the urges, recalling negative consequences of using, thinking of the benefits of not using, thought stopping, distraction, delaying a decision of whether to use or not, leaving the situation, and getting support from others [32]. Coping imagery is another cognitive technique that can assist with combating high-risk situations. Making use of guided fantasy, the therapist and client can make use of personally relevant imagery that can bolster the individual's self-efficacy to avoid relapse [66].

Seeking support for abstinence and recovery from a slip involves both cognitive and behavioral strategies. Individuals that have social networks filled with drinking or drug use that they cannot leave are more prone to relapse and need to recognize the need to change the composition of the network and build another one that is supportive of recovery [37]. Mutual help groups like Alcoholics Anonymous and Smart Recovery offer opportunities to listen and understand the perspectives and experiences of others and offer both cognitive and behavioral coping activities for the addicted individual [53].

Lifestyle Interventions

The final stage of the process of change is to integrate the new behavior into the lifestyle of the individual [20]. Replacing dependence with abstinence or excess with moderation generally involves a change not only in one behavior but in the addict's overall way of life. Lifestyle interventions for relapse prevention include lifestyle balance, substitute indulgences, positive addictions, and stimulus control techniques. Lifestyle balance is a global strategy to ameliorate stressful situations, promote appropriate coping, improve problem solving, and increase pleasurable activities such as hobbies or spending time with friends and family that were replaced by substance use. It is also important for clients to understand that their desires not to be depressed or to be social, which can lead to high-risk situations, are reasonable desires. However, they need to find alternative ways of fulfilling these needs without using substances or turning to other problematic, addictive behaviors [34]. Mutual help groups and activities can play an important role in offering a venue and a series of activities that can support the lifestyle changes.

Substitute indulgences are activities that are immediately gratifying and can serve as a substitute for the addictive behavior when a client experiences an urge or craving. One example is to take a hot shower or bubble bath instead of going to a bar to relax after a difficult day at work. It is important however, that the pleasurable activities are not harmful in the long term. Positive addictions have a similar function in that they replace the activity of substance use, but have more long-term rewards and value, rather than immediate gratification. Examples of positive addiction include taking up a sport, regular exercise, or a new hobby. It is important that positive addictions be practical and something that the client is able to perform and sustain on their own [34].

Stimulus control techniques attempt to address the physical cues for relapse. A frequent example is the strong association of drinking and smoking, either of which could serve as a cue for the other. While experiencing some cues is inevitable, it is an important step for a client to eliminate the cues under their control by changing their routine as much as possible. An example for a client who is quitting smoking would be to throw out all cigarettes, ashtrays, and lighters, rearrange the furniture so that a favorite smoking area is not present, and change the morning routine so that it does not revolve around the first cigarette of the day [34].

Mindfulness-Based Strategies for Relapse Prevention

Recently another set of strategies has been added to relapse prevention treatment called mindfulness based relapse prevention. The basic structure and goals of relapse prevention remain the same but there is an emphasis on the use of mindfulness techniques throughout the intervention process. Mindfulness meditation is a metacognitive skill learned through practice of meditation that allows the individual to achieve perspective, patience, and inner peacefulness that can reduce relapse cues and create lifestyle changes to promote recovery [8].

Mindfulness is a state of detached awareness of emotions, cognitions, and physical sensations. It is a state of attentional focus which can be used to change client's attitudes towards their thoughts, feelings, and sensations. Mindfulness based relapse prevention uses development of the mindfulness state to disrupt maladaptive cognitions by heightening awareness of cravings without identifying with, judging, or reacting to them. The mindfulness state interrupts the chain of cognitions and emotions that follow an urge or craving thus decreasing the likelihood of an action based on them [67]. Mindfulness appears to work differently than thought suppression, which prior studies have found to be an ineffective coping technique [8]. There have been promising initial findings regarding the usefulness of mindfulness in relapse prevention with incarcerated substance abusers, though more thorough investigation is necessary [8].

Medications for Relapse Prevention

Medications have also been found to be useful adjunct to promote change and prevent relapse in treatments for nicotine, alcohol, and opiate addiction. Since the 1990s both Naltrexone and Acamprosate (Campral®), have been added to disulfiram (Antabuse®) as approved medications in the United States to be prescribed for alcoholism treatment [36]. Use of disulfiram causes a flushing or sick reaction when alcohol is ingested, which results in extremely low compliance, and as a result has not been found to be superior to placebo. Meta-analyses have shown that both acamprosate and naltrexone can help reduce cravings and increase days abstinent [42]. Acamprosate may be more effective in promoting complete abstinence, while naltrexone may be more effective when the treatment goal is reduced drinking, though there have been mixed clinical outcomes [57].

Methadone, buprenorphine, levo-alpha-acetylmethadol, and naltrexone have been used to treat heroin addiction. Opiate maintenance using methadone, buprenorphine, or levo-alpha-acetylmethadol assist in decreasing the extremely high rates of relapse in treatment for opiate addiction, although the medications themselves can be addictive at high doses as well as have negative side effects [62].

Medications for nicotine cessation include a variety of nicotine replacement products, varenicline tartrate (Chantix®), and the antidepressant bupropion (Zyban®). In an analysis of over 6,000 articles, researchers found that use of medications for nicotine replacement therapy including gums, inhalers, patches, and nasal sprays, as well as the antidepressant bupropion at least doubles the likelihood of quitting compared with placebo. In addition, the effects of medications are substantially increased when added to behavioral interventions [16].

Although there have been studies of medications to treat cocaine addiction, they have not resulted in improved treatment outcomes with any consistency [42]. It is generally recommended that medications be administered in addition to a psychosocial intervention such as relapse prevention for opiate and nicotine treatment [15, 16, 62], though investigations of combined therapy and medication have showed mixed results compared with either alone for treating alcoholism [4, 57].

When Relapse Prevention Fails

All of the above strategies are designed to help the addicted individual achieve and maintain change once initiated. However, as many of the studies demonstrated, these strategies are helpful to some but not others [9, 28]. Even individuals who have been taught coping strategies and acknowledge the critical cues or triggers that make them vulnerable to relapse have not been successful in preventing relapse. This is when successful recycling promotion has to be substituted for relapse prevention. Clinicians and researchers working in addictions have to take a life course perspective, abandon the single attempt, linear model of success, and see the process of successful change as better represented by a cyclical process that in the long run yields success change [54]. We will discuss the life course perspective and the cyclical model below.

A Life Course Perspective on Recovery

Alcoholism and drug addictions are chronic conditions that can span decades and numerous periods of treatment, remission from drinking or drug use, relapse to uncontrolled drinking, and treatment re-entry. Treatment providers have a comparatively small amount of contact with clients in their overall treatment and recovery careers. It is important to understand the factors and context outside of treatment that are related to clients' entry into treatment and that precipitate relapse episodes. Taking the life course perspective of recovery is an important step for researchers in order to truly appreciate the full context in which a particular treatment episode "succeeds" or "fails" [21].

Some individuals with less severe dependence are able to avoid the cycle of relapse and maintain either continued abstinence or a lower level of non-harmful substance use [41]. However, the recovery process of many addicted individuals is marked by multiple transitions in their treatment career. In long-term follow-up studies spanning up to 16 years, researchers have consistently found that individuals who received treatment sooner and spent more time in treatment had longer periods of remission from alcohol dependence. Greater use of alcohol was predicted by less self-efficacy, greater use of avoidance coping, and less of a perception that drinking was a significant problem [49, 50].

Successive Approximations, Recycling, and Learning from the Past

As described earlier, learning how to overcome an addiction and to avoid relapse is essentially a process of successive approximations whereby addicted individuals try to modify the addictive behavior, fail to complete the change, then try again until they are successful or until death, disability, or prison intervenes. There is no guarantee of success even after multiple attempts since the learning may not be complete or the physiological or environmental barriers are too great for this individual to overcome. However, large numbers of individuals who have been classified as dependent on a substance have been successful in significantly changing addictive behaviors after multiple attempts. Half of the "ever smokers" in the U.S. have quit smoking successfully and we have over 40 million of these success stories [13]. A recent epidemiological study by Dawson and colleagues [19] examined over 4,000 individuals who had had a lifetime diagnosis of alcohol dependence. Based on past year drinking, they estimated that approximately 47% could be considered in full remission and were classified as either abstinent (18.2%), low-risk drinker (17.7%) or asymptomatic risk drinker (11.8%) with only 25% meeting the criteria for being dependent during the past year. This study highlights once again that the definition of relapse determines whether you consider someone in recovery or relapsed. Nevertheless, recovery does happen for many addicted individuals, demonstrating that over time there is significant change and successful self-management of addictive behaviors.

Relapse represents a problem in the preparation, planning, or implementation of the action plan. As such, it highlights some deficit or barrier that needs remediation or a different solution. Relapse then, should be viewed from a pragmatic and learning perspective. Trial and error are an integral part of psychological principles and medical practice. If one strategy or medication does not seem to help the individual completely manage the problem or begins to cause more problems than it solves (e.g., side effects), practitioners would quickly try another strategy or medication. However, often with addictions the inability to succeed has been viewed as a deficit of motivation, will, or character. A learning perspective that views the relapse as an opportunity to learn from the past and do something differently accurately reflects longitudinal research and would be critical to creating effective relapse prevention activities that reflect the reality of recycling.

Promoting recycling represents a valid relapse prevention strategy that accepts the occurrence of relapse. Recycling engages individuals who have relapsed in a review of past success and failure with a view of finding what went right or wrong and when or where it occurred so that the deficits in motivation, coping, or self-efficacy can be remediated and the types of barriers that led to the relapse surmounted. In longitudinal studies, many individuals get stuck in the process of change and remain in precontemplation or contemplation for months or years [11, 63]. The goal of recycling is to help individuals make another more successful attempt to change the addictive behavior more quickly and effectively. Policies and practices that limit access to services after a relapse or interpret relapse as a failure of the treatment undermine the recycling process.

Treatment Recommendations

There are several important considerations that summarize this review of relapse prevention and recycling in the addictions. Each of these considerations has important implications for treatment and research. We will highlight below the key considerations and implications.

1. Relapse is part of the process of successful behavior change. Partial success and outright failure offer opportunities for learning that are critical for long-term successful recovery. As in other areas of life, the important reality is not that you have fallen down, but that you get back up and try again, hopefully having learned important lessons about how to achieve the goal without falling down again. Relapse prevention begins at the start of the change process and should be an integral part of all treatment programs. However, addicted individuals may not be able to avoid and practitioners may not be able to prevent all relapse. In their efforts to promote maintenance and prevent relapse, treatments and treatment providers should concentrate on helping individuals manage motivation, engage in critical coping activities and support and increase their self-efficacy to perform the behaviors needed to achieve abstinence and recovery. In addition, special attempts should be made to engage or reengage individuals who relapse in a conversation and collaboration to promote recycling to remedy the problems in the process of change that contributed to the relapse.
2. Maintaining change is the goal of relapse prevention. A number of elements have been identified as important maintenance enhancers that also act to prevent relapse. Commitment fueled by solid decision-making leading to adequate planning, skills acquisition and implementation, and a long-term goal and perspective seem to be critical to sustaining significant modification of addictive behaviors. A comprehensive perspective on the process of change and a life course perspective appear to be essential when addressing and comprehending relapse.
3. Support sustains success. Support from family, friends and peers seems to play an important role in prevention relapse. Individuals who seek support and engage in mutual help groups have better outcomes [60]. Creating or supporting existing support groups and helping individuals access and utilize the support can assist in relapse prevention. Integrating the relapse prevention model perspective with the mutual help perspective offers social interactions and support that can enhance personal coping, motivation, and self-efficacy.
4. Multiple problems complicate maintenance of change. Pay attention to complicating life problems be they financial, family, social, medical, legal, and psychiatric in origin that can have an impact on successful recovery from addictions [44]. Psychiatric illness and emotional distress are risk factors for becoming addicted and act as barriers to beginning and remaining in recovery. Integration of treatment efforts across multiple problems seems to offer the best potential for successful change of the addiction as well as the other problems.
5. Stigma stifles success. Viewing relapse as a failure and relapsers as "defective people" who cannot change promotes the stigmatization of addictions in general, and relapsers in particular. Relapse is a problem of behavior change and not a unique problem of addictions. Addressing and managing relapse is part and parcel of all efforts to change established patterns of behavior and to manage chronic illnesses.

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Brief Interventions for the Treatment of Alcohol or Other Drug Addiction

Robert J. Tait and Gary K. Hulse

Contents

Drug Use and Problems

A broad range of treatment approaches are available and necessary for the management of persons with problem drug use. Individuals with problem drug use can present anywhere along a continuum from early-stage problems associated with acute, "recreational", or binge use to severe drug dependence with major physical and psychosocial problems. This latter group commonly has multiple health problems with poor or negligible non-drug-using social support and requires intensive intervention, often with the objective of achieving abstinence. Traditionally, most therapeutic resources were directed at the management of this group. These interventions have generally been intensive in nature and costly to deliver, and have failed to reach the majority of those using these substances [64].

While the impact of drug dependence on health and society is widely recognized, the effects of non-dependent excessive drug use are often underestimated by the community and the health-care system. For example, the number of non-dependent heavy drinkers far outweighs the number of dependent people [63], with most alcohol-related problems resulting from people drinking below levels that cause major physical dependence, so this group has a greater influence on the community's burden of alcohol problems: the so-called prevention paradox [42].

In 1990, a report by the Institute of Medicine recommended that given the number of people with mild or moderate alcohol problems, a range of therapeutic approaches needed to be developed to cover the full gamut of alcohol use problems [35]. Similar conclusions could be drawn concerning clinical and subclinical use of other types of substances. Table 1 summarizes

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_39,

Table 1 Categories of substance use disorders and problems

Category	Description
Dependence – DSM-IV [3]	A period of maladaptive substance use and the presence of three or more criteria relating to tolerance, withdrawal, and impaired control of consumption levels occurring anytime over a 12-month period. In addition, social, occupational, or recreational activities are largely abandoned and replaced by substance-related behaviors (obtaining, using, and recovering from substance use)
Abuse – DSM-IV [3]	A maladaptive pattern of usage that causes significant clinical distress or impairment over a 12-month period and impacts on social and functional capabilities
Dependence – ICD-10 [85]	A syndrome of psychological and biological symptoms that have occurred for at least a month or repeatedly over 12 months. The criteria cover impaired control, withdrawal, tolerance, and preoccupation with use of the substance and persistent use despite evidence of the harmful consequences
Harmful – ICD-10 [85]	Clear evidence of physical or psychological harm, including impaired judgment or dysfunctional behavior
Hazardous – WHO [22]	Use of a drug that will probably lead to harmful consequences for the user if it continues at the same level
Risky [33]	Those who drink/use other substances in a way that creates a risk of harm to themselves or others

Current United States alcohol guidelines recommend no more than two drinks (12 fluid ounces of regular beer, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof distilled spirits) per day for men and one for women, with zero drinks being the only safe option in some cases (e.g., pregnancy, whilst operating machinery, or with some medications) [77]
DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; WHO = World Health Organization

key definitions for problematic use of alcohol or other substances.

Drug Treatment in Primary Care and Non-Specialist Settings

People who consume hazardous levels of alcohol (use that will probably lead to harmful consequences for the user if it continues) rarely seek treatment [63]. Indeed, less than 30% of individuals with alcohol use disorders are likely to have sought professional care in the previous year [75], and only 14% of those with other substance use disorders seek professional help [4]. People with early-stage problem drug use commonly present to general practitioners or community health services for reasons that are not drug-related, whilst in hospital emergency departments, health workers typically encounter a greater proportion of cases, such as acute trauma presentations, accident, injury, and overdose, that are common consequences of drug use [16].

The non-dependent population, unlike their dependent counterparts, typically have an intact psychosocial fabric and, therefore, do not require the intensive interventions directed at dependent individuals [55]. The identification and effective management of these individuals before the development of more significant drug use, dependence, and associated major physical and/or psychosocial problems are clearly desirable. Those who have early problem drug use but who are not dependent are a major target group for early identification, with the most widely accepted method of achieving changes in drug use by this group being via use of brief interventions.

Screening of clients that is directed at the early identification of "at-risk" drug users and the use of brief interventions provide an efficient way of reaching a larger portion of those with alcohol or other drug problems than do traditional intensive interventions, and may be especially suited to those with less severe diagnoses [53]. By using opportunistic interventions, brief interventions may be able to reach a proportion of those who may never present at

specialist treatment facilities [12, 80]. Moreover, screening in primary care for subclinical alcohol consumption or other drug use to identify "at-risk" individuals allows preventive measures or treatment to be initiated before clinical-level disorders and the associated health and social problems develop.

A large number of short screening tests are available to aid in the systematic identification of alcohol or other drug use problems in primary care [10]. Two of the most commonly used tests are the Drug Abuse Screening Test [68] and the 10-item Alcohol Use Disorders Identification Test. The latter was developed by the World Health Organization and validated in numerous countries and populations [64, 65]. It is also available in three shortened versions and has been used widely [58]. The Drug Abuse Screening Test is available as a 28-item form [68] or a 10-item short form [29] and screens for general drug abuse rather than a specific class of drug. The brevity of these instruments and their ease of use make them suitable for a range of general medical settings. Biological screening tests (e.g., breath, hair, urine, saliva, laboratory markers) would appear to offer a more robust assessment, but to date these are of limited use in primary care, where results are needed quickly, must be inexpensive, and must show more than just recent use [1, 10, 36]. Therefore, biological assays may be more appropriate in specialist settings or where they are required to comply with judicial requirements.

What are Screening and Brief Intervention?

Screening and brief intervention are generally used as part of a consultation in a primary care setting—for instance, general practice or a community health service. However, as is explored in more detail below, some brief interventions may be initiated at a "teachable moment" such as in general hospital emergency, medical, or surgical departments, when individuals may be highly motivated to change their behavior.

Brief interventions are sometimes described as "minimal" interventions due to the less intensive nature of the intervention required to effect changes toward more positive drug use patterns in these non-dependent individuals, or as "early" interventions because they are directed at individuals who have not progressed to more serious drug use patterns. However, even at the extreme end of the spectrum, screening and brief intervention have a role in identifying people with dependence and enhancing referral for treatment.

There is no universally accepted definition of what constitutes a "brief" intervention. Babor provided a convenient heuristic where a single client contact with a professional constitutes a "minimal" intervention, 1–3 sessions constitute a "brief" intervention, 5–7 sessions a "moderate" intervention, and 8 or more an "intensive" intervention [7]. Miller and Wilbourne suggested that 1 or 2 sessions of treatment constitute a brief intervention [51], whilst Moyer and colleagues used a threshold of 4 sessions to define brief interventions [53]. In the first section of this chapter, the focus will be on interventions that can be delivered in 4 or fewer sessions. In the second section, the focus will be on brief interventions to increase compliance with pharmacotherapies used in the treatment of problem alcohol or other drug use, which often extend over 12 or more sessions.

Notably, none of these definitions delineate the length or content of the intervention. Interventions are typically of 30–45 min duration; however, within a community/primary care setting, interventions can be incorporated within a 5- to 10-min physician consultation [25]. Five key elements have been identified for inclusion in an intervention. First, the clinician assesses the quantity and frequency of alcohol or other drug usage and provides direct feedback to the client on information regarding health or psychosocial morbidity relevant to his or her level of use. Second, goals for alcohol or other drug use are established that are acceptable to both provider and client. These goals may be a reduction in consumption, such as using alcohol at a "safe" level, or complete cessation,

as is commonly employed with tobacco use. Third, the provider uses behavioral modification techniques—for example, to help the client identify high-risk situations and develop strategies to deal with these. Fourth, the clinician should supply support material on problems associated with substance use plus self-help techniques. Fifth, the provider should offer ongoing support [25]. Others have summarized the content under the acronym "FRAMES" [12]—that is, *F*eedback on personal risk, personal *R*esponsibility for the problem, *A*dvice that is clear and explicit, a *M*enu of options on how to change, an *E*mpathic style of counseling to avoid coercion or authoritarianism, and enhancement of the client's *S*elf-efficacy [12].

Babor and colleagues provided a thorough discussion of the psychological principles and behavioral change strategies thought to underlie early or brief intervention programs; these incorporate principles from social, cognitive, and behavioral psychology to increase motivation and commitment to change [9]. For example, a health professional can be seen as having social power, and, as a credible source of relevant health information, the provision of normative information allows social comparison and support networks to use social influence to modify behavior [9].

A concept that often arises in the screening and brief intervention literature is that of the "teachable moment" when a person is particularly likely to be open to changing his or her behavior—for example, when a major health event or hospitalization related to substance use occurs [30]. McBride and colleagues suggested a model to help determine whether a given event, such as hospitalization for a substance-related morbidity, will cue the client to reduce his or her substance use [50]. First, does the event (e.g., hospitalization or ill health) serve to increase perceived risk from the client's use of the drug and the potential for positive outcomes to occur if the use is reduced or ceased? Second, does the event provoke a strong emotional response? Third, does it lead to redefining the person's self-concept? For instance, a child being diagnosed with asthma may be associated with smoking by a parent, leading to the parent re-evaluating his or her role as a protective caregiver. Even in the presence of all these factors, pre-existing individual factors may override the impact of the event. Nevertheless, delivering interventions at a teachable moment is likely to amplify greatly the impact of the intervention—for example, increasing cessation of smoking by up to 70% compared with a background quit rate of about 5% [50].

Nevertheless, some have contended that the stress associated with a hospital presentation and the often chaotic environment in hospital emergency departments may mean that this is not a conducive setting in which to deliver an intervention. However, it may still be appropriate to use the opportunity to arrange a follow-up intervention [47], and there is the possibility of using motivational techniques to encourage people to attend treatment rather than attempting to deliver "treatment" under these difficult conditions. Indeed, one of the earliest brief interventions based in emergency departments was an attempt to facilitate referrals for treatment for those individuals with alcohol-related problems [15].

Screening and Brief Intervention—Effectiveness and Delivery

Alcohol

Of all the strategies and pharmacotherapies for treating alcohol use problems, there is more evidence, particularly from studies of high methodological quality, to support the use of screening and brief intervention than any other type of intervention. This is still true even when motivational interviewing is categorized separately from other forms of screening and brief intervention [51]. Brief interventions are also the highest ranked intervention in clinical populations, although this form of intervention is most effective when those with more severe disorders

are excluded [53]. The focus on clients with less severe alcohol use problems means that "safe" use of alcohol can be the goal of the intervention rather than complete abstinence, which has been the traditional goal of more intensive interventions.

Although there is robust and extensive literature on the use of screening and brief intervention for alcohol use problems [12, 53, 82], a criticism has been raised that these conclusions were based on select populations and from tightly controlled clinical trials [39]. From a health care perspective, a critical concern is whether or not this type of intervention can be translated into the clinical setting of primary care. A meta-analysis of trials conducted in primary care using interventions that would be suitable for inclusion in clinical practice (i.e., physician interventions of 5–15 min or nurse interventions of 20–30 min) identified 28 trials, including 5 that used the motivational interviewing approaches [39]. Overall, brief interventions reduced alcohol consumption by 41 g/week at 1 year. Brief interventions also seem to be effective at reducing binge drinking and heavy drinking, albeit that these conclusions are based on a limited number of studies and that the studies used different definitions to categorize heavy use of alcohol (criteria ranged from 20 to 35 drinks/week for men and 13–35 for women) [39]. The main caveat identified by the research was the lack of a significant reduction in alcohol use by women, but this may be related to lack of statistical power, with only 499 female participants out of the 7,286 included in the review [39]. This is a potentially important limitation as women are more likely than men to seek help from primary care providers [75]. On the other hand, a recent meta-analysis did not find gender differences in the effectiveness of screening and brief intervention [53], suggesting that lack of statistical power may indeed be the explanation.

Brief interventions also have a sound health economics rationale with a positive cost-benefit ratio, with significant savings through reduced health costs as well as reduced costs to society—for instance, in reducing vehicle accidents [27]. The magnitude of this effect has been estimated at 5.6:1 at 12 months and 4.3:1 at 48 months when considering just reduced health system costs [26, 27]. Thus, an intervention that costs $205 per individual to deliver resulted in an average benefit of $1151 [26]. Including savings to the wider community, the total benefit was $7985 per intervention [27].

Tobacco

All forms of intervention to encourage the cessation of tobacco use are cost-effective in terms of cost per life-year saved [79] and with the cost of these interventions comparing favorably with virtually any other health care program [76, 79]. Whilst improved rates of cessation accrue from more intensive interventions, these improvements do not keep pace with increased costs. However, this should not be used as a reason for not delivering more intensive interventions, which may be particularly efficacious in those with more severe problems, for whom brief interventions are typically less effective [79].

Guidelines are available for primary care practitioners, such as physicians, nurses, and dentists, to aid in the development of screening procedures and the delivery of appropriate interventions for users of tobacco [24, 81]. The United States guidelines evaluate a range of different psychosocial and pharmacological interventions as well as the management strategies for identifying and treating smokers in different primary care settings. The guidelines emphasize the importance of screening all patients for tobacco use and recommend strategies for approaching those willing to quit, those unwilling to quit, and those who have recently quit [24]. However, it also has been suggested that repeated advice to asymptomatic smokers may be counterproductive [67], contrary to the guideline recommendation that smokers should be asked about their use of tobacco on every visit. Potentially, the importance of this guideline may be derived from the development of systems that help to ensure that cessation of tobacco use is

thoroughly integrated into clinical practice rather than through increased benefits to an individual.

The initial approach recommended is a brief intervention that can be delivered in approximately 3 min, summarized under the mnemonic the "5 A's" (Ask, Advise, Assess, Assist, and Arrange). These guide the practitioner to ask every client about tobacco use at each visit, to advise them clearly and in a personalized manner to quit tobacco use, to assess their current willingness to quit, to assist them in forming a cessation plan, to provide them with access to counseling and appropriate pharmacotherapies, and, finally, to arrange a follow-up appointment, if possible within a week of the agreed-upon quit date [24].

If the client is not willing to quit, a further brief intervention can be delivered that focuses on increasing the motivation to quit (see Chapter "Motivational Interviewing" for detailed information on motivational interviewing). This brief intervention is formulated under the mnemonic the "5 R's" (Relevance, Risks, Rewards, Roadblocks, and Repetition). Thus, the intervention should focus on aspects that are personally relevant, such as current health problems, and should encourage the smoker to identify the risks of tobacco use and the rewards that will accrue with cessation. Any potential roadblocks to cessation should be addressed and solutions generated. Finally, the intervention should be repeated on each occasion that the client is seen.

Given the chronic relapsing nature of nicotine dependence and other addictive disorders, it is important also to plan and deliver relapse prevention interventions, especially in the first 3 months after a person has quit smoking. This typically involves the use of open-ended questions to encourage discussion of benefits, successes, and problems encountered as well as providing encouragement and help with significant problems, such as depression or withdrawal symptoms.

A recent meta-analysis of randomized trials with at least 6 months follow-up of brief interventions by physicians found that a single session lasting up to 20 min, plus up to one follow-up session, increased the rate of cessation by 1–3% over the background rate of cessation (2–3%) [69]. However, the effectiveness of this approach is derived from screening all participants and intervening with those who are smokers. The main drawback identified was the difficulty of persuading physicians to incorporate it into regular practice.

Brief interventions by nursing staff are also effective at producing small but significant increases in successful quitting. However, the authors of the analysis stress that statistical heterogeneity indicates that this finding may not generalize to all patient groups or clinical settings equally [59]. Nevertheless, the United States guidelines recommend that interventions by all non-physician clinicians (i.e., nurses, psychologists, and dentists) can be justified empirically compared with no treatment or self-help [24].

Smoking cessation interventions delivered in a hospital would appear to be an ideal opportunity, particularly with the expansion of "smoke-free" hospital policies in many developed countries. However, a recent meta-analysis concluded that high-intensity behavioral interventions initiated in a hospital that included at least 1 month of post-discharge support were effective, but that lower-intensity and shorter-duration interventions were not found to be effective [60].

Illicit Drugs

The weight of evidence supporting the utility of brief interventions in treating alcohol use or cigarette smoking is in striking contrast with the dearth of studies on the use of these techniques for illicit substance use problems. Two Cochrane reviews of psychosocial treatments for opiate use and of psychosocial and pharmacological treatment for opioid detoxification did not identify any studies that used brief interventions for the psychosocial component [2, 49]. Similarly, a Cochrane review of psychosocial interventions to treat cocaine and other psychostimulant disorders failed to identify any brief

interventions that matched the inclusion criteria [41]. A third Cochrane review of interventions to reduce drug use by young people conducted outside the school setting [28] and an earlier review of interventions for adolescent alcohol, tobacco, and other drug use [72] identified one brief intervention with adolescent substance users [54].

Oliansky and co-workers delivered different interventions at each of three sites that served different substance-using clients. An adolescent clinic and female-only clinic received a primarily information-based intervention on the adverse effects of substance use. The third clinic, which served general adult clients, delivered a 10-min intervention to empower clients to take responsibility for their drug use. Compared with usual care, the adolescents and the general adult group reported reduced drug use at 3 months [54]. A more recent brief intervention used the screening and referral approach where adolescents who presented to emergency departments with alcohol or other drug problems were encouraged to attend external agencies for treatment. The authors reported that this type of intervention could be successfully delivered in emergency departments but noted that the yield (proportion of adolescents attending treatment), although significant compared with usual care, was low [73, 74].

A number of programs have used brief interventions in individuals with cannabis use problems, but the dominant paradigm has been the motivational interviewing approach [8, 19, 48, 70]. Lang and colleagues conducted a pilot study using brief but intensive psychotherapy, which had promising outcomes in reducing the quantity and frequency of cannabis use [43]; however, the assessment and intervention took 2.5 h and the theoretical framework falls outside the basic information approach of brief interventions. In addition, the study did not contain an effective control group, so the improvements cannot be attributed reliably to the treatment. As with the interventions for cannabis use, motivational interviewing techniques also have been used in other illicit drug treatment projects [6, 13]. With respect to volatile substances, little research has been conducted on treatments specifically for inhalant users, so clinicians have adopted methods from interventions for other addictive disorders, including cognitive behavioral therapy and motivational interventions [83]. Similarly, there have been few studies of brief interventions to reduce the misuse of licit drugs [11, 20].

Conclusions—Screening and Brief Interventions

Brief interventions are a well-recognized and empirically validated approach to the treatment of addictive disorders, particularly in the primary care setting. However, the key aspect is initiating procedures so that all clients are regularly asked about their alcohol or tobacco use and appropriate actions are taken. Nevertheless, some key shortcomings have been identified. First, there are sparse data on the use of screening and brief intervention with illicit substances or the misuse of licit substances. Second, the effectiveness of screening and brief interventions with women, at least for alcohol use problems, has yet to be established definitively. Given the greater use of primary care by women, this potential deficit is of concern. Third, the effectiveness of non-clinician screening and brief intervention programs for tobacco use needs further clarification [24].

Future Research

In 2007, Wilson Compton of the National Institute on Drug Abuse concluded that there were currently few data to support the use of screening, brief intervention, referral, and treatment for illicit drug use and no research to support this with respect to prescription drug use [18]. However, this is likely to change in the near future, with the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration calling for research project submissions in this area. In addition, the Substance Abuse and Mental Health Services Administration-funded programs have already

screened over 500,000 people, with preliminary data indicating benefits in reducing alcohol and illicit drug consumption [66]. The increasing misuse of prescription and over-the-counter medications, with emergency department visits up 21% between 2004 and 2005 [71], is a cause of concern that has resulted in calls for research funds to be directed to this area, including the evaluation of screening, brief intervention, referral, and treatment programs to identify and intervene with the users of these licit substances [17]. Furthermore, whilst there is extensive evidence for the effectiveness of screening and brief interventions, further work is required to determine the best referral processes for specialist treatment for those who do not respond to brief interventions [10].

Improving Compliance/Adherence to Pharmacotherapies

The first section of this chapter assessed brief interventions that aimed directly to address problem use of alcohol or other drugs. One limitation was that these interventions were most effective with individuals who had less severe disorders. However, brief interventions also can be used to increase compliance with pharmacotherapies. Used in this manner, they can have a role outside the specialist addiction treatment setting in addressing alcohol or other drug dependence. The second section reviews two models that have been used under this rubric.

Brief Behavioral Compliance Enhancement Treatment

Brief behavioral compliance enhancement treatment provides a standardized manual [37] that aims to improve the outcomes associated with pharmacotherapy, rather than constituting an independent intervention. It does this by enhancing behavioral compliance with a pharmacotherapy, in particular by increasing expectations of the effectiveness of that therapy. Brief behavioral compliance enhancement treatment was developed from the clinical management used in the National Institute of Mental Health collaborative trial on depression [23]. The original trial included clinical management that aimed to maximize the effectiveness of the pharmacotherapy through improved compliance and, simultaneously, to minimize loss to follow-up to maintain the validity of the trial. It should, however, be emphasized that the clinical management used in the National Institute of Mental Health collaborative study did not include any elements that can be considered psychotherapy and that its content was not based on any validated data but on clinical experience [23].

A manual-driven and standardized version of brief behavioral compliance enhancement treatment has been developed for clinical trials in the addictions, especially in the alcoholism field, and has now been used in several multi-site studies. The brief behavioral compliance enhancement treatment program is spread over 13 10- to 20-min sessions and is usually provided as weekly sessions [37]. An advantage of the brief behavioral compliance enhancement treatment program over other brief interventions is that it is customized to suit the development of different types of medication. As part of this customization, brief behavioral compliance enhancement treatment can be adapted to treatment protocols that target either abstinence or a reduction in hazardous drinking as the clinical endpoint. Brief behavioral compliance enhancement treatment encourages compliance not only with pharmacotherapy but also with general treatment adherence. Indeed, providing encouragement to the patient, even for small treatment gains, is an important aspect of brief behavioral compliance enhancement treatment. Generally, the brief behavioral compliance enhancement treatment program consists of three phases covering initiation, maintenance, and termination of treatment. The initiation phase is critically important and seeks to engage the client in a positive and trusting relationship that fosters adherence with the treatment regimen and educates the patient with regard to the harmful effects of alcohol

and the potential side effects of the medication. The clinician performing brief behavioral compliance enhancement treatment emphasizes the importance of medication use, develops simple behavioral repertoires to enhance medication compliance, and builds a realistic expectation of success but also discusses how potential side effects can be managed. Indeed, a flexible and naturalistic clinical feature of brief behavioral compliance enhancement treatment is that it can be administered by a trained provider within the scheduled format for the collection and discussion of side effects. Also, from the first session, the clinician providing brief behavioral compliance enhancement treatment establishes a platform for ascertaining progress with drinking changes. Notably, a unique aspect of brief behavioral compliance enhancement treatment over other brief interventions is that the patient sets a weekly target drinking goal. The second phase aims to maintain compliance and particularly to avoid early termination of pharmacotherapy. The clinician explores the gains made by the client and addresses any medication side effects that have appeared. The final phase examines how medication use can be terminated while still maintaining improvement in drinking outcomes and how these gains can be maintained without assistance [37]. The moderate amount of time required to implement brief behavioral compliance enhancement treatment means that it can be incorporated easily within research programs [38] and has the potential to translate into primary care. The potential for brief behavioral compliance enhancement treatment to translate into primary care is important because it increases access to care for alcohol-dependent individuals. Studies are needed to determine the utility of brief or compliance-based treatments in severely disadvantaged groups [62] or among those who presently receive complex treatment regimens [32].

Medical Management

Medical management is another intervention that has been developed to enhance compliance in pharmacotherapy trials for alcohol dependence. Medical management was derived originally from brief interventions. It is designed to be delivered in a medical setting and provides a cohesive program of brief intervention, pharmacotherapy support, and information [57], with the aim of achieving abstinence [45]. However, in considering the content and delivery of medical management, it should be remembered that it was developed as part of a research intervention and, as such, was also constrained so as not to overlap with the alternative behavioral intervention delivered in that program (combined behavioral intervention) [46]. Given that limitation, medical management may not contain the optimum elements for an intervention. For example, medical management specifically excluded elements that require specialist training or that were deemed too intensive and would impede the contrast with combined behavioral intervention [45, 57].

Medical management focuses on three areas: education, adherence to medication, and support to aid recovery. The key element in the education program is an individualized report by the clinician to the client on his or her health status and the role of alcohol in the development of health problems. Although derived from brief interventions, medical management can be quite lengthy in its administration. For instance, the initial session typically takes 40–60 min. Additionally, information is provided on the medication that the client will receive (i.e., naltrexone or acamprosate). Like brief behavioral compliance enhancement treatment, medical management also emphasizes the importance of adherence to the medication regimen. This includes discussion of side effects, likely time scale for treatment, and, importantly, why the medication is likely to be effective. The final element of medical management is support and optimism about successful treatment. A detailed manual [56], including information sheets for the practitioner and client, is available from the Web site listed in the Resources section below.

Medical management was designed to be delivered over 4 months with nine sessions [45, 57]; thus, it falls outside the typical criteria for a brief intervention, and the extent to which it will be adopted in the primary care setting has yet

to be established. Indeed, medical management might not translate readily into primary care because the training of providers can be an intensive process. Nevertheless, within the research paradigm of the COMBINE study, medical management had the lower intensity of the two behavioral interventions (i.e., medical management and cognitive behavioral intervention) that were evaluated along with two pharmacotherapies [5]. In that study, naltrexone in combination with medical management, but not cognitive behavioral intervention, was effective at reducing heavy drinking [5]. A different approach to the delivery of medical management, termed BRENDA [78], was used in the evaluation of targeted nalmefene, a mu opioid antagonist, as a treatment for alcohol dependence. Study results suggested that targeted nalmefene might have utility as a treatment for alcohol dependence [40].

Conclusions—Compliance Enhancement

Brief interventions provide primary care health workers with a framework to deliver interventions to any client presenting with substance use disorders. Brief behavioral compliance enhancement treatment and medical management provide an extension to brief interventions if clients are interested in receiving pharmacotherapies to aid in cessation. Some elements of these pharmacotherapy compliance approaches appear simply to be "good clinical practice", such as advising clients on how medications should be taken and warning of potential side effects. However, by providing these treatments as a structured manual-driven framework, they enable the clinician to approach with confidence a group of clients who are often regarded as difficult to treat in a variety of settings.

Future Research

There is a growing literature on methods of improving adherence (now generally used instead of "compliance" due to its less pejorative connotations) to psychotropic medications, especially among individuals with severe mental illness, such as those with schizophrenia [14]. It is estimated that about 76% of individuals with physical health problems are compliant with medications, compared with 65% of those prescribed antidepressants and 58% of those prescribed antipsychotic medications [21]. However, the high prevalence of comorbid alcohol or other drug problems and other mental health disorders, with an elevated level of associated mortality and morbidity [44, 84] combined with the low rates of successful cessation in this population [31, 61], illustrates the urgent need for the development of cessation programs for this group. The existing literature on adherence to psychotropic medication and the compliance enhancement programs for pharmacotherapies in treating alcohol or other drug problems suggests that it should be possible to design effective programs for this highly disadvantaged group.

Compliance enhancement interventions may also prove beneficial in supporting the use of pharmacotherapies with other addictive disorders. For instance, oral naltrexone has been approved for the management of heroin dependence, but poor compliance means that it is not generally regarded as an effective treatment [52]. However, in highly motivated individuals or with daily supervision, the effectiveness is increased [34]. Therefore, a trial using brief behavioral compliance enhancement treatment with oral naltrexone in a general heroin-using population appears to be warranted.

Resources

Brief interventions (alcohol) on-line training for health professionals: http://dln.uvm.edu/webbi/index.html

Medical Management Manual: http://pubs.niaaa.nih.gov/publications/combine/Combine%202.pdf

Resources for professionals, clients, and families on alcohol use problems: http://www.niaaa.nih.gov

Screening, Brief Intervention and Referral for Treatment: http://sbirt.samhsa.gov/index.htm

Screening questionnaire for hazardous/harmful alcohol consumption (AUDIT): http://www.therightmix.gov.au/pdfs/HealthProviderAUDIT.pdf

Surgeon General Tobacco Use and Dependence Guidelines: http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf

Treatment Improvement Protocol 34: Brief Interventions and Brief Therapies for Substance Abuse: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5.chapter.59192

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Self-Help Approaches for Addictions

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Contents

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Defining Self-Help

Help from without is often enfeebling in its effects, but help from within invariably invigorates. [111]

Self-help behavioral treatments encompass those strategies designed to moderate or extinguish substance use or associated negative consequences. Inherent within the definition are two fundamental and essential properties of self-help: (1) the strategies are self-initiated and self-maintained, and (2) the strategies do not involve enduring relationships with professional care providers, professional supervision or authority, or illicitly obtained prescription drugs. Under this umbrella fall techniques such as non-prescription substance substitution or replacement, bibliotherapy, helplines, spirituality and mindfulness, and Internet resources, as well as a variety of self-help groups. Each technique ranges in cost, intensity, availability, and effectiveness depending on the type and severity of the addiction. This chapter begins with a brief review of relevant literature related to self-help in addiction including reviews of natural recovery [113] and processes of change described

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_40,

in the Transtheoretical Model of Change [99]. Following description of this literature, with the exception of self-help groups (discussed in detail in Chapter "Substance Use-Focused Self-Help Groups: Processes and Outcomes"), this chapter reviews several specific self-help approaches and their applicability to various substance addictions as well as their availability to self-administrators.

Why Use Self-Help?

There are several reasons why an individual may opt for self-help methods as an alternative to professional care to manage substance use. One reason may be barriers of access to treatment. In a national telephone survey of 14,985 residents from 60 randomly selected U.S. communities, of those who reported that they needed help for substance abuse, well over one-third received no professional treatment, less treatment than they needed, or delays in treatment [119]. A common barrier to formal services for drug addiction concerns the cost of treatment, which can lead some individuals who want help, but don't believe they can afford it, to manage their own care. Stigma and the associated negative attitudes that practitioners, medical staff, and other health professional may convey toward the addicted, as well as the person's own feelings of shame or embarrassment, can also deter someone from seeking professional rehabilitation services [86]. In these instances, certain self-help methods can allow for anonymity and affordability in the recovery process.

Is Self-Help Good for Everyone?

Addictive behaviors can be modified or even terminated through self-initiated processes [99]. As described later in this chapter, individuals who were once dependent on various addictive substances have managed, through means of self-help alone, to change their behavior. Notwithstanding this, there are certain substance addictions from which it is virtually impossible or impractical to attempt to recover solely through the means of self-help. In fact, many self-help materials are not available for certain substance addictions (e.g., heroin or cocaine) without adjunct supervision from a caregiver or institution. With the exception of natural recovery (see below), heavy drug users are unlikely to recover by relying exclusively on their own resources. Therefore, most of the sections in this chapter will cover self-help methods that are available and potentially effective for substance addictions.

Self-Help as Empowering

Lacking professional guidance, self-helpers run the risk of potentially acquiring inadequate or ineffective information. However, self-help has the advantage of enabling individuals to achieve the internal resources necessary to feel a greater sense of control over their behavior and their environment. This cultivated sense of power can have positive effects on self-esteem, self-efficacy, and personal responsibility [68]. These personal tools can breed the confidence and stimulation necessary to prevent relapse or sustain the recovery process [99]. It may also motivate individuals who need extra assistance to seek professional help for their addictions [56].

Can Individuals Help Themselves?

At least two somewhat overlapping and extensive bodies of research literature have directly addressed the extent to which people can and do transition from problematic substance use, abuse, or dependence to less problematic use, moderate use, or abstinence without treatment or attendance in "self-help" groups such as 12-step affiliated programs. These bodies of literature roughly correspond to the topics of

natural recovery and the *Transtheoretical Model of Change.*

Natural Recovery

Natural recovery refers to the process by which many individuals who experience considerable difficulties related to substance use change without any formal assistance. Some individuals appear to simply "mature out", whereas others change in response to a specific event or set of circumstances. The most comprehensive review to date of natural recovery from problematic alcohol and/or drug use (excluding tobacco) considered 40 samples of participants in 38 studies published between 1960 and 1997 [113]. The majority of studies of natural recovery have focused on alcohol, with heroin being a distant second. Studies of natural recovery have largely relied on retrospective reports of participants' reasons for changing. These narrative accounts raise questions regarding potential memory distortions, self-serving biases, and/or inaccurate attributions of the effectiveness of specific factors leading to change. Nevertheless, they provide potentially important insights into successful self-help strategies. In the Sobell et al. [113] review, health concerns were the most frequently reported reason for reducing or eliminating substance use by successful self-changers, followed by financial reasons and negative personal reasons (e.g., shame and guilt). More importantly, the factor most strongly associated with successful maintenance of change was *social support*. Other factors for which successful maintenance was attributed included: *development of or return to involvement in activities not related to substance use; work-related changes; general lifestyle changes; religion; willpower*, and *changes in residential situation*. Another factor that has been consistently associated with natural recovery is *cognitive evaluation*, where individuals begin to consider that the costs of their substance use come to outweigh the benefits. In many cases, this process may correspond to maturation and may occur in different stages of the life cycle.

Maturation Effects

Related to the idea of natural recovery is the process of "maturing out". Epidemiological literature and studies of "natural history" indicate that the highest rates of alcohol and other substance use occur during late adolescence and early adulthood [107]. Increasingly referred to as "emerging adulthood", the period of time corresponding from about high school graduation through the early 20s is associated with increased risk behaviors and experimentation. A majority of young adults who use substances as part of this period, even at problematic levels, reduce or eliminate use as they assume career and family responsibilities [107]. Individuals who experience substance use later in life and who reduce use without formal help tend to be in their mid 40s and report their heaviest use to be in their mid-to-late 20s [105], further suggesting that, for many, natural recovery may be a maturational process.

With respect to research related to natural recovery, the majority of the literature has focused on alcohol. Other specific substances have also been examined in the context of natural recovery, including nicotine, marijuana, cocaine, and heroin, with relatively similar findings across substances. Natural recovery from nicotine, alcohol, and marijuana is reviewed below.

Nicotine

The vast majority (>80%) of individuals who quit smoking do so without treatment [73, 113]. Narrative accounts of successful quitters versus temporary quitters or non-quitters suggest that successful quitters report more severe consequences, more focused reasons, and more negative affect in describing reasons for quitting [46, 49]. Successful quitters also are more likely to have and/or take advantage of good social support for quitting, to change their environment, and to feel less ambivalent about changing.

Alcohol

By far the majority of the literature on natural recovery from addictions has focused on alcohol. Consistent evidence now suggests that a large proportion of individuals who experience problems with drinking are able to transition to moderate use or abstinence without formal help [105, 112]. Nevertheless, public perceptions have remained more consistent with an incurable and progressive disease model of alcoholism. These sentiments are likely reinforced by 12-step programs, which begin with the assumption that individuals are powerless over alcohol use and that it is not possible ever to recover fully but only to keep the disease at bay by remaining abstinent [20, 21].

Individuals who successfully maintain natural recovery from problematic drinking often report initial motivation related to fear or anticipation of unacceptable life changes resulting from drinking, concern for the influence of one's drinking on his or her children, and religious inspiration [13]. Successful self-changers are more likely to have positive social support networks, be married, have higher self-esteem, and report less drug use and lower frequencies of intoxication [105].

Marijuana

Relatively little research has examined natural recovery from problematic cannabis use [113]. One 25-year follow-up of Vietnam veterans found that 82.5% of cannabis quit attempts were without treatment and that 88.3% were successful [98]. Consistent with findings from the alcohol literature, a recent study examining natural recovery from cannabis use [31] found that self-change was most often initiated in response to changing views of personal use (cognitive evaluation) as well as negative effects of use. Strategies associated with successful change included changes in lifestyle and the development of interests unrelated to cannabis use.

Processes of Change

Directly related to natural recovery, "processes of change" have been described as part of the Transtheoretical Model of Change (or Stages of Change Model) [28, 99]. The Transtheoretical Model of Change, which has been extensively applied to the field of addictions and beyond, began with interviews of former smokers regarding their experiences with change. The model describes a sequence of stages in which individuals who are not initially aware of a need to change, and are not in any way considering change (pre-contemplation), over time begin to consider the possibility of change (contemplation) and subsequently prepare for (preparation) and implement change (action). In the absence of relapse or regression to previous stages, individuals are ideally able to maintain change successfully (maintenance) over time. In the context of developing their model, Prochaska and DiClemente defined a number of processes that individuals identified as being important in their efforts to change. The processes of change include substitution, seeking information, cognitive evaluation, seeking support from others, self-rewards for change, affirmation of commitment, and restructuring one's environment.

Self-Help Drug Replacement

Substance substitution represents a potentially valuable self-help strategy for drug addictions. Drug substitution focuses on replacing harmful and addictive drugs with a less harmful substance and/or often a safer route of administration. The ultimate goal is to moderate, reduce, or extinguish substance use and the various adverse consequences associated with use. Although physiological dependence particular to each substance is discussed below, it is important to note that addictions to substances common in our culture, such as nicotine, caffeine, and alcohol, often involve a psychological component that may be difficult to overcome, particularly when the substance serves a social

role in one's life. These events may act as potential environmental triggers to relapse, and actively avoiding these social situations, whether they are interactions during a cigarette or coffee break or an evening out with friends at a bar, adds to the difficulty of quitting. Drug substitutions may serve as a beneficial self-help strategy by acting to replace the function of the addictive substance and/or alleviate the symptoms of drug withdrawal. Replacement in this manner may involve significantly lower doses or a safer route of administration of the same substance of use. Although there are a number of prescription pharmacotherapies that are administered under medical supervision, this section will focus on self-help drug replacements that are available over-the-counter, and will address drug substitution and replacement therapy for three commonly used legal substances with significant addictive potential: caffeine, nicotine, and alcohol.

Replacement and Caffeine

Caffeine is a plant alkaloid found in numerous species, which acts as a central nervous system and metabolic stimulant. It is believed to be one of the most widely used psychoactive substances in the world [34]. Caffeine is typically consumed to overcome lethargy, to promote vigilance and alertness, and to elevate mood. The major source of caffeine is coffee beans, but it is also commonly found in chocolate, tea, and soft drinks, as well as in energy drinks and over-the-counter medications for headaches, pain relief, and appetite control. Although unscheduled and recognized by the Food and Drug Administration [122] as a "safe food substance", caffeine is an addictive substance that can potentially lead to withdrawal symptoms after cessation of consistent use. Caffeine may be commonly overlooked as a drug of abuse, in part due to its nearly universal legal status and prevalence as a normative food staple. Furthermore, there is a great potential that people may be unaware of, or may underestimate, their daily caffeine consumption, as the drug is mainly associated in connection with coffee. These factors together may contribute to the development of caffeine dependence.

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition–Text Revision recognizes four caffeine-related disorders: caffeine intoxication, caffeine-induced anxiety disorder, caffeine-induced sleep disorder, and caffeine-related disorder not otherwise specified. The symptoms of acute caffeine intoxication may include restlessness, nervousness, hyperexcitability, insomnia, gastrointestinal disturbance, muscle twitching, rambling, tachycardia, and agitation. Very rarely, high doses of caffeine (>10 g) may produce respiratory failure or seizures. Regular users commonly develop tolerance to caffeine and may experience intense cravings after discontinuation. Withdrawal symptoms include headaches, flu-like symptoms, feelings of lethargy and reduced motivation, and depressive or irritable mood.

Individuals seeking to abstain from caffeine may find that the cravings can be managed by substance replacement. Because caffeine is less addictive than are other socially acceptable substances (e.g., alcohol or nicotine), replacement in social settings may be more easily achieved, providing a particularly effective way to reduce caffeine use and mitigate adverse health consequences. The most popular replacement for caffeine is decaffeinated coffee, which contains roughly 3 mg of caffeine per cup compared with an average of 85 mg per cup of regular drip coffee. International standards require that decaffeinated coffee beans are 97% free of caffeine, while the European Union standard requires beans that are 99% caffeine free by mass. This small amount of the active substance may help attenuate withdrawal symptoms including headaches, nausea, vomiting, muscle pain, and stiffness. Decaffeinated and herbal teas offer another option for caffeine replacement. Those individuals who are interested in reducing caffeine intake from soft drinks have a variety of brand options offering caffeine-free drinks. Although there is scant literature concerning the effectiveness of decaffeinated substitution for

caffeine use, replacement in this manner can be a helpful harm reduction approach to reduce significantly one's intake of the drug (in the case of decaffeinated coffee) or to eliminate intake altogether.

Replacement and Nicotine

Nicotine, another central nervous system stimulant, is a plant alkaloid found most abundantly in tobacco leaves and is thought to be the main factor responsible for the dependence-forming properties of tobacco smoke. Although inhalation of tobacco smoke is the most common route of nicotine administration, tobacco also may be insufflated or chewed. Tobacco smoke contains carbon monoxide, as well as a mixture of particulate substances generated by the combustion process that make up tobacco tar [34]. Inhalation of carbon monoxide and tar is primarily responsible for the various diseases resulting from long-term use. Researchers regard nicotine as one of the most addictive recreational substances in use [50, 51]. Similarly, the American Heart Association considers nicotine to be one of the hardest addictions to break.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition–Text Revision, the criteria for nicotine use disorder include any three of the following within a 1-year time span: tolerance to nicotine with decreased effect and increasing dose to obtain the same effect, withdrawal symptoms after cessation, smoking more than usual, persistent desire to smoke despite efforts to decrease intake, extensive time spent smoking or purchasing tobacco, postponing work, social, or recreational events in order to smoke, and continuing to smoke despite health hazards. Additionally, nicotine withdrawal is classified as a nicotine-induced disorder that includes symptoms such as difficulty concentrating, nervousness, headaches, weight gain, decreased heart rate, insomnia, irritability, and depression.

Because a majority of serious health hazards related to nicotine use result from smoking tobacco, nicotine replacement through other modes of administration may provide a successful harm reduction substitute. Such approaches are based on the concept that the administration of a maintenance level in a non-toxic format will alleviate the withdrawal symptoms associated with smoking cessation and reduce the risk commonly associated with the inhalation format. Indeed, nicotine replacement therapy may aid in abstinence from tobacco smoking by reducing general withdrawal symptoms, resulting in some psychological effects on craving, mood, and attention states [87, 115]. There are a number of nicotine replacement options available over-the-counter for individuals who are interested in smoking cessation. Unlike inhalation of tobacco, nicotine replacements lead to slower onset and more stable plasma nicotine concentrations [52]. Thus, the use of nicotine replacement therapy allows for the accurate titration of nicotine dose and enables a reduction of daily nicotine administration over time. A recent comprehensive review of nicotine replacement concluded that each commercially available form of nicotine replacement therapy increased significantly the rate of cessation over the placebo or no-nicotine-replacement-therapy groups and that these rates of quitting smoking increased by 50–70% [115]. Preliminary data from this review suggest that individuals who begin nicotine replacement therapy soon before their quit date may increase their success [115]. Additionally, the authors mention that there is evidence of a benefit from combining the nicotine patch with an acute dosing type (for acute cravings). Finally, they conclude that to date, there does not appear to be an overall difference in the effectiveness of any form of nicotine replacement therapy over another and, thus, the choice of which form to use should reflect an individual's specific needs and tolerability [115].

Nicotine Replacement Options

Nicotine-containing chewing gum was approved by the FDA as a pharmacotherapeutic prescription medication for use in the treatment of cigarette dependence in 1984. Now available over-the-counter in both 2-mg and 4-mg doses,

the gum leads to nicotine absorption (~50%) in the mouth through the buccal mucosa. Nicotine gum also contains 30 mg of sodium carbonate and sodium bicarbonate to enhance absorption of nicotine [50]. Individuals are instructed to chew the gum until it is soft and a peppery taste is felt, after which it is pressed between the cheek and teeth until the taste fades. Then the process is repeated. This procedure, known as "chew and park", seeks to maximize absorption of nicotine. Although individuals are instructed to chew the gum as needed, they are typically encouraged to chew at least 10 pieces/day (at a rate of 1 piece every 1–2 h) but are advised not to exceed 20 pieces of 4-mg gum or 30 pieces of 2-mg gum per day. A schedule of 10 pieces of 2-mg gum yields approximately 10 mg of nicotine, while the same number of 4-mg pieces yields approximately 20 mg/day. As the average nicotine intake per cigarette smoked is roughly 1 mg, chewing 10 pieces achieves about one-third to one-half the daily nicotine intake of a user who smokes 30 cigarettes/day [8]. A number of studies have demonstrated that the use of nicotine chewing gum when quitting smoking approximately doubles the rate of abstinence compared with placebo [54, 57, 106]. A recent comprehensive review of 53 trials assessing nicotine gum versus placebo concluded that the use of nicotine replacement gum alone significantly increased rates of abstinence [115]. Furthermore, heavy smokers have been shown to achieve greater benefit from the 4-mg gum [87, 115]. Potential side effects of chewing nicotine gum may include hiccups, nausea, indigestion, mouth sores, jaw muscle aches, headaches, dizziness, and insomnia.

The nicotine lozenge was first introduced in 2002 as another over-the-counter alternative for nicotine replacement therapy. The lozenge is a hard candy that releases nicotine slowly as it dissolves in the mouth and is available in the same 2 and 4-mg concentrations as the nicotine chewing gum. Individuals are instructed to use one lozenge at a time and to abstain from food or drink in the 15 min prior to and during use. Only one lozenge should be used at a time because using too many lozenges in a short time may increase the incidence of side effects such as heartburn and nausea. One should allow the lozenge to dissolve slowly (for up to 30 min) in the mouth, being careful not to chew or swallow the lozenge. During the first 6 weeks of nicotine lozenge treatment, individuals are advised to use one lozenge every 1–2 h. After this time, consumption is encouraged to be systematically restricted to one lozenge every 2–8 h. Heavy smokers and/or smokers who have their first cigarette within 30 min of awakening are encouraged to use the 4-mg lozenge. Consumption should not exceed 5 lozenges in any 6-h period. Similar to the nicotine gum, there is a recommended limit of 20 lozenges/day, and use is advised for up to 12 weeks. The most common potential side effects resulting from the use of the nicotine lozenge are soreness of the teeth and gums and throat irritation.

Transdermal nicotine patches, although first introduced in 1991, were marketed as an over-the-counter aid for smoking cessation starting in 1996. They consist of multilayered adhesive patches saturated with a lipid-soluble nicotine solution, leading to relatively stable transdermal delivery of nicotine throughout the day. Nicotine patches are currently available in doses ranging from 5 to 20 mg for duration of wear from 16 to 24 h. Patches come in several steps, enabling users to gradually phase out their use. This replacement method provides a continuous-release, long-acting mode of nicotine administration, resulting in relatively constant plasma levels of nicotine that are slightly lower than the concentrations produced by nicotine chewing gum. While wearing a nicotine patch, individuals are warned of the importance of abstaining from smoking as this may lead to nicotine overdose, potentially resulting in adverse cardiovascular events [34]. A number of reviews have documented that nicotine patches are a highly effective form of replacement resulting in a greater number of abstainers than placebo treatment [38, 39, 115]. A comprehensive meta-analysis found borderline evidence of a benefit of using the higher dose compared with the lower dose patch and further suggested that although the transdermal nicotine patch is generally easier to use than

other forms of nicotine replacement therapy, the patches are not effective for relief of acute cravings [115]. Potential side effects resulting from use of the nicotine patch may include skin irritation, dizziness, elevated heart rate, sleep disturbances, headache, nausea, vomiting, muscle aches, and stiffness.

Replacement and Alcohol

Alcohol is a psychoactive drug that acts as a central nervous system depressant and is a product of the metabolism of carbohydrates converted through the process of fermentation. Moderate consumption of alcohol decreases pain and anxiety, produces relaxation, elevates mood, and stimulates appetite. In higher doses, alcohol promotes drowsiness, reduces motor coordination and self-control, may lead to emotional volatility, memory impairments, and confusion, and can be fatal at extreme doses. Roughly three in four Americans are occasional drinkers, individuals who consume one or two drinks to "unwind" after a long day or participate in moderate alcohol consumption at social gatherings such as dinners and celebrations. This pattern of drinking is practiced by a majority of alcohol users without serious harmful consequences or development of dependence [34]. Conversely, the National Institute on Alcohol Abuse and Alcoholism states that roughly 1 of every 12 adults in America abuses alcohol or is alcohol dependent.

Alcoholism is defined by *The Journal of the American Medical Association* characterized by impaired control over drinking, preoccupation with alcohol, use of alcohol despite adverse consequences, and distortions in thinking [83]. Alcohol dependence includes the four symptoms of craving, loss of control over use, physical dependence, and tolerance as outlined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition–Text Revision. Mild-to-moderate symptoms of alcohol withdrawal are numerous and include nervousness, anxiety, irritability, depression, fatigue, headache, nausea and vomiting, and insomnia. Severe symptoms can be extremely dangerous and include delirium tremens (state of confusion often accompanied by hallucinations), fever, and convulsions.

Alcohol abuse can be extremely difficult to overcome, possibly requiring intensive medical treatment. There are currently three oral medications approved to treat alcohol dependence that are available by prescription under medical supervision. While it is highly recommended that an individual seek medical help for alcohol addiction, there are harm reduction measures that one may take for alcohol self-help. When dealing with alcohol abstinence, non-alcoholic beverages such as near beer and alcohol-free wine may serve as an effective replacement. These substitutes typically contain one-half of one percent or less of ethanol by volume—i.e., the maximum content that a beverage may contain to be legally called non-alcoholic in the United States. In addition to the strong pharmacological dependence, overcoming alcohol addiction can be difficult to overcome psychologically, in part because the environment associated with the substance may serve an important social role in one's life. The use of non-alcoholic replacement may help in the maintenance of abstinence by allowing an individual to continue to engage in social situations.

Drug substitution for alcohol may also be achieved with the use of herbal substances. As another legal central nervous system depressant and mild intoxicant that shares similar properties with alcohol, kava (piper methysticum) root is consumed in Pacific culture to alleviate stress and combat insomnia and has been demonstrated to be effective in reducing anxiety [95, 123]. Although there are no data concerning the effectiveness of kava use as an aid to quitting alcohol, the anti-anxiety and mildly intoxicating effects of kava may prove useful by replacing the role of alcohol in one's life and potentially mitigating some of the less severe symptoms of alcohol cessation. There is a clear lack of controlled studies concerning the effectiveness of drug substitution for substances other than nicotine and a need for direct investigation of this potentially useful strategy.

Bibliotherapy

Perspectives in Bibliotherapy

Bibliotherapy, the concept that positive change can be affected through an individual's relationship with the content of books or other written words, has been a recognized method of self-help throughout history [103]. In historic and contemporary cultures, religious materials such as the Bible serve as enduring and prominent examples of self-prescribed tools for growth and change. The concept of bibliotherapy has changed over time such that modern references may describe a spectrum of behaviors, from an individual reading a self-help manual to a professional care provider prescribing a relevant book chapter. The terminology has similarly evolved, revealing an array of alternative terms including but not limited to: biblio-counseling, bibliopsychology, biblioguidance, bookmatching, information prescription, library therapeutics, and literatherapy. At its most basic, the practice of bibliotherapy consists of a self-prescribed selection of reading materials that have relevance to an individual's life and situation. It also refers to the guided use of literature toward a desired therapeutic outcome, usually as a complement to traditional psychotherapeutic approaches [58].

Evaluating the efficacy of bibliotherapy proves more challenging than reporting on its varied uses. For the purposes of this chapter, and consistent with a number of published studies [5, 70], the term bibliotherapy will refer to the first situation, or any therapeutic intervention presented in a written format, which is designed to be read and implemented by an individual largely in the absence of professional guidance. Those empirical investigations employing congruent definitions of bibliotherapy related to substance abuse were restricted primarily to the reduction of nicotine, alcohol, and marijuana.

Bibliotherapy for Nicotine

A vast array of self-help materials designed to promote smoking cessation exist [43], from brief motivational pamphlets (e.g., American Cancer Society [2]) to comprehensive manuals addressing initial cessation through relapse prevention (e.g., American Lung Association [3]). These manuals are often based on cognitive behavioral models (e.g., social learning, transtheoretical model, and relapse prevention) and designed as translations of therapist-administered multicomponent cessation programs. Despite the assortment of literature available, the evidence for the efficacy of these resources is mixed (cf. [26]).

Although individuals who are interested in smoking cessation appear to prefer self-administered treatments such as bibliotherapy [37], research has not consistently demonstrated the ability of such materials to increase cessation rates above that of population quit rates [36], telephone counseling [25, 90], or nicotine replacement therapy [61]. This failure may be due at least in part to the populations used to evaluate self-help techniques, the majority of which have involved volunteer smokers who tend to be older, more addicted, and less confident and to have less social support than the general population of smokers [125]. Thus, the full potential of self-help interventions may not be reflected in this population, who would likely benefit from more intensive interventions [23].

With certain caveats, research has supported the efficacy of self-help interventions involving bibliotherapy for smoking cessation. Curry [23] notes that self-help materials are as effective as intensive group programs when individuals participate in the prescribed activities associated with the reading. With this qualification, the use of self-help materials is associated consistently with higher abstinence rates at initial and long-term follow-ups (cf. [23]). Some research suggests that this may be due to compliance with the program, inasmuch as individuals who are able to use self-help programs successfully are better able to adapt programmatic change into long-term lifestyle changes [24].

Bibliotherapeutic efficacy appears to be increased in some cases by tailoring the cessation materials to individual characteristics (e.g., stages of readiness to quit) relative to more general cessation materials [100]. Thus, a number of recent studies have investigated the influence of

tailored bibliotherapeutic resources, with varying degrees of success. For example, although attempts to tailor written material to firefighters by employing language common to the fire service did not produce benefits beyond the American Lung Association's guide [3] designed for the general public [89], the combination of tailored smoking outcome and self-efficacy-enhancing information produced a significant effect on smoking abstinence [29]. The most promising effects for bibliotherapeutic interventions appear to be found in combinations of personalized adjuncts, such as written feedback in conjunction with outreach telephone counseling [25, 90]. Thus, bibliotherapeutic interventions' greatest efficacy may be as an important component of a more comprehensive minimal-intervention smoking cessation strategy.

Bibliotherapy for Alcohol

Bibliotherapy materials designed to reduce at-risk and maladaptive alcohol use are conceptually similar to smoking cessation publications in that they are also often based on cognitive behavioral models, which are intended as translations of multicomponent, therapist-administered programs. Consistent with the smoking cessation literature, the evidence regarding these resources is mixed but appears promising, particularly when construed as the initial intervention in a stepped-care approach to alcohol treatment [70, 114].

Meta-analytic reviews of self-help programs designed to address maladaptive alcohol use have revealed differentially effective rates, largely dependent on the nature and severity of the treatment target. Some research suggests that maladaptive alcohol use may not be as amenable to bibliotherapeutic interventions relative to other problematic behaviors. A number of meta-analytic reviews found smaller effect sizes for bibliotherapeutic interventions addressing disruptions of "habit control" (i.e., alcohol consumption, smoking, nail biting, and overeating) relative to other treatment issues, such as mood disorders [45, 108]. In addition, a study conducted by the World Health Organization [129] found that among heavy drinkers, bibliotherapy alone was not as effective as bibliotherapy in conjunction with brief advice or counseling. Thus, some research suggests that bibliotherapeutic interventions may be more amenable to other clinical considerations, and, particularly among heavy drinkers, a more intense treatment approach may be required.

Despite these considerations, a number of studies support bibliotherapeutic interventions, particularly for mild alcohol abuse. In their 2003 review, Mains and Scogin [70] note that bibliotherapeutic interventions are better suited to address cases of mild alcohol abuse, with less proven efficacy for moderate-to-severe alcohol abuse. Moderate support was revealed for bibliotherapy in a recent meta-analysis of 22 studies evaluating self-help programs [5]. Overall, self-help treatments were found to result in decreased rates of at-risk and harmful drinking, and a small-to-medium-size effect for bibliotherapy relative to no-treatment controls was found. In a series of studies involving only limited professional contact (i.e., brief telephone contact and one 1-h session), Miller and colleagues found reductions in alcohol consumption associated with a self-help manual that matched reductions associated with more involved treatment options [78–80], which were found to be enduring at 2 [77] and 8 years [81].

In sum, although the research regarding bibliotherapeutic interventions for maladaptive alcohol use appears promising, several caveats exist. Bibliotherapeutic interventions have the benefit of being non-intrusive and inexpensive and, based on existing research, are perhaps best framed as an initial intervention in a stepped-care approach to mild or moderate alcohol abuse [70]. Consistent with the stepped-care approach, initial treatment failures or presentations involving more severe alcohol abuse may be best addressed with more intense and sophisticated interventions [109, 114].

Bibliotherapy for Marijuana

Based on a review of the literature to date, it is difficult to come to any sound conclusions

regarding the utility of bibliotherapy as an intervention for marijuana, particularly as a standalone intervention. Cunningham [18] reported that a mental health survey conducted in Canada revealed that individuals acknowledging weekly cannabis use were more interested in receiving an evaluative self-help book or a computerized normative use summary than telephone counseling or individual psychotherapy. This finding appears to suggest that similar to that for alcohol users, bibliotherapy may be a viable initial outreach intervention in a stepped-care approach among cannabis users. Cannabis users may be well suited to such minimally intrusive interventions since the majority, including those who meet the criteria for dependence, will never seek treatment [17]. However, further research is required to elucidate better the appropriateness and enduring benefits of bibliotherapy within this population.

Helplines

A helpline is a telephone-based service that provides help, information, support, and advice to callers with a wide range of problems or concerns. Common areas of service include financial advising, mental health, relational issues, technological support, and the focus of this chapter, substance addictions [40].

Helplines offer a variety of distinct advantages unique to other forms of self-help, which may make them more accessible or appealing than seeking face-to-face counseling or professional treatment. Helplines provide an efficient means for delivering treatment to populations across wide geographic areas by eliminating barriers of access (e.g., transportation, child care, or scheduling conflicts). Many helplines are government funded and free of charge to callers, which enables them to reach more underserved populations (e.g., uninsured or low socioeconomic status) [4, 9, 91]. Finally, helplines provide immediate treatment and support while preserving the caller's anonymity, a feature that may attract drug users who are already battling with the stigma associated with their drug use [55].

Helplines for Different Types of Addiction

Helplines for Nicotine

The majority of published research on substance-abuse helplines has focused primarily on nicotine dependence, often referred to as "quitlines". Therefore, the bulk of this section will be devoted to the evidence-based literature regarding quitlines. Quitlines took off in the early 1980s and have since spread throughout North America, Europe, parts of South America, Asia, Australia, and South Africa [4].

Nicotine Helpline Services

At a minimum, the majority of quitlines offer self-help resources and other mailed information to callers. This is the most ubiquitous and standard service provided by quitlines. Another common feature includes reactive smoking cessation counseling—reactive in the sense that the call is initiated by the smoker, who is able to speak with a counselor. Other services may include proactive counseling (counselor calls the client), replacement or cessation medication, chat rooms, and recorded messages [9, 59, 91].

Characteristics of Nicotine Helpline Callers and Specific Protocols

In general, smokers are four times more likely to use quitlines than face-to-face clinics [59, 130]. A recent study [91] examining the characteristics of callers to a national reactive telephone quitline found an overrepresentation of disadvantaged (i.e., African-American, women, poorer, urban, less educated, older) and heavier smokers compared with the general population. Due to the wide range of consumers, many quitlines have adopted specialized protocols to address the unique concerns of specific populations. Common specialized protocols exist for pregnant women, older adults, adolescents,

ethnic minorities, smokeless tobacco users, and callers with multiple addictions [16, 121].

Nicotine Helplines and the Transtheoretical Model of Change

Although individuals committed to smoking cessation appear to benefit most from quitline support, research suggests that quitlines may be efficacious for individuals in a wide range of readiness to change. Previous research suggests that many first-time callers to smoking quitlines have already made plans to quit, and that these individuals tend to benefit most from the quitline intervention [48]. Helgason and colleagues found that 22% of first-time callers were in the action stage (had quit for 6 months or less), 76% were in the preparation (planning to quit within the next 4 weeks) or the contemplation (interested in trying to quit within the next 6 months) stage, while only 2% were in the pre-contemplation stage (not interested in trying to quit within the next 6 months). Although those who were smoke free (action/maintenance) at the start of the intervention had the highest likelihood of being abstinent at the end of the study, there were also positive outcomes for callers in the other three stages. Half of the first-time callers in the pre-contemplation stage advanced to either the contemplation or the action/ maintenance stage by the end of the quitline intervention. Similarly, for those in the contemplation stage at baseline, half progressed to either the preparation stage or the action/maintenance stage, while only 10% (i.e., 1 of 10) regressed to an earlier stage [48]. Interestingly, although this research suggests that quitlines can help move callers from one stage of change to the next (e.g., from contemplation to action) [48, 92], many quitlines in the United States restrict services to callers who are planning to quit [16].

Helplines for Alcohol

Despite the abundance of alcohol helplines, there is a surprising dearth of research on their protocol, services, or effectiveness. In a controlled experiment based in Wisconsin [12], researchers recruited nearly 900 patients from clinic waiting rooms who were not necessarily seeking help for their drinking problems. Half of the participants received pamphlets about healthy living, while the remaining participants received telephone counseling in which counselors assisted in setting drinking goals and overcoming barriers to behavioral change. Telephone counseling reduced alcohol consumption by 17.3% for men and 13.9% for women, compared with 12.9 and 11%, respectively, for pamphlet-only conditions [12].

The most promising research on alcohol helplines has been conducted on the UK telephone-based service known as "Drinkline". Established in 1993, Drinkline receives about 6,000 calls a month, the majority of which are problem drinkers seeking help for themselves. Callers are given information about safe drinking levels, advice about how to control drinking or avoid alcohol, and suggestions for how to overcome any related problems. A survey of callers showed that 81% received the information that they needed and 91% intended to carry out a plan of action after calling Drinkline [127]. An extensive search failed to identify any comparable literature for alcohol helplines in the United States.

Helplines for Anabolic-Androgenic Steroids

One of the most advanced, established, and researched helplines that specializes in steroid use is the Anti-Doping Hot-Line founded by Swedish health authorities with the support of the Swedish National Institute of Health [30]. This helpline provides information about side effects and risks associated with anabolic-androgenic steroids, as well as facilitating contact between users and health care agents. The telephone service not only reaches out to anabolic-androgenic steroid users and concerned family and friends but also informs health professionals and organizations (e.g., public schools) about doping issues. In fact, the

majority of callers to the Anti-Doping Hot-Line are non-abusers [30]. Since the implementation and subsequent success of this Sweden-based helpline in 1993, Japan and other nations with high rates of anabolic-androgenic steroid abuse have followed suit with their own steroid helplines (primarily targeting athletes and adolescents) [121].

Helplines for Cocaine, Methamphetamines, and Opiates

Due to the highly addictive and harmful nature of drugs like cocaine, methamphetamines, and opiates, strictly outpatient and self-help methods of recovery, such as helplines, are less common. Tellingly, there is nominal research on the topic. However, 24-h, 7-days-a-week phone services do exist (e.g., National Meth Helpline, Cocaine Addiction Helpline, and Heroin Addiction Helpline) that offer no-cost assessments and dispense advice on how to stop, how to help a loved one quit, interventions, information, and various signs to look for in a potential addict. Upon calling these helplines, however, the most likely intervention is a referral to an inpatient treatment and drug rehabilitation facility.

Helplines as Self-Help

Helplines ride a fine line between self-help and assisted interventions. On the one hand, many first-time callers to drug abuse helplines have taken proactive and self-initiated measures to make the call. From there, it is often up to the caller to decide the extent or breadth of services that he/she desires. Staying within the definition of self-help, callers can have a few questions answered or request that some information be sent to their homes. Helplines start to cross over into the zone of assisted, professional help when multiple counseling sessions are involved, the individual is referred to the helpline by a hospital or medical professional, or the caller enters proactive counseling with multiple phone sessions initiated by the counselor.

Religion, Spirituality, and Meditation

The last decade has been witness to significant increases in research investigating the influence of religion and spirituality on physical and mental health, including addiction. Religion and spirituality are innately internal endeavors, albeit ones that often include corresponding external activities and, to varying extents, enduring relationships with professional providers and larger communities. A review of the literature did not produce research evaluating the role of religion or spirituality in recovery from dependence or addiction in a traditional, empirical fashion. The absence of such literature makes intuitive sense as it would be challenging to assign a random sample to a religion or spirituality condition or the absence thereof. However, given the emergence of significant research regarding these constructs in addiction, it is important to include a discussion of relevant findings. Thus, this section will include a brief review of contemporary literature on religion and spirituality in the sense that these constructs are self-initiated and self-maintained and are not externally imposed by scientists, physicians, or secular care providers. Additionally, this section will address empirical research involving meditation, which has received more recent attention as an intervention tool for addictions [10, 128].

Religion and spirituality are conceptually distinct constructs although they share some common features. For the purposes of this chapter, definitions of religion and spirituality will be based on those in the *Handbook of Religion and Health* [65] and consistent with existing literature [42]. Religion is defined as an organized system of beliefs, practices, rituals, and symbols designed to facilitate a relationship with the transcendent or sacred as well as with the greater community. Spirituality is defined as a less formal and more personal quest for

meaning, designed to address questions about life and one's relationship with the transcendent or sacred.

Religion, Spirituality, and Nicotine

Although previous research has found that both religion and spirituality act as protective factors against smoking onset [41, 44, 74], their utility as self-administered, independent interventions is less clear. Koenig and colleagues [64] found that among the elderly, individuals with a strong religious commitment were less likely to have ever smoked and, among those who did smoke, were likely to consume fewer cigarettes. With regard to smoking cessation, a review of the literature revealed one study examining religion as an intervention strategy. An intensive, culturally and religiously specific smoking cessation intervention designed to be conveyed through local churches for rural African Americans was more likely to promote positive movement in readiness to change than was a tailored, minimal self-help intervention [124]. The rituals and community associated with religion appear to have been instrumental agents for change in this population. However, these findings may better support the role of the church as a dissemination point for proactive health interventions rather than the efficacy of religion as a self-administered intervention. Further research is required to better identify the role of religion and spirituality as an independent, self-administered intervention for smoking cessation.

Religion, Spirituality, and Alcohol

Religion and spirituality appear to be influential in resiliency against maladaptive patterns of alcohol use as well as smoking. A substantial body of research delineates the protective role that religion [60, 62] and spirituality (cf. [76]) play in resiliency against alcohol use disorders. Lower rates of alcohol use disorders have been associated with private practices of prayer and scripture reading [63]. Consistently, research has demonstrated that alcohol-related negative consequences and alcohol use disorders among the highest-risk religious group, drinking members of conservative Protestant denominations [63, 71], are still only 40% of those for drinkers without religious affiliation [53].

In addition, the absence of religion or spirituality may be a risk factor for developing abusive and addictive patterns of alcohol use. Individuals with alcohol and drug problems generally report lower religious commitment and involvement relative to the general population [67, 126]. Consistent with these findings, descriptive studies suggest that individuals with alcohol and drug problems believe that receiving spiritually focused treatment would be helpful to their recovery [6, 27].

A number of sources suggest that religious or spiritual growth is an influential element in lasting recovery and a healthy life. Alcoholics Anonymous [1] frames addiction as a physical, mental, and spiritual disease requiring treatment in all three domains, the latter of which is an identified treatment stage (i.e., spiritual affiliation and growth) in their model of healthy and stable sobriety. Previous research has found that Alcoholics Anonymous members' spirituality is positively associated with life satisfaction [15], purpose in life, and duration of sobriety [14, 96]. Similarly, a study of individuals in recovery found that higher levels of religious faith and spirituality were associated with a more optimistic life orientation, greater perceived social support, higher resiliency to stress, and lower levels of anxiety [93]. Some speculate that inasmuch as religion and spirituality are protective against addiction, adoption of religious or spiritual variables may facilitate the process of recovery [84].

Religion, Spirituality, and Other Substances

Consistent with the alcohol literature, religion and spirituality appear to have protective influences against the onset of illicit drug use among

adolescents [75] and adults [41, 44, 74]. Also analogous to the alcohol literature, a lack of religious commitment may be a risk factor for illicit drug use [62]. Finally, the current literature regarding religion and spirituality and recovery from illicit drug abuse and addiction appears to be at a similar stage of development, where positive indications have been found to be associated but not yet fully elucidated.

Previous research suggests that religious and spiritual involvement exerts a positive influence in drug treatment. A recent study examining spiritual activities among heroin- and cocaine-dependent individuals revealed a weak but positive ($r = 0.16$, $p < 0.04$) association between spirituality and treatment outcome [47]. Individuals in this study who reported that they frequently spent time on religious or spiritual activities demonstrated significantly better outcomes in terms of subsequent drug use and treatment retention. Spirituality also has been associated with reduced severity of post-treatment relapses [82] and counselor-assessed treatment responsiveness [94]. In a study examining the effectiveness of coping techniques to reduce cocaine use after treatment, spirituality was one of a number of techniques associated with less cocaine use and abstinence at a 6-month follow-up [102]. While these studies are promising, they do not address the role of religion and spirituality independent of formal treatment. As such, questions remain about the utility of religion and spirituality as an independent, self-administered mechanism of change for addictive disorders.

Meditation and Mindfulness-Based Approaches

Meditation has been a spiritual and healing practice in some parts of the world for more than 5,000 years. It also has become an increasingly common practice in Western cultures within the last 40 years. In the recent past, meditation and mindfulness-based approaches to substance use disorders have received a resurgence of attention in the empirical literature and popular press. Consistent with the National Center for Complementary and Alternative Medicine, a division of the National Institutes of Health, meditation will be referred to as those techniques or practices intended to focus or control attention [85]. Similar to religion and spirituality, meditation has been characterized and defined a number of ways in the literature, often confusing the empirical picture. Also analogous to the findings on religion and spirituality, research has revealed some initial support for this technique in substance use disorders [11, 72] although a number of important questions remain.

Previous research suggests that meditation and mindfulness-based approaches to substance use disorders hold promise as a protective mechanism, intervention technique, and self-help approach. Research has demonstrated the protective influence of transcendental meditation against alcohol use disorders [7, 110]. Furthermore, some research suggests that transcendental meditation may be an effective coping technique for those at risk for developing alcohol use disorders. In a study evaluating various forms of relaxation techniques (transcendental-esque meditation, deep muscle relaxation, or quiet recreation) on patterns of heavy alcohol use among college students, Marlatt and colleagues [72] found that each technique produced reductions but that meditation demonstrated the most consistent and reliable reductions over a 6-week intervention period, an approximate 50% reduction in daily consumption. Similarly, among an incarcerated population, Bowen and colleagues [10] found significant reductions in alcohol, marijuana, and crack cocaine use post-incarceration among individuals who had participated in a Vipassana meditation course in conjunction with standard alcohol and drug classes. Those who completed the Vipassana meditation course also demonstrated decreases in self-reported psychiatric symptoms and increases in positive psychosocial outcomes. Successful addiction recovery is often related to an individual's ability to develop and employ a repertoire of coping behaviors. This research suggests that meditation may be an effective coping tool and thus may extend the duration of treatment effects by providing the skills to

prevent relapse [10, 11, 128]. However, questions remain about the mechanisms promoting change associated with meditation (cf. [128]).

In sum, existing research appears to support the positive influence of religion, spirituality, and meditation in a multidimensional approach to recovery from substance use disorders. In general, religion, spirituality, and meditation appear to increase resiliency against abuse and addiction. More specifically, religion and spirituality are associated with increased personal satisfaction and resiliency in recovery from alcohol use disorders, and all three are associated with decreased use following treatment among other substance use disorders. Thus, it seems practical to consider the positive impact of religion, spirituality, and meditation in self-initiated endeavors to address substance use disorders. However, further research is required to elucidate the influence of these constructs distinct from formal treatment and treatment groups, and to evaluate their efficacy as stand-alone interventions. Thus, although they may play a positive and potentially significant role in recovery, it is not yet understood how and in what ways religion and spirituality [76, 93] or meditation act to promote positive change (cf. [128]) and whether those effects will extend to self-initiated and self-maintained treatment.

Internet Resources

Recent years have witnessed a logarithmic expansion of reliance on the Internet for all types of health-related information. In 2004, an estimated 15% of all Internet users accessed health information related to problems with drugs, alcohol, or help in quitting smoking, corresponding to over 15 million individuals [116]. Research evaluating Internet self-help Web sites and brief interventions has expanded similarly in recent years. The bulk of the research in this area has demonstrated that the Internet is a feasible and potentially efficacious source for self-help. Relatedly, a recent meta-analysis evaluating 75 randomized controlled trials of computer-based interventions revealed that Internet interventions were associated with increased knowledge and changed attitudes across a wide variety of behaviors [97]. More specifically, the review found Internet-based interventions, in comparison with other methods of delivery, to be effective in changing tobacco use but less successful in changing the use of other substances.

A number of advantages of Web-based self-help resources have been identified, including, most notably, convenience, low/no cost, availability, and anonymity. The number of Web sites relevant to self-help for addictions is overwhelming in comparison with the relatively small burgeoning literature on Internet self-help. A quick Google search (May 21, 2008) on the phrase "quitting smoking" revealed over 2 million hits, with similar searches for alcohol (42,500) and marijuana (15,500) revealing smaller but still impressive numbers. Not surprisingly, a major challenge in using the Internet as a self-help tool is sorting wheat from chaff in identifying accurate and helpful information [117, 131]. "Webliographies", such as the one printed in *Substance Use & Misuse* in 2002 [88], can help in this process and typically include descriptions of content and purpose of a relatively small number of Web sites that are directly relevant and informative. However, the rate at which Web sites address change gives any static catalog of links a limited life span [131].

Internet Resources for Nicotine

Currently there are hundreds of commercial and free smoking cessation Web sites available, many of which have similar content, functions, and suggestions [33]. Typical content and functions focus on: setting a quit date; finding alternative activities; recruiting social support; choosing a medication; information regarding risks and benefits; chat applications, and automated e-mails. While limited research has evaluated these kinds of self-help resources, recent randomized clinical trials have shown significant but small effects on short-term abstinence,

with quit rates ranging from 3 to 18% for up to 3 months [32, 33, 69, 118, 120].

Internet Resources for Alcohol

In comparison with self-help Web sites for smoking, fewer options are available for self-help for drinking. Nevertheless, a large number of Web sites are available that offer suggestions and tools for reducing or eliminating alcohol use. Self-help Web sites related to drinking often include: a short questionnaire followed by feedback regarding responses, including how the respondent's drinking compares with population norms for same-age, same-sex individuals; assessment of risk based on a screening measure; information about alcohol's effects on the body; tools for calculating blood alcohol content; and contact information for professional help or self-help groups [19, 35]. Controlled trials of Internet-based self-help programs have generally demonstrated efficacy, with effect sizes in the small-to-medium range (e.g., [22, 66, 101]).

Internet Resources for Other Substances

Self-help options for substances other than nicotine and alcohol over the Internet are relatively sparse. While there are undoubtedly numerous Web sites that are relevant to self-help for substances other than nicotine and alcohol, the related research literature is virtually void, with the exception of a few feasibility studies (e.g., [104]).

Conclusions

Many individuals utilize self-help strategies in their efforts to overcome substance dependence and addiction. Existing research literature suggests that self-change (i.e., natural recovery) is in fact the most common route through which substance use changes occur. Self-help strategies seem to be less effective for individuals with more severe dependence. From a public health perspective, self-help strategies represent ideal mechanisms for reducing substance use-related problems because they are almost invariably low cost relative to formal treatment, and because they can be disseminated widely (e.g., bibliotherapy, helplines, and Internet). Moreover, the existing literature on self-help strategies is relatively promising, suggesting that in addition to being lower cost and widely available, self-help is also relatively effective.

The quantity and quality of the literature provide an important caveat for the rosy prospectus on self-help approaches. In comparison with the treatment literature, the literature on specific self-help strategies is considerably smaller and with fewer controlled studies. To some extent, this may be due to the inherent nature of self-help, the typical focus of health professionals on more formal treatment approaches, and perspectives on addiction that are incompatible with self-help as a viable option. By their nature, self-help strategies are less likely to draw attention from health care professionals or researchers in addiction. Thus, the prevalence of self-help strategies has remained under the radar until recently. While there is reasonably strong literature related to certain self-help approaches for some behaviors (e.g., replacement, bibliotherapy, and helplines) and substances (tobacco and alcohol), the literature related to other strategies (e.g., Internet resources and meditation) and other substances (e.g., steroids, cocaine, and heroin) is sparse. In some cases, this presents a quality control issue given the wide availability of Internet sites or self-help books with limited or no evidence that the specific suggestions proposed will be of benefit to the individual seeking change.

A number of deeper and broader issues underlie the consideration of self-help for addictions. To the extent that addiction is defined by one's inability to control use, self-help is somewhat of an oxymoron (i.e., if a person can stop, were they really addicted?). On the other hand, even formal treatment approaches require that

individuals help themselves—whether practicing thought exercises or driving themselves to an appointment with a therapist. Regardless of how either self-help or addiction is defined, it seems clear that a desire to change is fundamental in determining the success of change efforts. For many, experiencing negative consequences related to substance use is enough to initiate a self-correction process, although the form of that process may vary by individual and by substance. This chapter represents an attempt to provide a broad overview of self-help approaches for addiction, with specific examples for specific substances. Based on the available evidence, self-help strategies appear to work well for many, especially those on the less severe end of the continuum, but more nuanced questions, such as which ones work for whom under what conditions and for what substances, are in need of critical and systematic investigation.

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Part VII
Treatment and Application: Group Treatments and Specific Settings

Community Clinics

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Contents

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Introduction

The first section of this chapter traces the history of community clinic treatment for substance use disorders. Then the chapter reviews various venues for community treatment and the effectiveness of approaches used where this is known. We take our definition of substance use disorders from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision [2]. There, "substance use disorders" is defined and diagnostic criteria provided for: substance dependence, with or without physiological dependence and course specifiers; substance abuse; substance intoxication; and substance withdrawal. The disorders discussed in this chapter refer to these disorders as described in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision. Where reviewed publications do not use these definitions, other terms used by the primary source are reported.

Although alcohol and nicotine abuse and dependence are listed in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision, we limit our coverage

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_41,

of community treatment to exclude community interventions for these disorders. We define community clinic as an intervention that occurs in non-hospital settings and affiliated with individual health practitioners, or community organizations.

Literature Review Methods

In conducting this review we have used several forms of literature search software. Our primary sources have been PubMed and PsycINFO, but we have used Google Scholar as a backup supplement. Key words used were: community clinic treatment for drug dependence (abuse, addiction, substance use disorder); community treatment for drug dependence (abuse, addiction, etc.); history of community clinic treatment for drug dependence (abuse, addiction, etc.); history of community treatment for drug dependence (abuse, addiction, etc.); substance-related disorders, psychotherapy, group, community health services, and adult. In addition, where particular authors or groups of authors have published widely, we have searched sources by author names. Thus, by definition we have excluded other forms of addictive phenomena such as alcohol dependence, gambling, compulsive eating, sexual behavior, and other behaviors sharing similarities with *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision—defined substance use disorders.

History of Community Substance Abuse Treatment

We could find no historical marker for when group treatment or community clinic treatment for substance use disorders began. It is likely the first community treatment for substance use disorders in America originated in pharmacies when opium and laudanum were sold over the counter in community pharmacies. These drugs were widely available in the 1800s and much earlier before that in China, Great Britain, and other countries involved in trade with Asian sources of opium [49]. Historical sources document extensive morphine dependence as both a result of the U.S. Civil War treatment of wounded soldiers and sales of over-the-counter potions and tonics laced with opium and cocaine. The residual addiction among Civil War veterans was called “army disease”, and was extensively treated by physicians and community pharmacists with morphine or laudanum maintenance (our term), before the scientific discovery of the cause of addiction [52]. Likewise dependence upon cocaine laced tonics and potions was treated by community pharmacists in the same way by making maintenance or restorative doses of “Mrs. Winslow’s Soothing Syrup”, “Godfrey’s Cordial”, and other available over-the-counter tonics for those having the, as yet to be identified, withdrawal syndrome, and the modest fees to purchase them. Godfrey’s Cordial was a mixture of opium sweetened by molasses and flavored with sassafras [6]. It appears these early community treatments were individual ones rather than group interventions.

When the Harrison Act was passed in 1914, it required registration with the Internal Revenue Service by those involved in any phase of the opium or coca industry, and careful record keeping. The United States government made an effort to establish some 40 community clinics to treat those who were addicted to morphine, and other opioids, and for whom the new law restricted and cut off their supply [52]. However, these clinics became the source of much controversy and were soon abandoned when the Department of Internal Revenue declared them illegal and forced their closing. Those still addicted faced obtaining illegal supplies and risked arrest and incarceration for their opioid addiction. Some physicians continued to treat opioid addiction with prescription opioids, including morphine, even after the Harrison Act. However, in 1919 the Supreme Court ruled physicians could no longer prescribe narcotics for the purpose of treating addiction [39]. By making this community-based treatment illegal, the ruling curtailed this humane medical

practice, driving addicted individuals to sources of illegal drugs, to immediate withdrawal, or attempts at detoxification.

The period between the Harrison Act in 1914 and 1935 marked a period where there were strong cultural beliefs and community emphasis on legal and moral sanctions against all narcotic addiction. This social context, including court rulings and Internal Revenue Service actions, proscribed a more humanitarian approach to addiction. Thus, during this period there appears to be little, if any, available community clinic or group intervention for substance abuse disorders. However, 1935 marked a "sea change" in the United States government's approach to addictive disorders.

A New Era Begins

In 1935 the U.S. Public Health Service opened large institutions to treat narcotic addiction, first in Lexington, Kentucky, and three years later in Forth Worth, Texas. These programs were large federal facilities drawing clients from across the United States, mostly incarcerated addicts convicted of crimes. Though not community clinics, they marked a new and growing attitude toward addictive disorders. These facilities set a precedent for subsequent development of local community clinics, group treatment, and other resources to "treat" addicted persons. Opening of these two federal treatment facilities that used a civil commitment approach to treat addiction was the beginning of a new era. Addiction became increasingly accepted by society as a disorder in need of special intervention, including medical intervention by community physicians and non-medical individual and group intervention in various community agencies and programs. These were added to, but did not replace, the predominant community model and legal-based sanctions. Thus, more humane intervention for addictive disorders slowly developed and was accepted, if not widely supported, in subsequent years. Noteworthy is that research conducted at Lexington and Fort Worth greatly established a scientific understanding of the pharmacology and psychopharmacology of addiction, and many scientific behavioral principles which support and maintain addictive behavior, such as the function of drugs as behavioral reinforcers. These facilities also provided a platform for psychosocial assessment, individual and group treatment intervention and follow-up, and epidemiological methods that gradually spread to American urban areas where addictive disorders were prevalent.

The Impact of the Community Mental Health Movement

In response to federal court rulings, the community mental health movement spread across the country during the 1960s providing outpatient treatment for mental disorders. Many clinics developed group interventions for substance abuse and dependence. Most of these embedded substance use disorder clinics focused upon alcohol dependence, which was the most prevalent disorder. However, forms of drug dependence were treated in community clinics, most using the Alcoholics Anonymous model prevalent at the time. Also, during this period religiously affiliated clinics developed to provide spiritually guided individual and group intervention for substance use disorders. Several of these are described in Milby [52], but rarely, if ever, did reports of their work or evaluations of their effectiveness reach the professional health and addiction literature.

The Alcoholics Anonymous model can be conceptualized as a spiritually guided intervention that uses a manual. The manual, called the "Big Book," describes 12 steps guiding recovery from "alcoholism". The recovery process is guided for each individual by a recovering sober sponsor. A key component of this intervention was the use of ubiquitous Alcoholics Anonymous community groups. As the Alcoholics Anonymous movement grew, the model provided widespread community intervention for alcoholism and gradually came

to accept persons with other substance use disorders into their network of community Alcoholics Anonymous groups. Increased acceptance of individuals with substance use disorders was aided by the fact that most substance abusers also abused or were dependent upon alcohol. The expansion of Alcoholics Anonymous peer-led community group meetings to Narcotic Anonymous helped gather and focus those with substance use disorders to participate in aftercare and continued rehabilitation and recovery efforts. Many persons entered these community-based groups after formal medical or psychosocial-based community treatment. However, in spite of the fact that Alcoholics Anonymous was one of the most widely utilized community interventions to treat substance use disorders, it was rarely scientifically evaluated. Only over the last 20 years have the Alcoholics Anonymous interventions been scrutinized with rigorous scientific methodology to study its efficacy and effectiveness [65]. A problem for individuals with co-occurring mental disorders and alcohol/drug dependence who utilized Alcoholics Anonymous-model treatment, especially peer-run aftercare groups, was the cultural bias against using a medication to treat a co-occurring disorder. Individuals with dual diagnoses sometimes found a lack of peer support for their medication treatment.

As community group interventions expanded, two predominant models emerged across American communities. One was the Alcoholics Anonymous movement, which initially focused on alcohol treatment and was especially influential as an aftercare intervention for the other, a medical model intervention. The medical model conceptualized addiction as a drug-induced disorder or disease maintained by an artificially induced biological drive from chronic addictive drug use [21, 35]. Intervention required inpatient hospitalization for detoxification and restoration of abstinence and normalizing of natural biological drives devoid of addiction side effects and biological disruptions. To this medical approach was usually added various psychosocial models, especially group rehabilitation and recovery procedures to support a drug-free lifestyle. As medical detoxification was studied, outcomes defined as return to abstinence after medical detoxification were considered successful, especially for inpatient detoxification. But outcomes defined as sustained abstinence at follow-ups were recognized as a dismal failure [13, 30, 32, 38, 43, 44, 52, 53, 75, 85]. Such accumulating evidence provided the impetus for greater emphasis on developing psychosocial intervention to support behavioral life style change both during medical treatment but especially following hospitalization and in outpatient clinic group intervention and aftercare.

Community mental health interventions for substance abuse disorders and co-occurring mental and substance use disorders predominantly used a rehabilitation model for intervention, as distinguished from pharmacological and other somatic interventions [24]. Initial efforts to treat co-occurring disorders involved separate clinicians working for separate treatment agencies. These initial efforts met with failure, mainly due to problems in coordinating care and accessing needed services [69].

The development of second-generation neuroleptic medication for serious mental illness was concurrent with refinement of psychosocial treatments, including group interventions, which, within community mental health clinics, served as a floor intervention. These emphasized development of a trusting relationship to help clients cope with a chronic mental illness. Within this relationship, clinician and client establish goals to maximize self-control over symptoms and minimize interference from the illness. This intervention is collaborative, utilizing psychosocial education, especially about the illness, and cognitive behavioral therapy. The intervention often involves peer groups to supplement individual counseling, psychotherapy, and medication monitoring. The recent decade has seen increasing emphases on involving families and use of evidence-based family interventions, and psychoeducation [24]. Drake and colleagues have contended that since the 1990s psychiatric rehabilitation became the dominant method employed in most community mental health clinics.

In the 1990s specific approaches for treating co-occurring mental and substance use disorders began to be developed and tested [7, 62, 87]. However, as Drake et al. noted [25], though controlled research has provided support for effectiveness of these integrated approaches, they are yet to be widely adopted in community clinics.

Effectiveness of Community Clinic Approaches 1935–1980

Community methadone maintenance treatment was initiated in New York City by Vincent Dole in 1965 [20]. Based on a disease model of addiction, methadone, as a long-acting synthetic opiate, is given orally to opioid-addicted individuals as a treatment medication. It both alleviates withdrawal symptoms and blocks effects of illicit opioid use. It is a federally regulated, commercially pure medication, devoid of often dangerous adulterants (drug cutting/mixing agents), and administered in once daily doses in a medically supervised clinic. After initial assessment many clients are administered take home doses which require less than daily attendance. As originally developed, psychosocial counseling and access to other community rehabilitation services provided additional therapeutic leverage for a changed lifestyle and sustained abstinence. Dole and colleagues' outcome studies showed excellent treatment success as measured by ability of addicts to reduce criminal activity, obtain or return to jobs or training programs, and otherwise make lifestyle changes to support abstinence [20, 22, 23]. The success of this early work soon led to a proliferation of methadone maintenance treatment across the nation and was supported by government grants to establish and maintain them with community matching funds. Though not as successful as original efforts by Dole and Nyswander, subsequent research from other communities generally found successful outcomes defined as treatment retention, reduced illicit drug use, criminal activity, and increased employment and other measured lifestyle changes [4, 52, 55]. However, when outcomes were considered as successful detoxification from methadone and sustained abstinence at follow-ups, results were much less impressive [43, 53]. Detoxification success was complicated by the discovery of a detoxification phobia, which hampered about 20–30% of addicts in methadone maintenance from even attempting detoxification despite their goal to eventually do so [33, 54, 55]. Though it seems likely that some group psychosocial intervention was utilized in community methadone maintenance during this era, its use was not described in the studies cited here.

Much of predominantly opioid dependence treatment and most other polydrug abuse and dependence disorders were not treated in methadone maintenance programs. Rather they were treated by other interventions. Many of these are reviewed later. Hospital-based inpatient treatment usually utilized medical procedures for detoxification, but these were embedded within a floor psychosocial recovery and rehabilitation intervention. When first evolved, hospital stays of 1–2 months were common. However, these long stays succumbed to economic pressures from health insurance companies and gradually evolved to 28 day interventions.

Therapeutic community intervention usually involved the longest stays in a controlled access institutional environment of up to 6 months or more, and many utilized psychosocial intervention conceptualized as community, as the treatment intervention [18]. The community as intervention utilized peer group review and confrontation for antisocial and other non-adaptive behaviors which the community evaluated as non-adaptive for a drug-free lifestyle. These were usually staffed by few professional health personnel and relied heavily on recovering persons as peer mentors and group leaders. Lastly, by far the widest used community intervention was drug-free clinics where a variety of psychosocial and religious-spiritual intervention models were employed. Up until 1981 there was little scientifically sound clinical research on the effectiveness of any of these approaches. See Milby ([52], Chapters 9 and 10) for a review of these. Where outcome data were published,

because of flawed research methods, occasional reported successful outcomes were interpreted with much skepticism.

Community Responses to the 1980s Cocaine Epidemic

During the 1980s, cocaine abuse and dependence increased dramatically in the United States with the availability of less expensive free base "crack" cocaine crystals which could be smoked instead of snorted or injected. This caused a great influx of clients to existing substance abuse community treatment programs at a time where there was no scientifically based effective treatment (medication or psychosocial intervention) available. University and community clinics treated this influx of new clients with their usual care medical or Alcoholics Anonymous models. However, the few studies which assessed clinical outcomes showed very disappointing results of high treatment dropouts and high relapse rates after treatment established abstinence [28, 29, 40, 82, 83].

In response to this frustrating failure to provide a scientifically supported effective treatment for cocaine dependence, several empirically supported innovative interventions emerged in the 1990s. Two effective outpatient interventions emerged from university clinics and utilized either a group treatment model or a more individualized contingency management behavior therapy program [12, 34]. Soon after that, Milby and colleagues [57] described a sufficient effective community-based intervention for cocaine-dependent homeless persons that utilized contingency-managed access to abstinence-contingent housing and paid work/training along with a group-based behavioral day treatment. This effective community intervention has been improved and systemically replicated in three subsequent randomized trials [56, 58, 60] and found to be cost-effective [73]. However, to date there have been few efforts to transfer and systematically replicate this evidence-based intervention in other communities. Also, during this period other researchers developed community-based empirically supported effective group psychosocial interventions for cocaine dependence [16, 48, 57, 67, 76] .

Since initial studies by Higgins et al. [34] and Carroll et al. [12], there has been steady development of effective psychotherapeutic interventions for cocaine dependence from randomized controlled trials employing both different study populations and interventions [10, 16, 27, 48, 56, 63, 68]. All of these, except perhaps Higgins et al. (who utilized an individual focused intervention), utilized group interventions, which included psychoeducational group psychotherapeutic approaches, sometimes including couple or family interventions [27, 68]. Importantly, some of these recent studies have shown sustained abstinence at follow-up after initial treatment. This increased availability of research-based efficacious psychosocial interventions for cocaine dependence has led Carroll [9] to persuasively argue that manual-guided psychosocial treatment should be used as a therapeutic platform to evaluate the efficacy of new pharmacotherapies.

Categories of Community Clinics

Rodgers and Barnett [70] examined types of community treatment programs and defined two main types: public and privately funded programs. These were further divided into four main types: public non-federal programs (i.e., state-run or local programs), public federal programs, private non-profit programs, and private for-profit programs. Data were derived from the 1991 National Drug and Alcoholism Treatment Unit Survey, and included a final total of 8,865 programs. Some of these programs were inpatient hospital facilities, which are outside of the scope of this chapter, but this study provides an introduction to different categories of substance abuse programs, as well as providing information about differences among them. Overall, the largest number of programs were

private non-profit, followed by private for-profit, public non-federal, and public federal programs. Thus, the majority of programs were private programs composing approximately 82.7% of the sample.

A key issue examined in comparisons among categories was staffing. Rodgers and Barnett [70] found that public non-federal programs had the highest number of staff, followed by private non-profit and private for-profit programs. Although public federal programs had the fewest number of staff, they were the most likely to employ doctoral level staff, followed closely by private for-profit programs. When examining the size of residential programs, federal programs were the largest, and private for-profit programs were the smallest. Public drug-free outpatient programs were also larger than the private drug-free outpatient programs. For-profit programs were the smallest. For methadone maintenance programs, private for-profit programs were the largest, with the rest of the categories lagging far behind.

Rodgers and Barnett's study [70] also provided information on specific services offered by the different categories of substance abuse programs. Both public federal programs and private for-profit programs were most likely to offer aftercare and follow-up. Public federal programs were the most likely to offer medical care. All programs were equally likely to offer individual therapy; private non-profit programs were slightly more likely to offer group therapy than for-profit programs, and private programs were more likely to offer family therapy. Their survey of services for special populations (discussed in more detail later), showed public non-federal programs were more likely to offer special services for pregnant individuals and youth. Private for-profit programs were more likely to offer services specialized for cocaine users.

There were also differences in funding sources for the categories of substance abuse treatment. Both private non-profit and public non-federal programs were more likely to receive Medicaid funding, although private for-profit programs that did receive Medicaid funding received more money than did public non-federal programs. Also, private for-profit programs were more likely to receive funding from both private insurance and client fees, and they also received the most from these funding sources, followed by nonprofit programs. Public federal programs received the least funding from these sources.

Overall, Rodgers and Barnett [70] found that private for-profit programs were smaller (with the exception of methadone maintenance programs), more specialized, and had less staff, but had staff with a higher level of training. These programs were also more likely to receive funding from private insurance and client fees, as opposed to Medicaid.

Types of Community Clinics

Therapeutic Communities

Therapeutic communities are one of the more common treatment methods present in community programs, and have been included in large-scale studies such as the Drug Abuse Reporting Program [78]. The therapeutic communities are long-term, residential programs that utilize a social treatment approach. Therapeutic communities view drug abuse as a disorder of the person, and the recovery process as development and integration of both psychological and social goals [80]. The community as a group aspect of treatment is seen as the major impetus towards growth and change. The community is made up of the social environment, the peers, and the staff, many of whom are successfully recovered addicts themselves [18].

Both behavioral and social learning principles are utilized in therapeutic communities, and some techniques include efficacy training, social role training, and vicarious learning [80]. Physical addiction is seen as a symptom, and is secondary in importance to the behavioral and psychological aspects of the individual's drug abuse. Maintaining a drug-free lifestyle is the main goal of therapeutic communities, which also utilize a present-oriented approach that emphasizes personal responsibility as well as the

development of positive values such as honesty, good work ethic, and community involvement [80]. While each individual is responsible for their own recovery process, the role each individual plays in the recovery of others is also emphasized. Some of the daily activities of therapeutic communities include work, group sessions, and recreation. Individuals in the group serve as mediators and role models. They also confront misbehavior, rule violations, and share with one another during group sessions. Attitude and behavior change in relationships developed in the therapeutic communities serve an important function by helping maintain recovery after the individual leaves treatment [80].

Condelli and Hubbard [15] provide a comprehensive chapter that discusses client outcomes for therapeutic communities from admission to post-treatment. These outcomes were not derived from scientifically controlled studies using rigorous randomized control methods. However, they do reflect what happens to clients admitted to therapeutic communities in community settings. This chapter examines outcomes from a large-scale series of studies derived from the Drug Abuse Reporting Program. Clients in these studies showed a decline in drug use, including opioid use as well as non-opioid use; and also showed a decrease in arrest rates and incarceration rates. One of the most important and consistent predictors of the success of individuals was the amount of time they spent in therapeutic communities, although the length of time necessary to see positive outcomes varied from study to study. In a Drug Abuse Reporting Program follow-up study, therapeutic communities showed more favorable outcomes than outpatient detoxification and intake-only, they did not differ significantly from methadone maintenance or outpatient drug-free counseling [78].

In addition to the various categories of community clinics, there are also a variety of treatment approaches utilized. While the list of various specific approaches is very long, there are a handful of approaches that were most commonly seen. What follows is a list of some of the most commonly used approaches, along with a description of some of the techniques and results of research studies, when available. Approaches discussed are: contingency management, where group methods are employed, cognitive behavioral treatment (including relapse prevention), integrated group therapy for co-occurring bipolar and substance use disorders, 12-step facilitation, pharmacotherapeutic approaches (including methadone maintenance, buprenorphine, etc.), where group psychosocial or educational methods are used, and faith-based approaches.

Prize-Based Contingency Management

Prize-based contingency management is a viable option for community clinics and utilizes "an intermittent reinforcement contingency management approach" usually in the context of behavioral group therapy [64]. This differs from a voucher program in that prizes are not continuous, thus decreasing program costs. Many programs that utilize this approach offer draws from a container of chips that have different reward values marked on them, ranging from "Good Job" (no value) to Jumbo (gets to pick from prizes worth about $80–$100) [1, 46, 64]. These draws can be made contingent on negative urine samples, participation in planned activities, or any other behaviors that the clinicians wish to reinforce. Another option is to set the program up with prize drawings every week. In this approach, clients are allowed to place their names into a bowl for each session that they attend, and then names are drawn each day to receive prizes [1]. These techniques can be utilized independent from each other, or combined.

Petry et al. [64] utilized several programs from the Clinical Trials Network to look at the efficacy of prize-based contingency management in stimulant abusers. These programs all utilized the approach where clients earned draws from the container for chips with various reward values. The prize-based contingency management programs were compared with usual care, which was mostly group counseling. Participants in

the prize-based contingency management programs showed more negative urine samples, as well as longer periods of abstinence. Other studies, which looked at both cocaine- and opioid-dependent individuals, showed similar results, each showing that participants in the prize-based contingency management program demonstrated longer periods of abstinence compared with those receiving standard treatment [46], although the Alessi et al. [1] study failed to show an impact of contingency management prizes on attendance when prizes were awarded during group.

Day Treatment with Abstinence Contingencies and Vouchers

Day treatment with abstinence contingencies and vouchers [56, 58, 59, 74] is an intensive program that focuses on substance abuse rehabilitation of homeless crack-cocaine abusers. Clients participate in 5.5 h each day in the program for the first two months during which time they are provided with lunch and transportation to and from the treatment center. Treatment services include: individual assessment and goal setting, individual and group counseling, and multiple psychoeducational groups. During weekly goal review groups, clients review contract goals and provide support and encouragement to each other and receive vouchers for goal attainment that may be applied towards renting low-cost, drug-free housing. Participants may also earn vouchers by engaging in pro-abstinence social and recreational activities. After two months, participants enter a four-month vocational phase that includes both paid work and program provided housing which are abstinence contingent.

This day treatment approach has been shown to be effective compared with a treatment-as-usual individual and group counseling based on an Alcoholics Anonymous model, where clients were referred to community resources for housing and work. Subsequent studies have utilized a dismantling design strategy where investigators systematically replicated the original behavioral day treatment [57], while examining the contribution of key components [56, 58, 74].

Results from Milby et al.'s most recent study [58] are shown in Fig. 1. In this study, designated H4, abstinence outcomes were compared between the two treatment groups to which participants were randomly assigned. The "CM" group received contingency-managed abstinence-contingent housing, work training, and paid work. The "CM+" group received the same contingency-managed components as the CM group, but in addition received a manualized effective cognitive behavioral day treatment used in previous studies. As Fig. 1 shows, abstinence levels for both groups during active treatment (weeks 1–24) are moderately high ranging from 59 to 79%, with no differences between groups. However, at post-treatment follow-ups, at 12 and 18 months, the CM+ group receiving additional cognitive behavioral intervention showed a delayed treatment effect of superior sustained long-term abstinence, which was rigorously measured using urine toxicologies. In a meta-analysis of treatment components, Schumacher et al. [74] found contingency-managed components to be those associated with greatest abstinence. All of these studies have shown modest improvements in both reduced homelessness and increased employment for all treatment groups from admission to long-term follow-up.

Cognitive Behavioral Treatment

According to McCarty et al. [50], about one-third of treatment programs in the Clinical Trials Network utilized National Institute on Alcohol Abuse and Alcoholism treatment manuals, and 28% of those utilized cognitive behavioral treatment. In addition, approximately 26% of programs that utilized National Institute on Drug Abuse treatment manuals used *A Cognitive Behavioral Approach: Treating Cocaine Addiction*. The National Institute on Drug Abuse [63] provided a general description of cognitive behavioral therapy for substance use disorders as well as some information regarding its efficacy. Cognitive

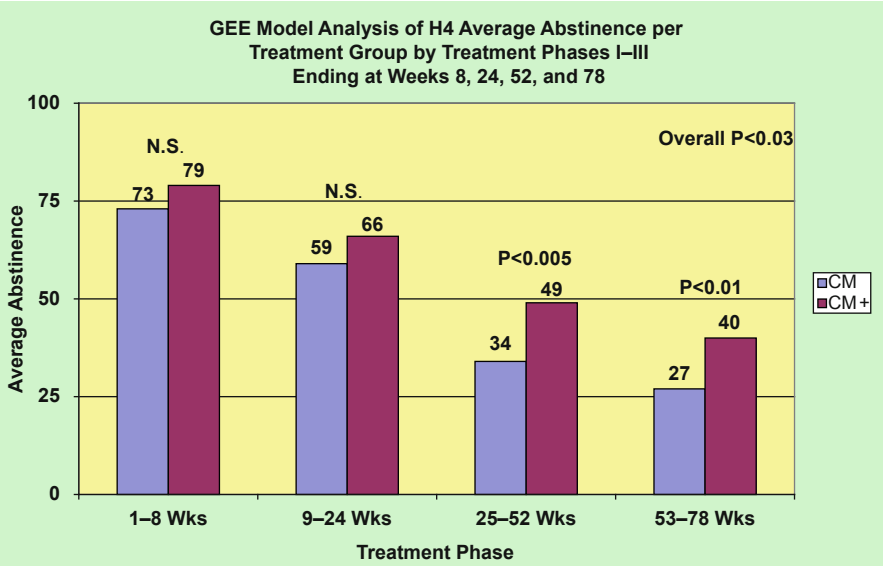

Fig. 1 H4 abstinence per group across phases: average abstinence per group across four phases of treatment as measured by observed urine collection and testing multiple times per week up to 24 weeks, and randomly thereafter through week 78 (18 months follow-up). H4 = the study by Milby et al. [58]; GEE = generalized estimating equations; N.S. = not significant; CM = contingency management. Reprinted from Milby et al. [58], with permission from Elsevier

behavioral treatment is based on social learning theory and can be applied in a group or individual setting. Some of the foci are on increasing self-efficacy and reducing positive expectations about substance use, as well as teaching coping skills, especially in relapse situations. He reports that there are several studies that provide evidence for the efficacy of cognitive behavioral therapy in treating substance use disorders. In addition, a study by Maude-Griffin et al. [48] of crack-cocaine abusers showed that clients in cognitive behavioral treatment were more likely than clients in a 12-step facilitation program to achieve consecutive abstinence for one month. Clients in cognitive behavioral treatment also showed significantly better abstinence results at each of the follow-ups (weeks 4, 8, 12, and 26).

Rawson et al. [68] completed a study comparing cognitive behavioral treatment, contingency management, contingency management + cognitive behavioral therapy, and standard methadone treatment in a community clinic affiliated with the University of California in Los Angeles. All of these treatments utilized group methods. During treatment and at the week 17 follow-up, clients in the cognitive behavioral therapy did not show significantly more positive abstinence results than the standard methadone treatment, while both of the other two treatment conditions did. However, at the week 26 and week 52 follow-ups, the clients in the cognitive behavioral therapy showed the most positive abstinence results of all the treatment groups.

Relapse Prevention

Relapse prevention is a cognitive behavioral approach that strives for eventual abstinence by emphasizing reducing the risk of relapse. It is based on the theory that substance use disorders involve learned maladaptive behavior, and clients have the potential to re-establish previously adaptive non-drug use behaviors and develop new behaviors.

Clients are taught to identify problem behavior and replace unhealthy behaviors with healthier substitutes. The cognitive behavioral treatment techniques are employed to identify risks and coping strategies to deal with those risks. Specific techniques utilized include (1) identifying disadvantages of continuing drug abuse; (2) self-monitoring drug use behavior to help identify situations that trigger maladaptive behaviors; and (3) developing effective coping strategies to curb craving and reduce stress. Though relapse prevention methods can be utilized in individual or group therapy, most community programs utilize groups.

Studies indicate that relapse prevention helps recovering drug addicts maintain abstinence longer by reducing the risk of relapse [8, 47]. This method has also been found to reduce the impact of relapse if it should occur by preparing clients ahead of time with knowledge and tools to cope during distressing situations. The interested reader will find an excellent review by Carroll and Onken [11] of behavioral and cognitive behavioral therapies, some of which were conducted in group format or combined individual and group behavioral interventions. The review included studies with families and couples.

Integrated Group Therapy

Integrated group therapy is a manualized 20-session, 1-h weekly group intervention that addresses substance use disorder simultaneously with co-occurring bipolar disorder. It emphasizes interaction between the disorders by examining similarities in cognitive and behavioral patterns involved in recovery from both [84]. Adverse effects of each disorder on the other are emphasized. For example, one session is "Dealing with Depression without Using Alcohol or Drugs". Sessions involve a "check-in" where clients report on substance use, moods, medication adherence, and risky and stressful situations confronted. The "check-in" is followed by a planned psychoeducational topic and discussion. Their randomized controlled trial compared 20 weekly sessions of integrated group therapy with group drug counseling focused on the substance use disorder. Group drug counseling was an adaptation of the treatment delivered in the National Institute on Drug Abuse's Drug Abuse Collaborative Cocaine Treatment Study [16], designed to approximate treatment in community substance use disorder programs. Group drug counseling also involved 20 weekly group sessions, each focused on a specific topic. Sixty-two participants with bipolar disorder and current substance dependence were treated with mood stabilizing medications for two weeks or more and randomized to $N = 31$ in each group. Main outcomes were number of days substance use and number of weeks ill with a mood disorder.

Results showed fewer days of substance use for integrated group therapy. Groups were similar for number of weeks ill with bipolar disorder during both treatment and follow-up; however, integrated group therapy had more depressive and manic symptoms. This study is notable for two reasons. First, the intervention was designed to be comparable to what many community clinics already do. That the integrated group therapy group showed better substance abuse outcomes, but not superior reductions in number of weeks ill with mood disorder, was a surprising finding. Integrated group therapy needs replication with larger N values and replication attempts in community clinic settings. If integrated group therapy is shown effective in community clinics, its manualized format and straightforward procedures could yield significant impact on the treatment of co-occurring mental and substance use disorders in community substance abuse treatment programs which rely heavily on group interventions. Integrated group therapy's potential impact on weekly mood disorder symptoms is troubling and could be a function of its weekly review of mood and medication compliance which could increase participant's sensitivity to their bipolar symptoms. This impact is another reason for further study and replication before extensive community adoption is encouraged.

12-Step Facilitation

According to McCarty et al. [50], of programs in the Clinical Trials Network that utilized National Institute on Alcohol Abuse and Alcoholism treatment manuals, 20% of those utilized 12-step facilitation. While literature searches did not identify many studies on the efficacy of this approach specifically in community clinics, except as a comparison or control group, we have included some more general information about it.

Moos [61] provides a general description of 12-step facilitation for substance use disorders as well as some information on its efficacy. Twelve-step facilitation is based on the ideology of Alcoholics Anonymous and the disease model of addiction. Some of the main foci of this approach are on getting clients to admit that they have a problem, and that they are an alcoholic or addict. The emphasis is on abstinence, without accepting controlled drinking as an option. Clients are directed to develop and maintain strong relationships with positive individuals who support their sobriety, such as their family and other sober networks. They are also encouraged to turn themselves over to a Higher Power. Coping skills are taught, and self-efficacy is enhanced. Twelve-step facilitation is an all-encompassing approach, in that clients are asked to attend 12-step meetings, get a sponsor, read the literature, and regularly attend 12-step groups. Moos reports there are several studies that provide evidence that 12-step facilitation is effective for several different types of substance use disorders.

Faith-Based and Religiously Affiliated Programs

The faith-based and religious approach to substance use disorders is fairly common in community clinics [52, 77]. However, there is little to no research on the efficacy of these approaches. Also, there is little to no information regarding standard practice or techniques of these programs, other than that which is available on individual program websites. Twelve-step facilitation is spiritual in its approach, although it is not affiliated with a specific religious organization.

An article by Cnaan and Boddie [14] discusses a section of the Personal Responsibility and Work Opportunity Reconciliation Act of 1996 called “Charitable Choice”. This section encourages the participation of faith-based organizations in federally funded welfare services, including health services such and drug and alcohol treatment. Also, since 1996, there have been other acts passed to further encourage the involvement of faith-based and religious organizations in social services. There is also more protection for religious-based programs to maintain their themes and religious methods by being able to keep all religious symbols, literature, etc., as well as protecting their ability to only hire employees who share or practice their religious beliefs and to fire those who do not.

Cnaan and Boddie [14] also discuss those studies that are focused on the effects of Charitable Choice. However, these studies only look at the awareness of Charitable Choice and an “assessment of the scope and nature of contracting relationships between faith-based organizations and the public sector”. They also state that there are no studies on the effectiveness of the services provided by faith-based organizations.

Interventions for Specific Populations

The Substance Abuse and Mental Health Services Administration at the National Institutes of Health conducted the 2006 National Survey of Substance Abuse Treatment Services [19]. Data were collected on treatment facilities in the 50 states, the District Columbia, and U.S. territories. The survey included information about programs tailored to treat specific populations. Specialized treatments include

the treatment of adolescents, older adults, individuals with co-occurring mental/substance abuse disorders, gays/lesbians, driving under the influence/driving while intoxicated offenders, other substance-related criminal offenders, adult men, adult women, pregnant/postpartum women, and individuals with HIV.

It seems likely that clinics servicing large numbers of individuals are more likely to have sufficient clients in more of these subgroups to enable the provision of specialized services. Thirty-two percent of facilities offer programs specifically for adult women and 25% for adult men. Services directed at treating pregnant or postpartum women are offered by 14% of facilities. Thirty-two percent of institutions also offer services designed for adolescents and 7% for older adults. Adolescent and senior services are offered most frequently by facilities operated by tribal governments (52 and 12%, respectively).

Women are often a minority in substance abuse treatment programs. Women have unique needs and problems associated with their gender, like child care and custody, and abuse by their partner, which may not be revealed or get much attention in male-dominated, mixed-gender group sessions. Thus, many clinics have developed women's recovery groups. An example of such a specialty program for women is that of Greenfield and colleagues [31] in Boston. They have developed and completed an initial study of a manualized 12-session Women's Recovery Group. Women were randomized to either Women's Recovery Group or mixed-gender Group Drug Counseling. No differences in substance use were found during the 12-week treatment. However, at 6 months follow-up, Women's Recovery Group, but not Group Drug Counseling women, showed continued reductions in substance use. Also, Women's Recovery Group women with alcohol dependence showed greater reductions in drinking. Importantly, these results were associated with greater satisfaction among women treated in the Women's Recovery Group. Though this specialty group is early in its development and needs replication, both by the authors and those in another setting, it does suggest such specialty groups can be supportive of longer-term clinical outcomes for women with substance use disorders.

Thirty-one percent of facilities offered special programs to driving under the influence/driving while intoxicated offenders. The majority of facilities offering offender services are private for-profit facilities (46%). Tribal government facilities offered 38% of substance abuse treatment specifically for persons with driving under the influence/driving while intoxicated charges. For other types of substance-related criminal offender populations, 28% of facilities offered tailored treatment. It is important to note that most, if not all, state and federal correctional facilities offer group interventions for inmates with substance use disorders, and some include within the correctional facility a residential therapeutic community where inmates are usually separated from the regular prison population.

Fewer facilities report offering services specifically designed for specialty populations such as individuals with HIV/AIDS, older adults, and gays/lesbians. Only 10% of facilities report offering services for people with HIV/AIDS. Only 10% of federal government-operated facilities report offering services for older adults; however, this was greater than most other facilities. For the gay/lesbian client population, only 6% of facilities report offering specifically designed services. The percentage increases slightly (8%) for private, for-profit institutions who offer targeted treatment interventions for homosexuals. The literature we reviewed did not mention whether these varieties of services are group services. However, we assume that many of these categories are conducted in group intervention formats especially therapy or psychoeducational groups.

Use of Evidence-Based Services in Community Clinic Substance Abuse Treatment

Treatment services operate with limited money and resources. Community substance abuse

treatment services strive to be cost neutral for their planned budget expenditures. For-profit/private clinics aim to make a profit so the program can sustain, if not expand, its services. Thus, a cost-effective program may come at the expense of maximizing treatment gains. Clinics using interventions that lack empirical evidence or have been deemed less beneficial than alternative methods, may prove in the long run to cost more to operate because of the need for longer treatment or increased risk of relapse. Thus, it appears to be in the best long-term interest of facilities to find the most effective treatment that also results in long-term abstinence or maintenance of risk reduction, relapse prevention, shorter treatment time, and less manpower required for implementation. Overall, a treatment program that is both effective and efficient may be most beneficial for most treatment centers and clientele. Realistically, however, few community clinics have the resources to collect valid treatment outcome data to inform administrative decisions about what interventions are most effective or most cost-effective.

Community clinics that specialize in treatment of substance abuse or co-morbid substance abuse and mental health disorders face an even greater need to maximize treatment gains in treating substance abuse because funding is often contingent upon these services. The 2005 American Psychological Association Statement defines effectiveness as treatment methods that are "... the integration of the best available research with clinical expertise in the context of patient characteristics, culture, and preferences" [3].

Treatment quality and effectiveness can be graded according to specific criteria. The Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services reported 40 systems of "grading the strength of a body of evidence." The National Guideline Clearinghouse, for example, requires developers to submit treatment guidelines based on quality of evidence criteria.

Standardization is important in promoting effectiveness of treatment by: (1) comparing outcomes of one treatment to another, and thereby holding facilities accountable to reach expected outcomes, and (2) training employees to administer treatment to clients while maintaining consistency of practice. Use of treatment guides and manuals can help employees check their actual treatment methods and behavior compared with what is specified and described in manuals or guidelines for high quality and/or effective treatment. In this way treatment delivery fidelity may be more likely to result in positive outcomes obtained in clinical research using these same treatment manuals and methods. Standardization also helps identify client variables that may contribute to good or poor treatment response by controlling for treatment methods. This form of standardization may facilitate practitioners to meet more needs of the clients.

Treatment guidelines are also published by agencies such as the National Institute of Drug Abuse [63]. Effective manualized interventions selected by or developed for the National Institute on Drug Abuse's National Drug Abuse Treatment Clinical Trials Network are available in the published clinical literature and posted on their website for use by community clinics outside of the network where original effectiveness research has been completed.

The Substance Abuse and Mental Health Services Administration has published and continues to provide an expanding library of treatment improvement manuals that are evidence-based and written for community substance abuse treatment program adoption. In our opinion there appears to be a slowly growing trend among the more stably supported community substance abuse treatment programs, most of which utilize group interventions extensively, to adopt evidence-based interventions. However, it also seems that the diffusion of these evidence-based interventions is slow, and that the majority of community clinics have not yet fully embraced evidence-based services for their clients with substance use disorders.

The National Institute on Drug Abuse has produced a comprehensive handbook of evidence-based substance abuse treatments entitled *Principles of Drug Addiction Treatment: A Research-Based Guide* [63]. The guide

outlines principles of effective treatment available in the United States and scientifically based approaches to drug addiction treatment as well as a list of resources and answers to some frequently asked questions for individuals and families seeking treatment. The document briefly describes studies supported by the National Institute on Drug Abuse that investigated interventions for substance use disorders, which were found to be efficacious and/or effective. Group treatment programs include long-term residential treatment, short-term residential programs, and outpatient drug-free treatment utilizing group intervention formats. The National Institute on Drug Abuse guide also describes agonist maintenance treatment (e.g., methadone treatment programs), narcotic antagonist treatment using naltrexone, and medical detoxification.

The National Institute on Drug Abuse's National Drug Abuse Treatment Clinical Trials Network

The mission of the Clinical Trials Network is to improve interventions available to persons with substance use disorders by studying the effectiveness of evidence-based treatment services in collaboration with community treatment agencies. Effectiveness research is conducted at collaborating community programs. The Clinical Trials Network aspires to replicate efficacious and effective treatment in clinical trials of substance abuse research by publishing findings from multiple community clinics and by allowing studies funded by other agencies to utilize Clinical Trials Network protocols. Also, the Clinical Trials Network provides capabilities for access to Clinical Trials Network Node facilities (community clinics), new investigations, and Clinical Trials Network Nodes to serve as National Institutes of Health Training Centers.

The Clinical Trials Network consists of: (1) 17 Nodes (Regional Research and Training Centers, all associated with 5 or more Community-Based Treatment Programs), (2) a Clinical Coordinating Center, and (3) a Data and Statistical Center. The network of multi-sites allows researchers to test the effectiveness of treatment on a large array of populations across the United States. The Clinical Trials Network also allows for new evidence-based practices to be diffused to and implemented by community clinics.

Virginia, Maryland, and Washington, D.C, for example, are regions overseen by the Mid-Atlantic Node. This Clinical Trials Network Node is operated out of Johns Hopkins University (a Regional Research and Training Center) and is linked to 7 Community-Based Treatment Programs such as the Chesterfield (Virginia) CSB Substance Abuse Service and the REACH Mobile Health Services in Catonsville, Maryland. The Mid-Atlantic Node, alone, has been involved in the implementation of 9 substance abuse treatment protocols throughout this Node's affiliated community clinics.

Analogous to the network of National Institutes of Health-supported national cancer centers, but on a smaller scale, it is possible the Clinical Trials Network could have a similar impact on community intervention for substance use disorders. Before national cancer centers were developed, effective treatments for cancers developed in academic medical centers were not transferred to local communities. Thus, best practices remained relatively non-implemented by local physicians. Treatment for substance use disorders is in a similar situation. Though there is an array of effective substance use disorder treatments, most studies at academic treatment centers have not yet been diffused to community clinics and programs. It is hoped that the Clinical Trials Network will increase the slow rate of diffusion of effective treatment and also accelerate discovery of the most effective of the efficacious interventions it studies.

Drug Abuse Reporting Program Studies

The Drug Abuse Reporting Program yielded a series of major large-scale studies that examined

community-based drug abuse treatment agencies and their short- and long-term outcomes. The Drug Abuse Reporting Program was initiated in 1969 by the Institute of Behavioral Research at Texas Christian University. An article by Simpson and Sells [78] describes both the studies and the outcome measures. The Drug Abuse Reporting Program originally started with six treatment agencies, and expanded to include 52 in the United States and Puerto Rico, totaling 43,943 clients. It utilized client intake records, bi-monthly treatment status records, and follow-up samples. Follow-up research began in 1974, after client intake records stopped being collected. Surveys lasted, on average, 5–7 years after admission, and 4 years after the end of treatment. The emphasis in the Drug Abuse Reporting Program was on community services and outcomes, not experimental interventions. Clinics included in the Drug Abuse Reporting Program continued with their normal procedures to collect data on client outcomes.

Follow-up outcome data were collected through a sample of reimbursed, face-to-face interviews. Interviews used retrospective self-reports on employment, drug and alcohol use, and return to treatment. The follow-up sample included 4,627 clients from 34 Drug Abuse Reporting Programs. Five different types of community intervention in the follow-up sample included: methadone maintenance, therapeutic communities, outpatient drug-free treatments, outpatient detoxification clinics, and the comparison group, which was intake-only. The clients were also separated based on their addiction status, and divided into three categories: active addicts (those who used opioids daily for 2 months before the Drug Abuse Reporting Program), former addicts (who had a history of daily opioid use, but not during the 2 months before the Drug Abuse Reporting Program), and non-addicts (who had no history of daily opioid use). Outcomes examined at follow-up were: illicit drug use, criminality indicators, alcohol use, return to treatment, and employment. The main outcome measures were illicit drug use and criminality indicators. Highly favorable outcomes were defined as having no drug use and no arrests or incarcerations. Twenty-seven percent of clients in methadone maintenance met these standards, along with 28% in therapeutic communities, 24% in outpatient drug-free treatments, 15% in outpatient detoxification, and 14% in intake-only. Moderately favorable outcomes were defined as no daily drug use and no major criminality indicators, which were further defined as no crimes against persons or crimes of profit and no more than 30 days in jail or prison. Forty-one percent of clients from methadone maintenance met these standards, along with 40% in therapeutic communities, 33% in outpatient drug-free treatments, 25% in outpatient detoxification, and 27% in intake-only. More detailed results are found in Table 1.

The Drug Abuse Reporting Program follow-up results suggested that overall those clients in methadone maintenance, therapeutic communities, and outpatient drug-free treatments had better outcomes than those in the outpatient detoxification and intake-only groups. Long-term follow-up outcomes (i.e., those interviews conducted about 4 years after the Drug Abuse Reporting Program ended) continued with the same trend. Outcomes for clients in methadone maintenance, therapeutic communities, and drug-free treatments were more positive with an increased length of stay, with main results appearing between 90 days and 2 years. The outcomes for those who only stayed short term (less than 90 days) in these categories showed no significant difference between these clients and those who were in the outpatient detoxification and intake-only groups. Inspection of the follow-up records for 990 opioid addicts showed that 61% of that sample achieved opioid abstinence after the Drug Abuse Reporting Program treatment occurred. Throughout most of the Drug Abuse Reporting Program studies, the most important predictor variable was criminal history (arrests and incarcerations before entry into the Drug Abuse Reporting Program).

The Drug Abuse Reporting Program is still considered to be one of the great sources of information regarding client outcomes in community clinics. Some of the limitations of the

Table 1 Pretreatment and posttreatment outcomes for the drug abuse reporting program group treatments

	Therapeutic community (%)		Outpatient drug free (%)		Intake only (%)	
Outcome measures	Pre-trx.	Post- trx.	Pre-trx.	Post-trx.	Pre-trx.	Post-trx.
Opioid drugs						
Any use	100	58	100	64	100	70
Daily use	100	39	100	44	100	53
Marijuana						
Any use	56	62	52	69	49	67
Daily use	17	23	20	30	14	27
Other non-opioid drugs						
Any use	60	40	54	45	48	50
Daily use	10	10	11	10	7	11
Drug abuse treatment						
In 1+ months	53	32	48	33	50	43
Alcohol use (80-proof)						
Over 4 oz per day	20	38	21	38	19	31
Over 8 oz per day	12	21	14	23	12	18
Employment						
Any employment	63	72	60	65	65	54
Employed 6+ months	20	61	24	52	21	44
Criminality						
Arrested 1+ times	95	33	87	34	86	39
Any jail or prison	83	33	66	34	68	41
Number of persons	582		256		152	

Adapted from data in Simpson and Sells [78]

Post-treatment data are for the first year after treatment, and persons included are black and white male opioid addicts

Drug Abuse Reporting Program studies include the fact that they were not controlled studies. There was no randomization of clients into the different treatments. This meant that equality among the groups for gender, age, or any other variables was not controlled. However, this could also be considered a strength, because the studies allowed a real look into how clients actually arrive into various treatments. Another limitation was the fact that outcome data relied mostly on retrospective self-report, although some of the variables, such as criminality indicators, could be verified through records. The findings from this study utilized pre- and post-treatment data, with no rigorous experimental controls, so these methods prevent firm conclusions regarding treatment efficacy and effectiveness. For example, one major limitation of pre-post treatment studies is that in a recurring disorder like substance use disorder, abstinence and other functional indicators of treatment success naturally fluctuate in their usual course. Individuals seek treatment when they are at their worst and thus may show improvement or success as the natural course of their chronic disorder continues, rather than as a direct causal result of treatment.

A major strength of the Drug Abuse Reporting Program studies was the huge breadth of the research. Treatment agencies that were included in the Drug Abuse Reporting Program were very diverse, both in location and treatment philosophy. The studies were very consistent and provided similar results throughout the course of the program. One of the interesting findings of the Drug Abuse Reporting Program was the fact that there were not any significant outcome differences between individual agencies or types of agencies. This could be considered a positive finding, showing more consistency than was necessarily expected. Overall, major Drug Abuse Reporting Program findings demonstrated positive outcomes for methadone maintenance, therapeutic community, and

outpatient drug-free treatments among daily opioid users who remained in treatment for more than 90 days.

Additional Treatment Models

Some group methods investigated through the National Institute on Drug Abuse's support include Relapse Prevention (some have utilized individual therapy), the Matrix Model, Community Reinforcement Approach Plus Vouchers, and Day Treatment with Abstinence Contingencies and Vouchers. All are reviewed in the National Institute on Drug Abuse's *Principles of Drug Addiction Treatment* [51], but this is not an exhaustive list of empirically based treatments. Numerous other substance abuse treatments, not listed include an eclectic mixture of methods, theoretically driven techniques, or variations of other treatment procedures. Some evidence-based group treatments have not been extensively evaluated, or have been found to be insufficiently efficacious or ineffective when rigorously evaluated in clinical settings. Still other substance use disorder treatments being utilized have been determined to be less effective than alternative evidence-based comparative treatments (for example, see Schumacher et al. [74]).

The Matrix Model

The Matrix Model [66, 76] is a multifaceted manualized approach aimed at helping stimulant abusers obtain abstinence. Group treatment incorporates educating clients and their family members about addiction and relapse as well as self-help techniques. Abstinence is monitored by regular urine testing. A therapist acts as a mentor by educating, guiding, and supporting clients during recovery. Treatment focus is on positively reinforcing progression towards abstinence. The relationship between the therapist and client is positive, promoting an open and honest dialog between the two, avoiding authoritative and confrontational interactions. The matrix emphasis is on building clients' self-worth and confidence, helping clients resist temptations for using, and increasing the importance of the self, while reducing potential harm that may ensue through using drugs.

Treatment procedures incorporate effective elements of other empirically supported treatments [67]. As summarized by the National Institute on Drug Abuse's *Principles of Drug Addiction Treatment* [63], specific techniques utilized in the Matrix Model include work sheets for individual sessions; group intervention components include family educational groups, early recovery skills groups, relapse prevention groups, conjoint sessions, 12-step programs, relapse analysis, and social support groups.

The Matrix Model has been shown in many studies to be effective at treating both drug and alcohol abuse as well as improving quality of life and reducing risky behaviors that may increase risk for acquiring HIV [76]. Matrix treatment has been found to be equally effective for methamphetamine and cocaine abusers as well as enhancing the effectiveness of naltrexone treatment of opiate abusers [36]. Recently the Matrix Model has incorporated abstinence contingency management based on Higgins et al.'s voucher approach [34].

Challenges to Community-Based Clinics

In the previous section a number of empirically supported community treatments utilizing group interventions for substance use disorder have been described. These interventions have been carefully designed and rigorously tested. However, substance use disorder is still a major national problem. For example, despite some reduction in the prevalence of cocaine use since its peak in the 1980s, the prevalence of heavy cocaine use has not diminished [72]. In rural communities, methamphetamine has come to replace cocaine use in recent surveys [81].

These alarming substance abuse trends have been observed despite a wealth of evidence documenting the detrimental cognitive and physical effects of these substances.

A recent review of substance use disorder community treatment programs revealed a 15% closure rate within the first year of operation. Among those programs that survive the first year, as many as 25% undergo a major shift in organization [51]. Most are taken over by a different administrative structure. The vast majority of programs report collecting more administrative data than clinically relevant information. Only 54% of programs perform on-site physical examinations at admission. A startling 28% of programs report no electronic information system, email, or even voice mail capabilities while only 30% (largely housed under hospital and university settings) had full access to advanced information technology. The remaining 40% only had an information system available for administrative duties (i.e., budgeting, payroll, and billing), but the technology was not available to staff members that interact face-to-face with clients [51].

It appears we are facing a paradox in the national effort to reduce substance use disorders. Health professionals have an increasing variety of effective interventions to treat persons with chemical dependencies, yet treatment programs in the community are struggling to remain open, let alone to address the rising population of persons with substance use disorders. Why is this? There are a number of barriers to the dissemination and maintenance of community addictions treatment programs. Most of these barriers can be categorized into one of three categories: (1) funding; (2) staffing, and (3) client-centered barriers.

Funding

Substance use disorder treatment programs have a myriad of funding sources to navigate. Each source has different eligibility requirements and payment mechanisms. The funding categories include: single state agencies, federal grants, local government, third-party reimbursements (e.g., private insurance and HMOs), private grants, client fees, and fundraising [86]. Community substance abuse treatment funding sources can be categorized as either the public or private sector. Funding sources, regardless of source, pose a number of barriers to substance use disorder treatment service delivery. The majority (more than 80%) of the nation's substance use disorder treatment programs are specialty care programs. Specialty care programs are small—typically treating fewer than 300 clients per year, community-based, outpatient, non-profit organizations. Most utilized group interventions of various types with mostly unknown effectiveness. They are rarely affiliated with large medical care facilities. As freestanding entities, specialty care substance use disorder programs operate outside the realm of the mainstream healthcare system. The majority of their funding is government mandated (e.g., Medicaid and Veterans Administration) or provided by state and/or local criminal justice systems [41]. In most cases, these resources are limited, and the documentation and procedural requirements can be very time consuming. This is despite the fact that cost-benefit analyses overwhelmingly support a move toward increased government support of substance use disorder treatment programs [79].

A few suggestions have been proposed to address the funding challenge facing substance use disorder treatment programs. A basic concern regarding program funding difficulties is the lack of information about available sources utilized by struggling agencies. This can be addressed by compiling a comprehensive list of available funding resources, such as the 1995 review by Zarkin and colleagues. Additionally, it may prove beneficial to provide program directors and administrative staff with basic budget and resource allocation training. The use or expansion of self-funding may help some substance use disorder treatment programs. Self-funding programs can operate by placing fees for specific products to fund services that address the detrimental effects of its consumption, like cigarette taxes being used to fund

cancer research [79]. In the case of illicit drug use, which, unlike alcohol and tobacco, is not commercially marketed, restitution payments from those convicted of drug charges could be used to fund rehabilitation centers. The idea of self-funding programs is still relatively new, but if it proves to be a viable option for mitigating the pubic harm caused by alcohol and nicotine, it may be useful to consider for substance use treatment.

Staffing

A number of staffing difficulties face substance use disorder treatment programs. Some of these issues include: clinical staff training, caseloads, and staff retention/stability. McClellan and colleagues' [51] sample of community treatment programs found that 15% of program directors had no college degree, 58% had a bachelor's degree, and 20% had a master's degree. Nearly 72% of the directors for these programs worked full-time. While 71% of the directors had worked within their program, most in a clinical position for more than a year, over half (54%) had been in the director position for less than a year. These statistics imply there is a problem of instability at the top administrative level of these programs.

If we look further at staff credentials, we find differences between private and public sector programs. The main difference is typically based on the program's funding source. Those who receive at least 50% of their funding through public grants and/or contracts can be considered public sector programs. By this definition, private sector programs receive the majority of their funding from affiliated institutions, direct client payments, and third party reimbursements [71]. One very notable distinction in staffing is that private sector programs, partially due to their hospital affiliations, are more likely to have a physician and master's level counselors available. This may have implications for these programs' viability, treatment quality, and success. Having higher educated staff allows more private sector programs to offer more innovative approaches, such as pharmacotherapy and other evidence-based psychosocial interventions—particularly those that require supervised training for implementation [45].

Staff caseloads often present challenges for these programs. A number of treatment programs have been described as "choking on data collection requirements" [51]. Administrative data reporting requirements are often time-consuming and cumbersome. This is particularly true for programs that hold contracts with multiple state agencies and managed care organizations. Each of these entities, for example, employment organizations, welfare departments, and criminal justice agencies, has unique requirements for record-keeping and billing. Case workers at many community programs report devoting 2–4 h to collecting administrative data alone for each admission. This time and effort appears not to contribute to actual clinical assessment or treatment planning. Nevertheless, staff members in most treatment facilities find themselves busy completing a sizeable amount of paperwork and still left with the task of providing client care, in many cases without access to computers, email, fax, or even voicemail capabilities.

The most salient staff-related barrier to community treatment vitality is staff retention. Data from the National Treatment Center Study reveal an average turnover rate of 18.5% among addiction counselors [45]. This is much greater than national annual rates for other occupations that traditionally have high turnovers, such as teachers (13%) and nurses (12%) [37]. Retention difficulties create numerous problems. In addition to recruiting costs, hiring, and training new counselors, high turnover rates compromise consistency of treatment and service delivery [45]. These staffing problems can have a variety of negative effects for clients such as increasing treatment drop-outs and exposing clients to rapidly changing staff—who may not be competent in delivering evidence-based, effective clinical interventions for their substance use disorders and other common comorbid mental disorders.

What can be done to address staff concerns? A survey of counselors and administrators in attendance at a 2003 training workshop yielded the following suggestions to address staff-related barriers to substance use disorder treatment programs: provide more relevant training, increase program support of staff, provide lighter workloads, and less redundancy in staff duties [5]. There is also a need to offer meaningful incentives to recruit physicians, nurses, psychologists, and counselors [51]. For instance, national educational loan forgiveness could help recruit health care professionals and make clinical careers in addiction treatment more valuable and rewarding if it were more accessible to community treatment programs. There is also a need to incorporate relevant continuing training opportunities, along with training for administrators in personnel management, accounting, budgeting, and other cornerstones of the small business industry. Administrators should streamline the amount of non-clinical data collection that is required [51]. Perhaps, by combining the administrative data with clinically pertinent information from admission, progress notes, and discharge assessments, the burden associated with required documentation can be partially alleviated.

Client-Centered Barriers

There are a number of barriers to substance use disorder program viability that are related to client-issues. One of the primary client-centered problems is motivation/treatment engagement. Client motivation has been shown to be a considerable predictor of treatment success [42]. This is even more evident when examining clients who do not enter treatment under criminal justice supervision. Surveys of substance use disorder programs have shown that clients are more likely to engage and remain motivated if they feel the staff has a vested interest in their recovery. This is especially true when clients feel a connection with their counselor. Good client-counselor rapport has been shown to be related to client engagement and subsequent success. A survey by Kirk and Amaranth [42] revealed a majority of clients preferred counselors with their own stories of recovery who are of the same gender, same cohort group, and with sensitivity to their client's culture.

In addition to client motivation/treatment engagement, many clients face practical obstacles that prevent their individual success, and when taken as a whole, become detrimental to the substance use disorder treatment program. Some of these challenges include transportation, child-care, and missed work. In order to address these issues, programs could offer incentives (e.g., meal and travel vouchers), day-care services, and vocational training to mitigate challenges, while maximizing the benefits of program attendance.

Opportunities to Expand Evidence-Based Substance Use Disorder Interventions

A great opportunity to expand program interventions is through university-affiliated translational research. Translational research emphasizes evaluations of treatments and interventions in clinically relevant settings. Continuing to increase knowledge about the efficacy and real-world implications of substance use disorder interventions is the first step toward increasing their availability. An additional way to improve substance use disorder program availability and effectiveness is with integrated mental health services. Despite barriers to prevent its occurrence, there remains a strong consensus to integrate mental health services with substance abuse treatment [17]. This is particularly important given that people with mental illness are 4–5 times as likely to develop a substance abuse disorder as the general population. Dual diagnosis significantly complicates treatment outcomes [26]. Drake and colleagues [25] concluded

Table 2 Key components of Davidson and White integrated substance abuse and mental health treatment approach

Domain	Mental illness Addiction
Goals of care	Assist people to reduce the interference, impairment, disability, and discrimination associated with the condition(s)
	Support person's own efforts to manage his or her condition(s) while pursuing a dignified and gratifying life in the community
Role of the person with the condition	Take ownership of his or her own recovery process
	Active involvement, including daily decision-making, for initiating and sustaining recovery
	Individual/family involvement, from policy development through service delivery and evaluation
Underlying values	Sustained health care partnership model (vs. expert model)
	Hope-based
	Person- and family-centered
	Culturally competent
	Choice philosophy
	Promotes growth
	Builds on strengths and interests
	Focuses on overall life, including wellness, health, and spirituality
	Recovery-focused outcome measures
Guiding principles	Recovery has multiple pathways and styles
	Recovery flourishes in supportive communities
	Recovery is enhanced by person–environment fit
	Recovery is voluntary
	Recovery outcomes vary across a heterogeneous population
	Recovery is a longitudinal, developmental process, and a continuum
	Recovery is nonlinear
	Family involvement in recovery is helpful
	Peer support in recovery may be crucial
	Spirituality may be a critical component of recovery
Strategies to facilitate recovery	Identify and engage early
	Carry and instill hope, offer role modeling
	Increase motivation for change (recovery priming)
	Offer information and education about the condition(s), recovery, available resources, and ways to self-manage the condition(s)
	Provide interventions effective in resolving crises, reducing or eliminating symptoms and/or impairments associated with condition(s), and improving health
	Provide opportunities, rehabilitation, and supports for persons to gain needed skills for occupying valued roles (e.g., student, spouse)
	Assertively connect person to other people in recovery, mutual support, recovery advocacy organizations, and indigenous recovery communities
	Provide post-treatment monitoring (recovery checkups) and support; active recovery coaching (stage-appropriate recovery education and advice); and, when necessary, early re-intervention
	Offer community supports to enable person to lead a self-determined and meaningful life in the communities of his or her choice (e.g., supported housing, supported employment, supported education)
	Legal advocacy to counter stigma and discrimination, ensure the person's rights, and enable the person to regain the status of being a contributing member of society

Table 2 (continued)

Domain	Mental illness	Addiction
Essential ingredients of recovery-oriented systems	Motivation-based outreach and engagement interventions	
	Basic (material and instrumental) support	
	Pre-treatment, in-treatment, and post-treatment recovery coaching/mentoring	
	Assessment processes that are global, continual, and strengths-based	
	Respite for people in recovery and families	
	Rehabilitation and ongoing provision of community supports	
	Peer support	
	Family education and support	
	Legal aid/advocacy	
	Intensive clinical services, including crisis prevention and response, pharmacological and psychosocial treatments	
	Acute inpatient care	Detox
	Illness management and recovery	Contingency management
	Assertive community treatment	Motivational interviewing

Adapted from an article by Davidson and White [17]
Note suggestions for how substance use disorder and mental health treatment can be structured to impact both disorders

that "treatment in parallel and separate mental health and substance abuse treatment systems is remarkably ineffective". An integrated approach would make recovery the focus of treatment and would address parallel challenges associated with addiction and mental illness. Davidson and White [17] provided a thoughtful conceptualization of integrated treatment. Their table (adapted here as Table 2) details the key components of their integrated substance abuse and mental health treatment approach and illustrates how an integrated substance use disorder and mental health treatment approach might be structured.

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Unhealthy Alcohol and Drug Use in Primary Care

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Contents

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Introduction

The Institute of Medicine has provided a working definition of primary care:

> Primary care is the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients and practicing in the context of family and community [41].

This definition emphasizes several aspects of care that impact individuals who use alcohol, tobacco, and other drugs.

1) continuity of care over a "sustained" time period
2) responsibility for addressing the majority of health care needs, including behavioral or psychological problems
3) Coordination of "integrated" care that may include multiple consultants and groups
4) Inclusion of community and family issues that may challenge or promote health
5) Being "accountable" for care is meant to imply some regard for efficiency and cost effectiveness, and for long term outcomes across multiple conditions
6) Care is not in the sole purview of physicians: a team of nurses, counselors, physician's

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_42,

assistants, and others are the key to effective care.

The Institute of Medicine goes on to describe core functions of primary care relevant to substance users.

(1) Primary and secondary prevention, including screening for modifiable risk factors before they become problems
(2) Education of patients to help them live healthfully and to self-manage problems
(3) Initial evaluation and treatment of problems as they emerge

Primary care may be practiced by many medical professionals. Most readers will be familiar with general internists, family practitioners or pediatricians in this role, but gynecologists, and other subspecialists, such as those in infectious disease, nephrology or endocrinology, often provide primary care. In the United States, about half of the approximately one trillion doctor visits made in 2004 were to primary care clinicians (internal medicine, family medicine and pediatrics) [2].

Given primary care's ubiquity and the multiplicity of functions (particularly the "ownership" in the long run of a patient's care), primary care providers are poised optimally to help patients with chronic behavioral health problems, especially those that manifest with physical or emotional troubles that may cause someone to seek medical attention. Indeed, the setting for which the literature best supports the efficacy of brief interventions for alcohol is primary care practice. Problems that are accompanied by shame and secrecy may need a trusted relationship with a professional to catalyze healthy change. The primary care provider may be the only person in a patient's life who can fill that bill. Tobacco smoking, unhealthy alcohol use, and other drug and alcohol problems are common among patients seeing primary care practitioners. About one in five adults visiting primary care clinicians drink above recommended limits or have problems related to alcohol. Studies of primary care practices have demonstrated the success of care provided to people with substance use problems, but also the large gap between the prevalence of problems and the rates of screening, detection, and treatment of those problems.

This chapter addresses those gaps. Primary care providers are optimally positioned to identify, assess, manage and refer to specialty care as needed for drug and alcohol problems as well as psychiatric and medical problems that accompany or are caused by the substance use. The challenge to primary care in this arena is great; so too is the opportunity to make a profound difference in the lives of patients and their families [42].

Screening

Unhealthy alcohol and drug use are highly prevalent in the community and among primary care patients. They can result in physical and social deterioration and in increased use of costly medical resources. The primary care provider can detect preclinical at-risk or problem use, and intervene effectively prior to the development of a substance use disorder (i.e. abuse or dependence). This paradigm is best studied and supported for alcohol and tobacco, but weaker support exists for detection and intervention for other drugs. It is for conditions for which we know that early versus later intervention can delay or diminish disease severity, morbidity or mortality that a strong argument can be made for screening.

Screening for Alcohol Use

Surveys have found that screening is far from universal, and that only 13% of primary care providers use a validated instrument or tool to do so. When problems are identified, most primary care providers recommend self-help groups, but about a fifth of primary care providers offer no formal therapeutic intervention [34]. In a review of thousands of records, McGlynn et al found

that about one-half of recommended health services were provided to adult patients. Services for alcohol dependence were at the lowest level: only 10% of patients with alcohol dependence documented in the medical record had it addressed in any way [52].

The United States Preventive Services Task Force recommends screening and brief intervention for unhealthy alcohol use for adults and pregnant women. The United States Preventive Services Task Force found that screening and brief intervention improves important health outcomes and that benefits outweigh any risks. The recommendation is as strong as that for screening mammography for women aged 40–50, osteoporosis screening for women aged 65 or older, or cholesterol screening in young adults with other risk factors for coronary artery disease. One clear difference between screening and brief intervention for alcohol use and the other preventive services listed is that screening and brief intervention is a more time-consuming interaction with a patient than is ordering a radiologic or blood test. In a revenue-driven healthcare environment, test ordering may add revenue to an institution. Prevention of alcohol disorders and their consequences, in contrast, may slow down the primary care provider, decreasing volume-based-revenue, even with the prospect of downstream cost-savings. (This scenario may be mitigated in part by the current existence of a billing code for screening and brief-intervention for substance use). Indeed, screening and brief intervention is likely to be cost savings as well as cost-effective, at least from a societal perspective [76]. Screening and brief intervention for alcohol ranks in the top five of preventive services for cost-effectiveness [85].

Unhealthy Alcohol Use: Definitions

In the United States, about 70% of men and 60% of women over the age of 18 years drink alcohol [25]. While there is evidence that low-level consumption is low risk and may confer health benefits [77], higher amounts risk medical consequences. Thus, one dimension of screening for unhealthy alcohol use is solely based on quantity and frequency of intake. The other dimension that screening can address is alcohol consequences.

The National Institute on Alcohol Abuse and Alcoholism has defined cut-offs for unhealthy use that are empirically based in epidemiologic literature. Risky drinking amounts are those above these cut-offs. For men, this level is greater than 14 drinks/week or > 4 drinks on an occasion; for women this cutoff is >7 drinks/week or > 3 drinks on an occasion. For those over 65 years of age, the cut-off is that for women. A "drink" is defined, in the United States, as 12–14 g of ethanol (12 oz of beer, 5–6 oz of wine, and 1.5 oz of 80 proof spirits) (Table 1). Drinking risky amounts without associated consequences is risky drinking. If there are consequences/problems, patients may have problem alcohol use, alcohol abuse or alcohol dependence (the latter two are alcohol use disorders as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition) [4]. An important exception to using consumption to define unhealthy use is when even low-level use risks consequences. Examples include pregnant women, people taking medications that interact with alcohol, and those with health conditions worsened by even small amounts (e.g. hepatitis C infection). The key distinction among those with unhealthy alcohol use is whether or not dependence is present. Identifying dependence is important because management differs, as discussed later in this chapter.

What is the best way to screen for unhealthy alcohol use? While we usually think about face-to-face discussions or questions in the clinical setting, screening runs the gamut from these to telephone or web-based instruments [49]. These should be considered and adapted as appropriate, with an eye to optimal efficiency and effectiveness, for system-based approaches.

Any interaction between the primary care provider and patient should serve to build the therapeutic relationship. Therefore even rote history-taking should be conducted in an empathic, nonjudgmental way. Embedding

Table 1 Alcohol use definitions

		Quantity	Alcohol-related problems/consequences
Lower risk use[a]		Below NIAAA-recommended limits cutoffs	None
Unhealthy use	Risky use	Above NIAAA-recommended limits	None
	Problem use	Not part of definition	Present but not meeting criteria for abuse or dependence
	Abuse	Not part of definition	Meets DSM-IV Abuse Criteria
	Dependence	Not part of definition	Meets DSM-IV Dependence Criteria

[a]The possible exceptions to the "lower risk" category are conditions in which any drinking may pose health risks. These include alcohol dependence (e.g., past), family history of alcohol dependence, pregnancy, use of medications that interact with alcohol, disorders or symptoms usually made worse by alcohol (e.g., for psychiatric symptoms or medical disorders such as hepatitis, peptic ulcer disease, or epilepsy)
Adapted from Refs. [4, 29, 56, 71]

questions about alcohol use among other routine medical history questions may serve to decrease resistance and improve both the tenor of the discussion and the quality of information generated.

The first order of business is to ascertain whether the patient drinks at all. The clearest question is: "Do you sometimes drink beer, wine or other alcoholic beverages?" If the patient does not drink at all, inquiring into the reasons may reveal that the patient is abstaining after prior problematic use. If the patient drinks at all, then quantity and frequency of drinking should be evaluated.

One wants to assess the average number of drinks in a week and whether there are any heavy drinking episodes, i.e. drinking in excess of the single-occasion cut-offs delineated by the National Institute on Alcohol Abuse and Alcoholism. This brief screen can be done with three questions [56]

- On average, how many days per week do you have an alcoholic drink?
- On a typical drinking day, how many drinks do you have?
- What is the maximum number of drinks you had on any given occasion during the past month?

With the first two responses, the number of drinks per week can be calculated, and if weekly cut-offs are exceeded, then there is risky drinking. Similarly, if limits per episode are exceeded, the patient is drinking at a risky level.

The most recent version of the National Institute on Alcohol Abuse and Alcoholism Clinician's Guide recommends a single question to screen people who drink for unhealthy alcohol use [56]:

> "How many times in the past year have you had X or more drinks in a day?" where X = 5 for men and 4 for women. A response ≥ 1 is considered positive. This single item is both sensitive and specific for detecting unhealthy alcohol use (from risky use through abuse and dependence) [75].

Vinson tested a similar single item for screening for risky drinking:

> When was the last time you had more than X drinks in a single day (where the value for X is 4 for a woman and 5 for a man)?

A "positive" response is anytime within the last three months [24].

These single-question instruments are brief, valid and therefore efficient.

The Alcohol Use Disorders Identification Test (see Fig. 1) is a ten-item instrument developed by the World Health Organization with good performance characteristics for identifying unhealthy alcohol use. It is scored from 0–40 with a score of 8 (for men) and 4 (for women and those over 60 years of age) considered positive. It requires scoring so may be better suited to a

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential, so please be honest.

Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

***Note*: This questionnaire (the AUDIT) is reprinted with permission from the World Health Organization. To reflect standard drink sizes in the United States, the number of drinks in question 3 was changed from 6 to 5. A free AUDIT manual with guidelines for use in primary care settings is available online at *www.who.org*.**

Fig. 1 The alcohol use disorders identification test. From Ref. [56]: NIAAA, "Helping patients who drink too much", NIAAA Publication No 07-3769; updated 2005 edition, printed May 2007

pen-and-paper or automated process than to verbal interview.

A briefer validated screening tool is the Alcohol Use Disorders Identification Test-C. It is comprised of the 3 quantity/frequency questions from the Alcohol Use Disorders Identification Test and also requires scoring [18, 68]. Using a score threshold (or cut-point) of 4 for males and 3 for females will identify unhealthy alcohol use while choosing 5 and 4 respectively is more useful for identifying alcohol use disorders.

If a patient is NOT drinking above recommended cutoffs and has no absolute contraindication to any drinking, then the patient should be congratulated on the healthy pattern, educated about the risks and benefits of moderate drinking (the best evidence being for an increased risk for breast cancer and decreased cardiovascular risk) and educated about optimal limits. If the screening is "positive," however, then further assessment is recommended for confirmation and to determine severity.

Screening for Tobacco Use

Evaluating the use of tobacco is by-and-large a simpler process than that for use of alcohol. The healthiest level of tobacco intake is none. Since efforts to make smoking a "vital sign," whether the patient smokes is now frequently recorded as a matter of routine at contacts with health care providers. Caution should be taken with patients who define smoking as regular or current use; they may report they are non-smokers despite sporadic or recent but not current regular use. Finally, the presence of past or current smoking may itself raise concern for concomitant unhealthy alcohol use [53].

Screening for Other Drug Use

The CAGE-AID is identical to the CAGE, one of the earliest validated alcohol screening questionnaires, with the exception that the clause ". . .or drug use" is appended to each of the four questions [21]. For example, the C question is: "Have you ever felt you should cut down on your drinking *or drug use*?" One affirmative response is a positive test. The CAGE-AID, like its source the CAGE, is limited in its focus on consequences, being less useful for identifying risky use.

THE DAST-10 is a screening questionnaire that asks about drug use and consequences. A score of 3 or more is positive. Its length, but particularly the lack of validation studies in primary care settings, limits its utility [74]. The ten questions probe for physical and social consequences (e.g. blackouts, withdrawal, relationship problems) and loss of control over use.

The Alcohol Smoking and Substance Involvement Screening Test is a complex instrument of 80 items yielding independent scores for each of multiple substances. A "positive" screening test can be defined as a score of 2 or greater (indicating any drug or alcohol use in the past 3 months), though the cutoff of 4 or greater is probably more clinically useful (indicating either weekly use or less frequent recent use accompanied by consequences of use). It has been validated internationally. Although there are 80 items, if no use of a specific substance is reported, only 10 items need to be answered. If the patient reports any use of a substance, then a series of questions are asked about that substance. Its complexity, length and need for scoring limit its utility in routine clinical primary care practice though where computers are integrated into clinical or research settings the test may be usable. Another major limitation of the Alcohol Smoking and Substance Involvement Screening Test is that the results do not directly identify use of risky alcohol amounts per se, a critical target of screening in primary care settings because of the prevalence and the proven value of brief intervention for such patients [88].

A shorter, more convenient screening test, but with limited validation, consists of two questions, the Two-Item Conjoint Screen [20]:

> "In the past year have you ever drunk or used drugs more than you meant to?"
>
> and
>
> "Have you felt you wanted to cut down on your drinking or drug use in the past year?"

Responses of 0, 1, and 2 positive answers indicated approximately 7, 35 and 70% chance of a current substance use disorder, respectively, in one clinical population. The sensitivity and specificity are both approximately 80%. The validation study for this test has not been replicated and the questions have not been studied for detecting drug use without abuse or dependence.

A Substance Abuse and Mental Health Services Administration [80] consensus agreed that the following would be a useful question for a single-question screening test. It has not been validated.

"Have you ever used street drugs more than five times in your life?"

While streamlined, "prescription" drugs will be missed as pharmaceuticals bought on the street (illegally) may not be detected. It is also not clear how a diverse sample of patients in primary care will respond to being asked about "street drug" use, and the "ever" time frame requires the primary care clinician to ask a series

of follow-up questions before deciding whether current use is present and needs to be addressed.

Assessment

For any patient with unhealthy alcohol or drug use, further assessment should delineate the role of the substance use in the patient's life. This runs the gamut among physical, emotional, interpersonal, and social/vocational functioning. Ultimately, ruling-in or –out the diagnosis of a substance use disorder, in particular dependence, is desirable, because management differs.

If the patient is screens positive for drinking above recommended limits, then there are several next steps: The primary objective of the evaluation is to determine if there is alcohol dependence. If there is no dependence, then brief counseling has proven efficacy and is indicated. If there is dependence, then the effectiveness of brief intervention is less certain, but brief counseling with a goal of further care by the primary care provider or via referral is desirable [70]. Dependence warrants an offer of pharmacotherapy, mutual help, and counseling. This can be provided by the primary care provider if expert, and time permits, and/or by referral to specialty care, generally the favored approach if available and the patient is willing to go. The other important objective of assessment here, whether or not dependence is diagnosed, is to gather information about the impact of alcohol in the patient's life, both positive and negative, to be able to counsel the patient appropriately. Such insight is necessary to enable use of motivational interviewing to assist with behavior change [54].

One approach to assessment (recommended by the National Institute on Alcohol Abuse and Alcoholism Clinician's Guide) [56] is to ask the patient about alcohol dependence symptoms. The cardinal elements of dependence are loss of control, use despite negative consequences, and significant negative impact of use. A patient meets criteria for the diagnosis of dependence if three or more of the following are present in a year, accompanied by significant impairment or distress:

1. Tolerance
2. Withdrawal
3. Use despite known consequences
4. Using more than intended
5. Inability to stop or cut-down
6. Spending substantial time getting, using and recovering from use
7. Giving up important activities

Abuse is more common and less severe. Criteria for abuse are one or more of the following in a year [4]:

1. Repeated use in hazardous situations
2. Use despite negative social consequences
3. Recurrent use despite interference with significant roles or function
4. Recurrent legal problems related to drinking.

Further assessment for psychiatric comorbidity is indicated when an alcohol use disorder is identified because it is common and needs to be addressed.

Some screening tests provide information regarding the presence of alcohol use disorders. While a detailed interview is recommended for assessment, primary care providers often will not have such time available, particularly at the same visit during which a patient screens positive. As such, screening tests that provide information about consequences can help suggest the presence of dependence.

Although not designed as an assessment tool, the 4-item CAGE questionnaire at a score of 2 or greater indicates a high likelihood of lifetime abuse or dependence. The four questions with which many primary care providers are already familiar, are:

Have you ever felt you should *Cut down* on your drinking?

Have people *Annoyed* you by criticizing your drinking?

Have you ever felt bad or *Guilty* about your drinking?

Have you ever taken a drink first thing in the morning (*Eye-opener*) to steady your nerves or get rid of a hangover?

A positive answer is worth one point, and a score of one is 85% sensitive and 78% specific for an alcohol use disorder; a score of two is 71% sensitive and 91% specific [1, 22].

Vinson and colleagues [87] tested two concepts to see if their presence or absence could separate those who screen positive into two groups—those with and without an alcohol use disorder (abuse or dependence),—to determine urgency of need for intervention and likely long-term management. The concepts (which came from several research studies that asked about them in slightly different ways) were summarized by these two questions:

1. In the past year, have you sometimes been under the influence of alcohol in situations were you might have caused an accident or gotten hurt? and
2. Have there often been times when you had a lot more to drink than you intended to have?

The test is considered positive if either question is answered affirmatively. The approach has promise though further validation will be important.

Management of Unhealthy Drug and Alcohol Use

Brief Intervention

Brief intervention is an essential part of the primary care provider's management of patients with unhealthy behaviors in general and unhealthy drug and alcohol use in particular. It is covered in detail in Chapter "Brief Interventions for the Treatment of Alcohol or Other Drug Addiction". Brief intervention is a brief, patient-centered counseling of no more than 40 but usually 10–15 min. Using a motivational interviewing approach, the primary care provider provides feedback to the patient about their substance use and any consequences (or risks thereof) of importance to the patient (e.g. social, occupational, legal, medical, psychological), and how their use compares to norms (Table 2). Along with the assessment should come clear advice about change. The patient's desires and understanding about and need to change should be elicited, as should their ability and readiness to change. Then with the patient's agreement, a menu of options for courses of action should be discussed. Their commitment, including an agreement about the next step and (long- and short-term) goals should be agreed upon and recorded. Finally, arrangement for follow-up should be made. The approach must be empathic, and must support the patient's self-efficacy.

More specifically, the clinician should determine the patient's perception of their use and need for change (e.g. "Do you think your drug use is a problem?") [70]. For those who are not ready to change, the goals are to increase problem awareness, express concern, and agree to disagree. Sometimes a trial of abstinence or cutting down can be useful. For those considering change, the goal is to tip the balance towards change by eliciting positive and negative aspects of drinking and not drinking, to demonstrate discrepancies between patients' values and actions. Once the patient has decided to change, working on motivation is not helpful but reviewing options is. The patient will need support and encouragement, and a reminder that the therapeutic relationship will continue regardless of continued unhealthy use or success in cutting down.

Management of Nondependent Unhealthy Alcohol and Drug Use

Brief intervention has been demonstrated to significantly improve drinking outcomes when delivered in many clinical settings and by varied clinical personnel, though the best controlled trial evidence is for screening and brief intervention in primary care settings by primary care providers [16, 31, 32]. Although they are

Table 2 Alcohol epidemiology: drinking levels by age and sex of community dwelling adults in the United States

Cumulative percentile of drinks per week by age and gender										
Men age	0	1	2–3	4–5	6–8	9–12	13–19	20–29	30–39	40+
18–20	32	65	71	76	80	84	87	90	93	100
21–25	20	49	59	65	73	79	85	90	93	100
26–29	19	53	63	71	78	84	91	94	97	100
30–34	21	57	68	76	82	88	93	96	97	100
35–39	25	57	67	73	80	86	91	95	97	100
40–44	26	60	68	74	80	86	91	94	95	100
45–49	27	59	69	75	81	86	91	94	96	100
50–54	28	61	70	75	81	86	92	95	96	100
55–59	32	65	72	78	84	89	94	97	98	100
60–64	36	68	74	77	83	88	93	96	97	100
65+	45	73	78	82	87	91	95	98	99	100
Total	29	61	69	75	81	86	91	95	96	100
Women age	0	1	2–3	4–5	6–8	9–12	13–19	20–29	30–39	40+
18–20	40	81	86	90	92	94	96	97	98	100
21–25	27	72	81	85	90	93	96	98	99	100
26–29	30	80	88	91	94	97	98	99	99	100
30–34	32	80	87	92	94	97	98	99	99	100
35–39	32	78	86	90	93	96	98	99	99	100
40–44	35	80	86	91	94	96	98	99	100	100
45–49	36	79	86	89	93	95	97	99	99	100
50–54	42	82	87	90	94	96	98	99	99	100
55–59	43	82	88	91	93	96	98	99	99	100
60–64	50	85	90	93	95	98	99	100	100	100
65+	63	89	92	94	96	98	99	100	100	100
Total	41	81	87	91	94	96	98	99	99	100

This table may be useful for helping patients understand how their level of drinking objectively compares to that of Americans of the same age and gender. For example, a 50 year old woman who drinks 2 drinks every day can be provided with the fact that she drinks more than 98% of American women her age

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less-well studied, brief interventions can also be written, phone, or computer/Web-based, and can be single or multiple contacts [49]. The best evidence for efficacy is for multi-contact interventions. Implementation depends on the particular practice setting.

Fleming and colleagues demonstrated in a randomized controlled trial of a multi-contact brief intervention, that significant effects on drinking and health care utilization and expenditures can be detected for up to four years [33]. One meta-analysis demonstrated brief intervention for alcohol decreases mortality [26]. Meta-analyses predict that on average alcohol intake will decline by 38 g per week (a 15% decrease) [15] and that the proportion of people drinking risky amounts decreases to 57% in brief intervention groups and 69% in controls [13].

The evidence supporting brief intervention for drugs other than alcohol and tobacco is more limited. Only three controlled trials have tested brief intervention for drugs after screening in outpatient settings. Bernstein and colleagues studied patients who used cocaine and or heroin presenting for care in outpatient (not primary care) settings. A single motivational brief intervention delivered by a trained health promotion advocate reduced cocaine and heroin use at 6 months more than written advice alone [14]. For example, more cocaine users who received brief intervention were abstinent than were controls (22% vs. 17%). One small trial (in 59

adolescents) demonstrated efficacy of brief intervention in primary care for marijuana and ecstasy use and problems [27]. Finally, the World Health Organization Alcohol Smoking and Substance Involvement Screening Test phase 3 trial found that brief intervention had efficacy (in 3 countries but not the United States) for decreasing a score on a screening test that reflected use and/or consequences [88].

Brief interventions can decrease substance use but even under the best circumstances (e.g. the evidence for alcohol brief intervention in primary care) many people continue to have unhealthy use. The effectiveness of repeated brief interventions is unknown, but primary care settings do provide the opportunity to address such behavior-change issues over time. Over the course of time, with repeated education and intervention, the case for change can build in breadth and depth. As the clinician learns more about the patient and their substance use, the advice and rationale may become more personally salient and effective. The key for clinicians delivering longitudinal care is to maintain an empathic alliance and continue to address substance use. Drinking despite known negative consequences is a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criterion for dependence, so clinicians should remain alert to any consequences and the development of dependence.

If there is an important person in the patient's life, it may be effective to bring this person into the discussion, with the patient's consent. This person should be invited into a face-to-face visit with the patient. They may offer an important perspective, for instance by furnishing information about consequences of drinking or by assisting in the process of change. It may also be necessary for the behavior change to be a goal shared by the two people for success to take hold.

Once a patient has been able to reduce drinking to healthier levels, then the clinician should recognize and affirm this success, and monitor for any recurrence.

This discussion of management of nondependent drinking may be applied to non-dependent use of other drugs. It should be noted that in virtually all cases in the United States, the illegal activities involved in procuring illicit drugs is an obvious risk that can be used in motivational brief interventions. Several drugs, depending on route of administration, induce dependence at high rates, so non-dependent use will be rare; for instance, smoked free-base or crack cocaine is rarely a casual behavior over which there is robust control.

Management of Alcohol Dependence

Several approaches to alcohol dependence can be effective in primary care settings, namely, pharmacotherapy, counseling, and referrals.

Pharmacotherapy

For the management of alcohol dependence, acamprosate, naltrexone, and disulfiram have proven efficacy (see Chapter "Pharmacotherapy for Alcoholism and Some Related Psychiatric and Addictive Disorders: Scientific Basis and Clinical Findings") These medications, to be most effective, should be given along with counseling which can be done in primary care settings [78]. Medications for alcohol dependence are not magic bullets and should be considered as one of several effective approaches. Even with pharmacologic support, many patients find initiating and maintaining change to be challenging. We emphasize the importance of continued motivational counseling, mutual-help and peer support in the community and attention to relapse prevention with or without medication use. But no single approach is 100% effective for this chronic and serious condition so no known effective interventions should be excluded from consideration. As such, offering and discussing medications with patients should be routine and realistic, addressing efficacy without falsely raising hopes. Because medication adherence is one of the hardest challenges to overcome in primary

care for all chronic diseases, let alone for behavioral problems, minimizing and managing any side effects are critically important. Counseling designed to enhance medication adherence is also recommended.

Acamprosate has been approved for use in Europe since 1989 and in the United States since August 2004. It has generally been studied in patients abstaining from alcohol for at least five days. It is an oral medication that is taken three times a day (two capsules each time for a total of six capsules daily). A congener of homotaurine, it is active at the gamma-aminobutyric acid receptor and thought to modulate glutamatergic activity at the N-methyl-D-aspartate receptor. Its use is associated with an improvement in abstinence rates (15% in placebo vs. 23% for acamprosate treated patients at 12 months) time to first drink, and days of cumulative abstinence, with a number needed to treat of 7.5 to achieve a 13% absolute risk reduction in relapse at 12 months [17, 50, 69]. In one study, it was effective when administered for a full year, and also reduced relapse for an additional year of follow-up. It is relatively well tolerated, reflected by low drop out rates in clinical trials. The main side-effect is diarrhea. Renal insufficiency is a relative contraindication (dictates a dose reduction) [62, 63].

Oral naltrexone has been approved to treat alcohol dependence in the United States since 1994 and long-acting injectable naltrexone (monthly) since 2006. It is a mu opioid receptor antagonist that is considered to block central endorphins and to decrease levels of dopamine released in the nucleus accumbens, a key event in euphoria and reward. Naltrexone has also generally been studied in abstinent patients [79]. Orally it is taken daily usually at a dose of 50 mg. Most published studies are limited to a few months' duration, but there is support for its use up to six months [7]. Over weeks of ongoing treatment, measures of "craving" for alcohol diminish with time [73]. It may diminish craving and preoccupation with alcohol more than acamprosate [46]. There is good support for its role in decreasing rates of relapse to heavy drinking from 48% in controls to 37% in those on naltrexone, but weaker support for that of increasing continuous abstinence rates. Its effectiveness may be enhanced with cognitive behavioral therapy [6] but it has also been effective in protocols with minimal counseling components [60], making it well suited to the primary care setting. Other secondary outcomes are improved, including density of drinking and number of days without drinking. Medical outcomes, such as liver enzyme levels, improve with treatment as well [11]. It cannot be used in patients who require the use of opioids and should be withheld prior to elective procedures requiring opioid analgesia. Management of patients taking naltrexone with unanticipated need for opioid agonists, for example trauma victims, may be complex, requiring high doses and careful monitoring. It can be associated with gastrointestinal side effects but these are generally self-limited and minor [17, 64]. Despite the relative advantage of acamprosate with respect to its effect on abstinence, naltrexone has re-emerged in practice because of its significant superiority in a head-to-head trial versus acamprosate [5, 7]. The injectable long-acting form may help address the challenge of medication adherence [36].

Disulfiram is an inhibitor of aldehyde dehydrogenase, a step in the metabolism of alcohol. This causes the accumulation of acetaldehyde that causes a range of reactions from an uncomfortable flushing reaction and nausea, to more severe problems such as vomiting, dehydration, and death. It is used as an "aversive" treatment to heighten the negative consequences of drinking. In placebo-controlled trials it fails to show efficacy. In more structured settings, such as when a family member may supervise and witness administration of the medication, it may be efficacious. Several trials confirm that supervised administration is more effective than unsupervised dosing [71]. Because it has a high risk-to-benefit ratio, even in optimal settings, we do not typically choose this medication first. When it is prescribed, written informed consent should be obtained, reinforcing the supervisor's role as well as the possibly fatal consequences of co-administration with alcohol. Hepatitis is a feared side effect [28].

Counseling in Primary Care

Even within the time constraints of the primary care practice, there are models of counseling that can be adopted and adapted as feasible. Motivational interviewing is adapted as motivational enhancement therapy. Four sessions of motivational enhancement therapy was as effective as 12 sessions of cognitive behavioral therapy or 12-step-facilitation in one large randomized trial. Motivational enhancement therapy, while more extensive, has many parallels to motivational brief interventions done in primary care settings.

One model of adherence enhancing counseling with the acronym BRENDA has been tested with oral and injectable naltrexone. The elements of the model, described below, are individually or in combination supported by literature in depression and substance abuse management [78].

The acronym indicates that the model begins with a *Biopsychosocial* evaluation. This emphasizes that there is more to alcohol dependence than physical dependence. Providing feedback to the patient with a *Report* on this assessment is akin to brief intervention. *Empathic* understanding of the patient's situation as opposed to a confrontational style is a key element of interactions that fosters a strong therapeutic alliance. Rather than recommending one treatment to all patients, it is recommended that support and therapeutic interventions reflect the *Needs* collaboratively identified by the patient and the treatment provider. The many treatment types that have been demonstrated to improve drinking outcome with little evidence or clear superiority of any one, argue for acknowledgement of patient preferences. These first four BRENDA steps create a patient-centered, empathic alliance; they set the stage for and are recommended to precede the giving of *Direct* advice to the patient on how to meet the identified needs. Soliciting the patient's reaction to the advice and checking in as to the relevance and feasibility of the plan is key. This last step, to *Assess* reaction of the patient to advice and adjust as necessary for best care, permits the primary care provider and patient to arrive at a mutual plan. The patient role here may enhance self efficacy, motivation and ultimately behavior change.

An approach dubbed "medical management" tested in the "COMBINE" study calls for an initial discussion lasting 45 min and eight follow-up sessions of approximately 20 min over the ensuing 4 months, on average every two to three weeks. The sessions covered a review of drinking, medication use and effects, and global functioning [65]. In the COMBINE study, medical management as described here proved more efficacious in increasing the number of days of abstinence than a more intensive behavioral counseling intervention. While perhaps not a generalizable finding, this does reinforce the message of effectiveness of counseling that could be administered in the primary care setting [7]. Even if physician time is too limited for such counseling, health behavior change counselors in these settings could deliver it.

Primary care providers should adopt a proactive stance to supporting recovery activities. The counseling techniques described here are consistent with that general stance. It may be beneficial to discuss patient's participation in self-help groups in the community as a routine part of every visit. Exploring resistance to and benefits from meetings, suggesting active versus passive participation (e.g. working on "steps" or getting a sponsor) and recommending persistent and methodical attendance all promote engagement [40, 57].

Management of Tobacco Use

Brief interventions have been demonstrated to reduce smoking significantly. For patients who do not respond to brief counseling, the primary care provider should be familiar with medication and counseling approaches to tobacco cessation [10, 38, 44]. Chapter "Nicotine" contains a detailed guide to the use of nicotine replacement therapies, bupropion, and varenicline for

the treatment of nicotine dependence. The essential approach described for alcohol dependence is applicable to tobacco: focus on the patient's distress, maintain an empathic connection; support medication use by monitoring side effects and responses, and continue to work toward sustaining all positive behavior changes.

Management of Opioid Dependence: Pharmacotherapy

Rates of relapse to opioids are high when patients are not taking maintenance opioids for substitution therapy, so called opioid maintenance or opioid agonist therapy. A small minority of opioid dependent patients will be abstinent at one year if not receiving substitution therapy. From 30 to 60% of patients provided opioid maintenance with methadone or buprenorphine are not using illicit drugs at 6 months. Under the federal Drug Abuse Treatment Act of 2000 [84], specially qualified physicians may prescribe buprenorphine for sublingual administration for a limited number of opioid dependent patients. The management of opioid dependence with maintenance therapy, formerly legal only in methadone maintenance programs, has now begun to shift to outpatient clinicians outside of specialty settings and into the hands of primary care providers [82]. Qualifications for prescribing buprenorphine under the Drug Abuse Treatment Act of 2000 are listed in Table 3. With documentation of qualifications, application is made to the Food and Drug Administration for a special Drug Enforcement Administration number to use when prescribing buprenorphine. In the first year, qualified physicians can have 30 patients with active prescriptions at any one time. After a year of practice, application may be made to expand the allowed number of patients to 100.

Buprenorphine is a partial mu receptor agonist, meaning that it is active at the same receptor as morphine (and heroin, and oxycodone, etc.) but with only partial activation. It therefore produces a weaker drug effect than the "pure" agonists with less euphoria, less fatigue and fewer side effects such as respiratory depression or constipation (i.e. it has a ceiling with respect to these effects). It is more tightly bound to the receptor; therefore, agonists with stronger activity but weaker binding cannot occupy and activate the receptor. In fact it precipitates withdrawal from such substances. The only medication approved thus far for use under the Drug Abuse Treatment Act of 2000 is buprenorphine. It is available alone, or in combination with naloxone, the opioid antagonist that is usually administered intravenously. The buprenorphine and the buprenorphine/naloxone tablets are administered sublingually; via this route a negligible dose of naloxone is absorbed. The purpose of the addition of naloxone to the tablet

Table 3 Physician qualifications for prescribing buprenorphine for opiate dependence

Valid medical license (M.D. or D.O.)
Ability to refer to or provide appropriate psychosocial treatments
Must meet one or more of following:
+ Subspecialty board certification in addiction psychiatry from the American Board of Medical specialties
+ Subspecialty board certified in addiction medicine from the American Osteopathic Association (AOA)
+ Addiction certification by the American Society of Addiction Medicine
+ Successful completion of a qualifying 8-h educational offering by the American Academy of Addiction Psychiatry, American Medical Association, AOA, or any Department of Health and Human Services-approved organization
+ Physician is an investigator in a clinical trial that led to approval of buprenorphine
+ Training or experience as determined by a State Licensing Board
Adapted from Ref. [84]
U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment Clinical Guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) 40. Publication No. (SMA) 04-3939, 2004.

is to decrease the desirability of diversion of the medication to parenteral use: when the combination is injected, the naloxone is fully active and blocks the effects of any opioid at the mu receptor, causing an abrupt withdrawal in patients who have circulating or bound mu opioid agonists.

Patients meeting criteria for current opioid dependence (or in some cases those in remission but at high risk of relapse) may be managed with the use of buprenorphine. Detoxification or maintenance is possible, although relapse (and mortality) rates have been high after detoxification, and short-term outcomes of maintenance are superior. Patients who can do well in the relatively less-structured setting of the primary care provider's office generally can adhere to office procedures and protocols, and have no major comorbid psychiatric disorder and no dependence on a variety of other substances. The initial dosing of buprenorphine, evaluation, and follow up require assiduous attention and can be complicated. Physicians who have qualified and have obtained their special Drug Enforcement Administration number may receive ongoing advice and support through a Center for Substance Abuse Treatment-sponsored mentorship program, the Physician Clinical Support System (www.pcssmentor.org).

Referral to Specialty Care

For patients whose drinking or drug use meets the definition of dependence, the primary care provider may refer to and collaborate with specialty care clinicians, and should be familiar with available resources. Physicians should be familiar with how to refer to 12-step programs so that they can more effectively refer patients. Primary care providers should be aware of resources listing local meetings, and should attend meetings to be familiar with where they are sending patients. Many groups have representatives willing to come to physician offices or to meet patients to make referrals easier.

Primary care providers should also, as they would be for medical subspecialties, be familiar with local counseling resources, knowing what treatments are offered, how, if and which patients can access them. For patients with opioid dependence, referral for methadone (or buprenorphine) should be considered. Finally, the primary care provider should become aware of all local resources for referral of patients who exceed the clinician's expertise or available time for appropriate management.

Patients in Recovery

Primary care clinicians will care for many patients in recovery from dependence on drugs or alcohol [35]. Primary care providers who screen all patients will be aware of such personal history. Supportive discussions about recovery should be part of every routine visit. When situations that may increase risk for relapse are encountered, or anticipated, problem-solving and recovery enhancement discussions should ensue. Any significant change in routine can signal risk. If patients change housing, relationships, or jobs, discussing relapse potential may be prudent. If the patient or a relative is experiencing significant medical illness, or is diagnosed with a life-changing disease, the possibility of relapse should be discussed. If a patient with an active recovery routine, for example with regular participation in 12-step meetings, interrupts this practice, reasons should be explored, as such a change may herald relapse. And finally, when abstinent patients begin to experiment with "controlled" use of the problematic substance, empathic, clear concern should be expressed. If the patient is resistant to the notion that such use is itself problematic, it is good to discuss what warning signs would concern the patient. The sound of the patient's own voice describing such a scenario is sometimes enough to clarify the risk and catalyze improvement.

Patients newly achieving sobriety often feel shame and regret. This may extend to the maltreatment of their own bodies. Frequently patients worry about the state of the liver, heart, brain, immune system or kidneys after

a prolonged time using substances. This worry is often inaccurate or unrealistic. The primary care provider can support recovery by attending to such patients' concerns without being dismissive, but without augmenting the sense of urgency. It is normal for patients in early recovery to feel malaise or fatigue; these are probably not symptoms of underlying disease. Changing sleep patterns and appetite are part of recovery as well. It is acceptable practice to monitor patients closely over time rather than sending off batteries of tests. An exception to this approach of using the "test of time" would be for common infectious diseases that respond to treatment. Therefore repeated testing, for example, for exposure to HIV or hepatitis C would not be misplaced effort.

Treatment of Psychiatric Comorbidity

The details of the evaluation and management of comorbid psychiatric conditions are touched upon in various chapters throughout this book. There are higher rates of affective disorders among individuals who use alcohol, tobacco, and other drugs. There are several core principles that inform our practice and bear repeating for the primary care provider. First, the primary care provider should arrive at a mutual understanding with the patient about which symptoms are to be followed and evaluated as markers of the mental health condition. These may or may not be the most troubling for the patient. Those symptoms with higher frequency will be more sensitive bench marks than infrequent ones. Target symptoms should be clearly documented (e.g. sleep quality or quantity for people with depression; or numbers of episodes of tearfulness or guilty feelings). Second, patients should not titrate medications without speaking with the clinician. In part, substance dependence may be thought of as disordered self-pharmacotherapy. As such it may be counterproductive to ask the patient to focus on and respond with self-medication to perceived internal distress.

It can be useful to try to ascertain whether there is a psychiatric diagnosis independent of the substance use problem. It is helpful to elicit a history of psychiatric problems during periods of protracted abstinence, when they are less likely to be due solely to the substance use. Still, the diagnosis is usually tentative rather than definitive. Management of symptoms or treatment of possible diagnoses with medications does not establish an independent diagnosis. The patient may have substance-related symptoms or syndromes that respond to treatment but do not meet criteria for a diagnosis. Nonetheless, it is important to treat these symptoms as the approach will help management of the substance use disorder.

Consideration of withdrawal of the psychiatric medication when the patient is stable reduces the probability that patients without primary psychiatric problems will erroneously carry such a diagnosis long term. It is also important to remain vigilant about the emergence of new psychiatric problems. Recovery may have disparate effects on psychiatric symptoms. While in general recovery is associated with mitigation of psychologic distress and diminution of unpleasant psychiatric symptoms, abstinence may conversely elicit recrudescence or emergence of serious psychiatric distress, occasionally after months of seeming stability. Patients often discover persistence of guilt, poor sleep, or anxiety. Symptoms of post-traumatic stress disorder or mania may emerge in recovery. Moreover, there are well described prolonged abstinence syndromes, such as the depression-like anergia and anhedonia of protracted cocaine abstinence that not only create a high relapse risk, but may benefit from pharmacotherapy [37]. Finally, medications that themselves can be abused or induce dependence should generally be avoided. The risk of development of abuse or dependence is higher among those in early recovery or with current or past dependence [3]. Such medications are almost never to be the first choice, and it is a rare situation that demands the use of risky medications at all. Benzodiazepines and psychostimulants should be avoided.

When treating depression or depressive symptoms in the setting of drug or alcohol

dependence, the primary care provider needs to have a sense of how severe the symptoms are and how confident the patient can safely and effectively engage in outpatient treatment in the primary care setting. When there is doubt, bringing in expert consultation of a psychiatrist versed in addiction is warranted. Occasionally, when the patient or others is at risk of imminent harm, emergency referral for safety is warranted.

For patients within the primary care provider's comfort zone, management can be straightforward. The mainstays, as with the non-addicted, are psychotherapy and medication. Sometimes patients are resistant to a trial of medication for a variety of reasons, and their rationale should be discussed openly, though studies of depression management in primary care suggest patients are generally more willing to accept medication than counseling [86]. Often, the notion that depression, like addiction, is a chemical disorder of the brain can be what enables an individual to accept pharmacotherapy. The primary care provider may allay fears of dependence on a new drug or of stigmatization in abstinence-oriented therapy. Additionally, the evidence that treatment of depression in this setting has positive effects on addiction outcome should be reviewed [58]. Serotonin reuptake inhibitors such as citalopram or fluoxetine have demonstrated this dual efficacy in managing depression symptoms. Tricyclic antidepressants such as desipramine have been studied and supported in this setting as well, but may have a less favorable side effect profile.

Among the most distressing symptoms of early abstinence are disturbances of sleep. Hypersomnolence may be part of the "crash" from recovery from psychostimulants or the body's need to restore and heal itself after metabolic derangements associated with many drugs. It may also be one of several cardinal symptoms of depression. Other than treating depression if the diagnosis seems likely, we recommend no specific pharmacologic intervention here, other than to maintain good sleep hygiene and to avoid hazardous situations. Insomnia is also frequent. While patients often cite insomnia as a primary reason for relapse and persistence may be quite debilitating, randomized trials have not demonstrated an effect of insomnia treatment on abstinence rates. Nonetheless, many practitioners would use trazodone or a sedating antidepressant at least when depressive symptoms coexist. As with hypersomnolence, insomnia can be a symptom of affective disorders which should remain in the differential diagnosis, as they would guide pharmacotherapy. In the absence of affective disorder, the physician should review good sleep hygiene practices with the patient [55]. Among the mainstays of good sleep hygiene are: minimal or no caffeine; 30 min of sunshine in the morning; exercise early in the day; a light meal in the evening; using the bed for sleep only; relaxation before bed; and maintaining a regular schedule.

As with depression, anxiety is associated with substance use disorders, and for some the anxiety disorder is primary. For others, periods of relative or complete alcohol or other substance abstinence, associated with adrenergic drive, causes or exacerbates anxiety symptoms, complicating early recovery and risking relapse due to self-medication. Patients may struggle with intolerable symptoms that threaten sobriety. If the history is clear that anxiety symptoms abate during abstinence, supportive counseling and cognitive therapy may suffice. However, diagnosis can be challenging. Symptoms may be part of generalized anxiety disorder, specific phobias, or post-traumatic stress disorder. Primary management in all cases should include non-pharmacologic care. Support groups, cognitive therapy, and exposure based therapies (for desensitization and coping strategies) are all possibilities. Post-traumatic stress disorder presents a challenge as to timing of therapy, with experts advising delay of intensive therapy to periods of stability. Pharmacotherapy for generalized anxiety disorder or post-traumatic stress disorder should involve a selective serotonin reuptake inhibitor as the gold standard. Treatment with buspirone can also be effective for anxiety symptoms and may have beneficial effects on alcohol consumption [19, 48]. Benzodiazepines should

generally be avoided for this indication in the primary care setting.

It may be challenging to tease apart whether anxiety is a manifestation of mania or bipolar disorder, in which case an antidepressant as a sole agent may be contraindicated. When in doubt here, a mood stabilizer or sedating antipsychotic, such as quetiapine, may be preferable. Mood stabilizing agents (such as valproic acid and carbamazepine) may become more common in such situations as we witness the possible emergence of topiramate, an anticonvulsant and a second-line mood stabilizing agent, for use as a primary pharmacotherapy in alcohol dependence (controlled trials have demonstrated efficacy for alcohol dependence but it is not currently approved for this indication by the Food and Drug Administration) [43].

Management of Withdrawal from Alcohol and Other Drugs

"Withdrawal syndrome" refers to the physiologic and behavioral response to sudden cessation or abrupt decrease in the intake of a drug to which physiologic dependence has developed. In dependence, the brain becomes adapted to the presence of the drug and develops compensatory mechanisms to function. When the drug is withdrawn, those compensatory changes are no longer opposed by the drug, and the result is the withdrawal syndrome. A simple analogy would be driving an automobile with the hand-brake partially engaged. To maintain speed, supranormal acceleration is applied. If the brake is disengaged, the car will surge forward, until a new balance is achieved.

Different drugs are associated with different withdrawal syndromes. Some are outwardly noticeable, as with the tremor of alcohol withdrawal or the dilated pupils of opioid withdrawal, and others may be invisible, as with the mental slowing and depression of cocaine withdrawal. The rate of decrease in drug dosage, as well as conditions of the patient, will affect the severity and manifestations of withdrawal.

In the primary care setting, it is critical to be familiar with withdrawal syndromes and their management. In particular, there are situations where the likelihood of complicated or dangerous withdrawal necessitates admission to an inpatient service. For frail or elderly patients, or those with unstable medical conditions, such as recent myocardial infarction, then the risk of outpatient management is too great.

Even in otherwise healthy people, barbiturate and benzodiazepine withdrawal can be dangerous, as can severe alcohol withdrawal. Opioid withdrawal can lead to dehydration and metabolic abnormalities, but in healthy young people is usually tolerated. Psychostimulant, nicotine, and cannabis withdrawal are not typically dangerous, although they may be associated with subjective suffering that is real and significant. The management of withdrawal is termed "detoxification" and simply means supervised or medically treated withdrawal. Detoxification is not treatment of addiction per se; rather it is merely the process of ridding the body of the drug safely or with mitigated discomfort. As such, referral for detoxification should not be confused with addressing addiction treatment needs. In fact, in the United States, detoxification is most commonly not followed by effective addiction treatment.

Being aware of the withdrawal syndrome and attention to it are necessary to establish trust and to permit reasonable interactions with patients. It is inadvisable to engage in a long or complicated evaluation with a patient experiencing significant discomfort or craving because of withdrawal. Acknowledging and attending to a patient's comfort continuously to the extent possible is necessary. ("When did you last use? When will you need to again? Can we speak now?" are questions that may inaugurate all interactions with addicted patients seeking help).

There are other, non-"medical" features that will make admission advisable. If the patient does not have a safe place to go where temptation or access to the substance is limited, then outpatient management is less likely to succeed, and offering inpatient admission is indicated. If there is no-one to support the patient or to provide safe

transportation, then inpatient observation may be preferable. The American Society of Addiction Medicine has specific patient placement criteria that can help with such triage decisions [9]. Your office capabilities are also important in the decision to admit. Can you or staff see and evaluate the patient at sufficient frequency for safety? For moderate alcohol withdrawal, for example, evaluation daily with easy telephone availability throughout the first few days may be necessary.

In general, outpatient withdrawal can be achieved with reliable and motivated patients by advising them of safe symptom-driven and self-tapering schedules. Many patients will explain that they have done this on their own many times. Patients who are at low risk or using a low-risk drug may try this safely. Depending on the level of physiologic dependence, a typical recipe for self-tapering for short-acting opioids, benzodiazepines, and alcohol is to reduce the dose of the drug by 20% per day, achieving abstinence in about a week.

Many clinicians are reluctant to advise that a patient use the offending substance, even if it is part of a program to forestall withdrawal symptoms and to achieve abstinence. In this case, other medications can be prescribed. In principle, medications that are active at the same receptor or produce similar effects as the offending drug (i.e. cross-tolerance), have been demonstrated to help. Finally, patients may experience withdrawal from many substances simultaneously. It is often advisable to obtain objective identification of recently ingested drugs if possible, for instance with a urine toxicology panel or by confirming history with a trusted companion of the patient.

Alcohol Withdrawal

The primary care provider should be familiar with inpatient detoxification, and can adapt protocols to the outpatient setting [59]. We address this section to the clinician interested in providing ambulatory detoxification because it is a complicated and intensive process requiring a high level of commitment personally and programmatically. Alcohol withdrawal can be fatal or result in prolonged and complex hospitalization. Therefore the reflex may be to advise inpatient evaluation and management as a default. Most alcohol withdrawal, however, never comes to clinical attention and is not significant. Distinguishing cases that can be safely managed in the ambulatory arena from those requiring inpatient management can be challenging and may make the difference between life and death. Some patients will not be willing for myriad reasons to consider inpatient detoxification, so distinguishing those cases where admission is elective can be critically important [39].

In general, the severity of withdrawal can be predicted based on the severity of prior episodes. There is a loose relationship between intensity of drinking or blood alcohol level and severity of symptoms. But regardless, older patients, those with a history of head trauma or concomitant sedative use, and those with comorbid acute medical, surgical or psychiatric illness are at risk for more severe withdrawal. Outpatient management is generally safe in those who report their last drink over 36 h prior (since significant symptoms are unlikely to develop), have no other risk factors for severe withdrawal, and have a responsible other to accompany and monitor them. Inpatient detoxification should be considered when there is a history of seizure, other drug use, an anxiety disorder, multiple detoxifications, and a blood alcohol level over 150 mg/dL (the latter a sign of great tolerance and a risk for more severe withdrawal symptoms). Inpatient management is advisable for those over age 60, those who have concurrent acute illness, seizure, or moderate to severe symptoms (because of the risks for delirium) as measured by an objective assessment scale such as the revised Clinical Institute Withdrawal Assessment for Alcohol scale [81].

Patients who are uncomplicated may be advised to taper alcohol on their own at home. If instead, medications are to be used, several medications may be efficacious, including anticonvulsants. Despite the potential advantages of anticonvulsants that have fewer effects on cognition and alertness, we favor benzodiazepines because they are the only medications

proven to decrease the severe and fatal complications of withdrawal in placebo-controlled trials [51]. Chlordiazepoxide and diazepam are convenient, rapidly absorbed orally, have long half-lives of elimination, and are inexpensive. The half-life of diazepam is 33 h and that of desmethyl diazepam, its active metabolite, is 50 h. For patients with significant liver impairment (hypoalbuminemia or coagulopathy but not the more common mild transaminase elevation), benzodiazepines that are not hepatically metabolized are preferred. Oxazepam and lorazepam are frequent choices, having renal excretion. An objective measure of withdrawal should be used to monitor severity and response to treatment. For patients with moderate to moderate-severe withdrawal, that is a revised Clinical Institute Withdrawal Assessment for Alcohol scale score of 8–20, diazepam 20 mg orally should be given, and the patient reassessed after 2 h. If the revised Clinical Institute Withdrawal Assessment for Alcohol scale score has increased, then inpatient admission should be considered. If the score remains above 8–12 (i.e. severity is more than "mild,") another dose of 10 or 20 mg should be given. If after 2 more h, the revised Clinical Institute Withdrawal Assessment for Alcohol scale score has not decreased by two or more and /or remains above 15, admission should be advised. The median number of doses required for patients with moderate to severe uncomplicated withdrawal is three [72].

If the revised Clinical Institute Withdrawal Assessment for Alcohol scale score has decreased then the patient should be advised to take the same dose of benzodiazepine every 6–8 h for three to four doses and be re-evaluated within 48 h, preferably the next day. Patients may need additional doses between these scheduled doses to treat re-emergent symptoms. The revised Clinical Institute Withdrawal Assessment for Alcohol scale is administered at every clinical evaluation though patients and their significant others should be told which symptoms to follow themselves (e.g. tremor, anxiety, agitation). The tapering of benzodiazepine can occur over three to five days with clear follow-up and instructions to call for indications of over- or under-dosing but tapering is not necessary if the long-acting medications are used and given frequently until symptoms resolve.

Opioid Withdrawal

Like alcohol withdrawal, the intensity of opioid withdrawal syndromes is quite variable. Decisions about the choice between in- and outpatient detoxification, as with alcohol, depend on factors of social stability, comorbid illness, and the ability to resist illicit drug use as an outpatient. Unlike alcohol withdrawal, however, opioid withdrawal is less often life-threatening in the absence of underlying disease. The most effective class of drugs for relieving withdrawal symptoms are opioids themselves, and many inpatient detoxification programs use long-acting oral drugs such as methadone or sublingual drugs such as buprenorphine for this purpose. In the absence of a special license (such as that under the Drug Abuse Treatment Act of 2000 permitting use of buprenorphine), however, it is currently illegal in the outpatient setting to prescribe opioids for the treatment of drug dependence or detoxification. Specially qualified physicians may prescribe buprenorphine and no other opioid for this purpose. Anyone with prescriptive authority may treat opioid withdrawal with non-narcotics, however.

In general, all medications used for opioid withdrawal aim to attenuate the symptoms of withdrawal. Prominent symptoms or signs and the medications used to treat them are:

Anxiety—benzodiazepines, buspirone, sedating antipsychotics
Diarrhea or indigestion—hysocyamine
Insomnia—trazodone
Muscle and bone aches—nonsteroidal anti-inflammatory drugs such as ibuprofen.
Tachycardia, tremor—central alpha agonist clonidine either orally or transdermally.

Severity of withdrawal should be assessed using an objective scoring system such as the Clinical Opiate Withdrawal Scale or the Clinical Institute Narcotic Assessment Scale for Withdrawal Symptoms [84]. Treatment should match the pace of withdrawal. Therefore short

acting opioids that result in withdrawal syndromes that are themselves short will likely lead to a commensurately brief course of medication for withdrawal symptoms. Heroin withdrawal may gather intensity over 24–48 h, so the dose of medication may need to be higher on the second day of withdrawal than the first [47]. Similarly, protracted withdrawal from, for example, methadone, may require several days or weeks of treatment. The severity of withdrawal symptoms is most effectively reduced by opioid replacement (e.g. methadone or buprenorphine). But the outcome of short term detoxification alone, beyond symptom relief, is dismal with respect to relapse, unless the patient remains in a structured setting. As such, methadone or buprenorphine maintenance therapy is often indicated. This is best begun by referral for opioid agonist treatment of withdrawal followed by continuation as maintenance.

Medical Management (Including Preventive Care) of People with Unhealthy Alcohol and Drug Use

Regardless of whether or not substance use continues, a number of other health issues should be attended to. If use continues, driving habits should be assessed and clear advice given to abstain from driving when using alcohol or other drugs. For those who continue to use opioids by injection, safer sterile injection techniques should be discussed (e.g. use of new syringes, avoidance of sharing, bleach cleaning of needles, and needle exchange programs). For those with continued opioid dependence, provision of naloxone for use in the event of overdose can be lifesaving.

Preventive Care

Patients with unhealthy alcohol or drug use often do not receive routine preventive healthcare. They may not have a primary care physician or health insurance, and they may not seek this care in part as a result of substance use and related priorities and disorganization [42]. Furthermore, the physician-patient relationship may be less than optimal for people with addictions, leading to lower quality of care received. Thus, regardless of the status of the substance use, clinicians should make sure to offer such patients routine age- and gender-specific preventive care as is indicated for all adults (e.g. colon and cervical cancer screening, vaccines, cholesterol testing), and facilitate its receipt to the extent possible. In addition, clinicians should be alert for signs of interpersonal violence, and should ask about and recommend receipt of dental health care. On physical exam, cardiac auscultation is important for drug users who may have had endocarditis. Vaccination against hepatitis B should be considered in this high-risk population (particularly for those with a history of drug injection or risky sexual practices, or simply youth). Hepatitis A and B vaccination series are recommended when a patient is demonstrated to be non-immune and at-risk (e.g. injection drug use, unsafe sex). Pneumococcal vaccination is indicated for people with alcohol dependence. Risky sexual behavior is common in drug and alcohol using populations, so education and advice about risk, assuring access to condoms, and screening for sexually transmitted diseases, especially HIV (now recommended universally for all adults by the Centers for Disease Control), are prudent. Cervical cancer screening, also routine for adult sexually active women, is of particularly important in smokers and those with risky sex practices, who are at higher risk for the disease. Similarly breast cancer screening should be done, particularly in women with unhealthy alcohol use who are at greater risk. Osteoporosis screening (bone mineral density testing) is indicated for older women with risk factors, particularly smoking and heavy alcohol use. Consideration should also be given to screening for vitamin D deficiency because of poor diets and possible lack of sun exposure. Empirical recommendation of a multivitamin is another

approach. Folate should be recommended for women of childbearing age. Other routine tests for those with alcohol and other drug use include the serum creatinine, tuberculosis skin testing, and liver enzymes and tests of synthetic function. Patients maintained on methadone, as with any drug that may alter cardiac conduction, should have periodic electrocardiograms as indicated.

Managing Medical Consequences in the Face of Ongoing Substance Use

When patients are bothered enough by symptoms to bring them to the primary care provider's attention, an opportunity often arises to link the unhealthy substance use to the symptom. This link, when pointed out by the physician nonjudgmentally and recognized by the patient, can serve as a discrepancy that motivates the patient to change.

A recurrent practical dilemma will arise for which there is no strong evidence to assist the primary care provider in management. When a symptom or condition is likely related to the use of substances but can be treated with medication, primary care providers may be tempted to withhold medication, emphasizing instead the patient's responsibility to address the behavioral component (i.e. substance use). A common and representative scenario is hypertension related to excessive drinking of alcohol. An economical and healthy alternative to medication use is reduction of alcohol intake. The challenge to the primary care provider is to decide with the patient what the best course of action will be. The use of medication in this case may be reasonable, especially if the hypertension is severe. First, the reduction in the risk due to hypertension may be achieved more quickly with medication. Second, even if the blood pressure is only marginally elevated, the significance of the risk may be made more salient by the physician's prescription of a medication. The behavioral component of the problem may thus be helped more than if medication were withheld. Clearly neither response precludes the other, so pursuing both courses is often the best option. If and when the drinking improves, pharmacologic management may no longer be necessary. There are no hard and fast rules, here, however, and full and honest negotiation with the patient, while minimizing risk, is the optimal course. Prescription of known effective treatments even in the face of a behavioral etiology of or contributor to disease seems to be generally well accepted (e.g. medication for hypercholesterolemia in patients with poor diets; bypass surgery for people who smoke cigarettes).

The vast number of signs, symptoms and illnesses related to the entire spectrum of alcohol, tobacco and other drug use preclude detailing them here. But several highlights most relevant to primary care clinicians follow.

Because tobacco smoking is a well established risk factor for certain cancers and atherosclerotic disease, the primary care provider will interpret symptoms with this risk in mind. Whereas pain in the arm in a non-smoker may represent benign conditions, a Pancoast tumor or coronary insufficiency should be in the differential diagnosis for a smoker. Shortness of breath and fatigue, among the most common symptoms brought to the primary care provider's attention, may have serious causes in a smoker.

Heavy drinking is associated with disturbed sleep, gastro-esophageal reflux disease symptoms, hypertension, peripheral neuropathy, hepatitis and cognitive problems. It is sometimes not clear when and how intensively to investigate causes other than alcohol of a particular medical condition. When the condition does not improve with abstinence or moderation, then further testing is indicated, especially when these problems may be treatable or may represent important underlying conditions. Even when drinking is ongoing, however, it is prudent to rule out common, treatable problems and not simply attribute a sign, symptom or condition to alcohol use. In the case of hepatitis, it is prudent to test for viral hepatitis or iron excess. If hypertension is refractory or severe, one may screen for

secondary causes. Chronic esophagitis symptoms, refractory to proton pump inhibitors, may be an indication for endoscopy, even if drinking is ongoing. Cytopenias may represent a primary marrow dyscrasia. Neuropathy may be caused by a paraprotein (e.g. in multiple myeloma), diabetes, toxins or other primary problems. Fatigue, tremor, and insomnia may all be referable to thyroid dysfunction. Cognitive decline, coordination problems, seizures or confusion may represent a subdural hematoma, cerebrovascular accident, or other central process.

Hypertension or cardiac ischemia may be an acute presentation of cocaine use. If there are electrocardiographic changes consistent with ischemia, the patient needs to be observed. In the presence of enhanced beta- and alpha-adrenergic tone that results from cocaine use, beta-blockers can cause unopposed alpha-adrenergic effects, such as vasoconstriction and hypertension, that can be dangerous if not fatal. Anxiolytics and calcium channel blockers are preferred treatments.

Patients using parenteral drugs often present with skin problems caused by the needle use. Abscesses, ulcers and cellulitis are common. Some ulcers are ischemic rather than infectious, typically when cocaine or other vasoconstrictive agents are injected subcutaneously or into muscle (e.g. when "skin-popping," the preferred route when veins become sclerosed and unusable after chronic intravenous administration). Needle use is also a risk for systemic infection. Viral infections include HIV and hepatitis. Fever in a parenteral drug user should always raise the possibility of systemic viral or bacterial infection. The venous system or right side is more likely affected than the arterial or left side, thus endocarditis is more often of the pulmonic or tricuspid valve. Pulmonary infiltrates may represent embolization of bacteria to the lung.

Viral hepatitis is common in injection drug users. Hepatitis C, usually leads to chronic infection, and in a minority leads to cirrhosis, liver failure or hepatocellular carcinoma. Effective treatments can result in permanent viral suppression. Current treatment involves prolonged administration of interferon, often three times per week. While the side effects are variable, the majority of patients experience a flu-like syndrome that may mimic opioid withdrawal and lead patients to relapse. Interferon therapy often causes or rekindles depression. The primary care provider can help the patient to manage both risks. In general, the primary care provider should delay hepatitis C treatment until recovery is stable, evaluate for depression, treat if present, and prevent the depression that can accompany the interferon treatment (often with *prophylactic* selective serotonin reuptake inhibitors), and augment recovery activities and support during treatment.

Pain Management

Among the most challenging problems for people with addictions is that of pain management. Perhaps because of the riskier lifestyles of people who use drugs and alcohol, trauma and pain are common. And pain thresholds are altered as either a cause or consequences of substance dependence. Use of opioids for analgesia or other drugs as muscle relaxants can lead either to abuse of the prescribed drugs or relapse to the original drug of abuse [67]. There is a higher incidence of problems among chronic pain patients who have addictions than among those without [89]. But pain can also be a trigger for relapse, and when necessary, opioids may be prescribed. The key to navigating the difficult course here is to engage the patient in honest collaborative planning with the dual goal of minimizing both pain and the risk for relapse.

Clear enunciation of the risk of relapse may help the patient embrace, along with the primary care provider, protocols that minimize such risk. Primary care providers might be wise to adopt some of these processes as "universal precautions" irrespective of a patients' prior history of addiction. Medications should be prescribed in small amounts, e.g. for days or weeks at a time, rather than for longer periods. Face-to-face visits should be frequent; initially prescriptions should

be refilled only at visits. While assuring adequate analgesia, clinicians should prescribe alternatives that have a lower street value, less abrupt onset of action, and longer half life; such choices reduce the likelihood of misuse of prescribed drugs. It may be the case, paradoxically, that more aggressive pharmacologic management to ablate pain may spare the patient the stress of discomfort and thus lower the likelihood of relapse, so long as the provider and patient both keep the specter of relapse on the discussion agenda, and mutually agree to maintain tight control over drug quantities.

Discussion about perception of the drug effect may reveal that the patient is experiencing a high or euphoria or that the drug entrains preoccupation with the next dose or illicit drugs. Conversely, withdrawal may be experienced as pain. It may be impossible to distinguish the two; patient trust in the expertise and benevolence of the primary care provider in these cases may permit trials of changes in drug or dose. For patients with chronic pain, whatever the cause, it is useful to identify measures other than the perceived severity of pain to monitor as the benchmarks for successful analgesia. It may be difficult for some patients to distinguish drug-hunger from somatic pain. Thus, objective measures, such as duration of performance of an activity or distance walked, are preferable to severity of pain.

Two commonly adopted protocols for the management of chronic pain with opioids in patients with addiction are contracts and urine toxicology testing. Neither is well supported in objective literature, so the primary care provider needs to think through the risks, benefits and costs of either [8]. Many contracts specify expectations and the consequences of failing to meet them. Many of the behaviors that contracts seek to minimize are those that often accompany the development of pathologic dependence. Requests for early refills, lost medication, requests for brand name narcotics and other behaviors may represent inadequate pain control. Diversion of medication for use in ways not prescribed (e.g. chewing or snorting rather than swallowing whole sustained-release oxycodone), buying illicit drugs, or clandestinely obtaining medication from many prescribers, however, are clearer signs of addiction, although none of these is itself a reliable indicator. It is the pattern, intensity and persistence of these behaviors that ought to raise suspicion of problems. As soon as the use of or desire for the drug on the patient's part becomes highly preoccupying, then the strategy ought to change. The existence of a clear contract may make changes in management easier.

Contracts may present certain risks as well. If they are not utilized universally, they may stigmatize one group more than another and raise fairness or discrimination issues. They may undermine trust. If not adhered to by the provider, they appear to point out poor-quality care, as the primary care provider is failing to adhere to a self-professed and written standard. This internal contradiction could raise the risk of litigation.

Written agreements might outline routines for monitoring urine toxicology tests [23] expectations about non-pharmacologic therapy (e.g. physical therapy), the prescribing physician(s), designation of a single pharmacy, provisions for replacement medication for lost prescriptions or medication, the frequency of face-to-face visits, and the option of random call-in for pill counts and/or toxicologic screening [9, 30]. Sample contracts can be reviewed online [61]. Office protocols for coverage and shared responsibility should also be established to facilitate good continuity and communication. The checking of urine toxicology tests for the presence of illicit drugs (or the absence of prescribed drugs), although a common element of patient management, is complex, yielding false positives and false negatives. It has not been demonstrated to improve outcomes of management of pain [45]. Nonetheless it can be useful in certain situations (e.g. to confirm that the patient is taking any of a prescribed controlled substance).

Because drug and alcohol dependence have both genetic and environmental causes, one should expect that family members of patients in recovery are at risk of addiction themselves. Thus it is wise to discuss openly the risk of diversion of medications that may not be securely

stored. Clear explanation of the patient's responsibility to protect medications and close monitoring of the rate of medication use are advisable. Primary care providers should know that some seemingly innocuous medications have abuse liability or a street value, either because of their direct euphorogenic effects or their role as adjunctive medications to augment euphoria. A partial list of such adjuncts includes: quetiapine, gabapentin, carisoprodol, cyclobenzaprine, clonidine, baclofen, hydroxyzine, and promethazine [12, 66].

Other Challenging Medical Situations

Situations likely to be encountered by primary care physicians in the care of patients with drug or alcohol problems include problems related to medications and medical procedures. For example, some patients report that opioids and anxiolytics prescribed for procedures, such as for colonoscopy, may lead to craving for illicit drugs. Similarly, use of needles for phlebotomy or medication injection may trigger craving. Anticipating this problem may prevent a relapse. Discussing it with the patient, having plans of patient action in place and for an increased intensity of supportive services may be indicated.

Confidentiality

The primary care provider may not be familiar with laws concerning medical records and confidentiality of patients with substance abuse issues. Patients may be ashamed of their problems with drugs or alcohol, and explaining the confidential nature of discussions can be reassuring. Indeed such assurance may be necessary for good communication, though the assurance may not be enough as patients are often concerned that those with legal access to medical records (e.g. health insurers, employers, others to whom patients often must release information), will find out about their substance use (as is also true for cancer, diabetes and other health problems). The sharing of general medical records and information broadly comes under the Health Insurance Portability and Accountability Act of 1996 [83]. By this federal law, providers who share the care of a patient may communicate with one another about the patient. Such communication is critical for high quality patient care and safety. This does not, however, apply to certain types of information or treatment settings. Notably, drug and alcohol dependence and psychiatric issues *sometimes* come under a *more stringent* set of Federal regulations (42 CFR Part 2 revised in 1987) [83]. Under these statutes, there are very few situations in which information can be released to institutions, health care providers, or others *without express and detailed written permission from the patient*. Not only does such written consent need to be obtained, but it must describe the purpose of communication and the duration of permission. When *covered* information about drug or alcohol problems is communicated, written notice that this information cannot be re-communicated should be provided to the recipient. Information covered under CFR 42 Part 2 is highly protected and patients can be reassured it will not be released without their permission barring a court order (though patients can be required to sign such releases for various purposes, and insurers have access).

There are, however, a few important *exceptions* to the inviolability of this privacy. In a *medical emergency*, all relevant information should be shared. Many states have *mandatory reporting laws* with which primary care providers should be familiar. States vary, but in general primary care providers are required to report to the relevant state authority certain high-risk situations when reason to suspect harm or risk of harm is substantial. Among these situations is suspected abuse or neglect of an elder or child, or specific intent to harm another person. Under some state mandatory reporting laws, it is illegal *not* to breach confidentiality and report the suspected risk to the mandated authority. Primary care providers need to know these laws so as to be clear with patients about the bounds of

confidentiality. It may be helpful to let patients know that, barring an emergency, the primary care provider will inform the patient *before* reporting a dangerous situation. In general, the situations requiring reporting are ones from which patients themselves would want to be protected, and knowing that the primary care provider will intercede, with warning, may be welcome.

Because many have misconceptions about alcohol and drug use health information privacy laws, the most important information for primary care providers to know about CFR 42 Part 2 is when it does not apply. In general it does *not* apply to primary care settings. CFR 42 Part 2 applies only to federally assisted individuals, entities, or identified units in medical facilities who hold themselves out as providing, and provide, alcohol or drug abuse diagnosis, treatment or referral for treatment, or to healthcare personnel whose primary function is to do this and who are identified as such. Primary care settings generally do not fall under this definition, though there may be exceptions.

Summary and Conclusions

The primary care provider is ideally positioned to identify patients with unhealthy alcohol or drug use. The primary care provider should be able to assess the severity of the substance use, to identify dependence, and perform brief interventions as appropriate. While identifying and managing comorbid problems, be they medical or psychiatric, incorporating the assistance of consultants and substance abuse specialists when needed can augment the quality of care. In addition to treating and referring, primary care providers have a critical role for patients with addictions who often need medical, mental health, and addictions services, as they coordinate and integrate care across these disparate and often poorly connected systems. Primary care providers can prescribe pharmacotherapy or refer to specialists who can prescribe, for alcohol and opioid dependence, and be the source of primary or adjunctive counseling. They can also treat comorbid psychiatric symptoms and syndromes. Finally, primary care providers should be familiar with treating medical problems, managing pain, and delivering preventive care to patients with substance related diagnoses. With this knowledge and skill, primary care clinicians can make a difference for patients suffering from substance use conditions by doing the right thing at the right time. Such practice is among the most rewarding activities in primary care settings.

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Criminal Justice System and Addiction Treatment

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Contents

Introduction

Compared with other nations, the United States incarcerates the largest percentage of its citizens, with over 8 million adults and 650,000 youth under some form of criminal justice supervision, including prison, jail, and probation or parole supervision in the community [70, 79]. Incarceration in the United States costs nearly $65 billion each year and 40–60% of prison intakes result from failures in community supervision related to drug relapse [30, 46, 62]. Research consistently demonstrates the close connection between drug use and criminal justice involvement, with over 70% of offenders involved with drugs or alcohol at some point in their lifetimes [80]. About 36% of violent crimes involve alcohol and 40% of criminal offenders reported using alcohol at the time of their offense [34]. Many offenders are caught in a cycle of drug use, crime, arrest and reincarceration [4, 31, 75]. Drug charges account for about one-third of re-arrests following release from prison or jail. About one-third of offenders are re-arrested within 6 months of release and over two-thirds are rearrested within 3 years of release [78]. Numerous studies have shown that involvement in community alcohol and drug treatment services delays re-arrest and re-incarceration. The purpose of this chapter is to provide an overview of the drug and alcohol treatment needs of offenders and the mechanisms available in the criminal justice system to address these needs.

Prevalence of Substance Abuse and Dependence

Substance abuse is four times greater in the offender population than in the general population; 37% of offenders are estimated to have a substance abuse disorder, compared with 9% of the general population [63]. Over 80% of

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_43,

state prisoners reported a lifetime history of drug use [54] and 95% of state prison inmates met *Diagnostic and Statistical Manual of Mental Disorders* criteria for at least one form of substance abuse or dependence [44].

Compared with the non-offender populations, offenders are more likely to abuse illicit and prescribed substances [26]. For example, about 11.3% of male and 20.8% of female prisoners reported daily opioid use in the 6 months preceding incarceration; 10% had a history of lifetime opioid dependence and 8% met criteria for current opioid dependence [8]. Abuse of prescribed opiates is a recent phenomenon and, according to the 2008 National Survey on Drug Use and Health, an estimated 5.2 million Americans aged 12 or older used prescription opiates non-medically in the past month, an increase from 4.7 million in 2005. Among individuals aged 18 and older who were arrested between 2002 and 2004, almost 30% had used prescription drugs non-medically in the past year [63]. A recent study of prescription drug abuse among a large sample of prisoners found that 34% of males and 62% of females reported nonmedical use of prescription opiates [92]. Individuals who abused prescription opiates were more likely to have been involved in criminal activity and reported more drug charges, shoplifting, forgery, disorderly conduct, charges resulting in convictions, number of convictions, months incarcerated, and days incarcerated within the last month than individuals who had never abused prescription opiates [92].

A recent study concluded that 58% of county jail inmates had a lifetime history of drug dependence and 51% met criteria for current dependence, suggesting a large need for substance abuse services in facilities that are not equipped to offer such services. Since almost all arrestees are initially housed in jails while awaiting trial or sentencing, it is left to the jail facilities to treat the acute effects of drug use and withdrawal. For example, one-quarter (25%) of inmates reported withdrawal symptoms from active drug or alcohol use upon entering jail, but only 16% reported receiving medication for relief of withdrawal symptoms [8].

Substance Abuse Comorbidities

Smoking

Smoking is the leading preventable cause of death in the United States, resulting in over 440,000 premature deaths each year and implicated as a causal agent in an increasing range of cancers [76, 77]. Prisoners, as a class, are especially vulnerable to the negative health consequences of smoking. Smoking rates are 3-4 times higher among prisoners than among individuals in the general population and smoking is normative and non-stigmatized within the correctional environment [17–19]. Among male prisoners, smoking prevalence is 70–80% [13, 14, 17, 18]. Smoking rates among incarcerated women range from 42 to 91%—two to four times greater than among women in the general population [16, 17].

Ninety percent of prisons prohibit smoking in medical, chapel, and vocational and educational areas; however, about 40% allow unrestricted smoking in common areas, housing units and cells, or in prison yards [42, 84]. Cigarettes and other tobacco products are readily available in prison and tobacco products are sold in prison commissaries. Some prisoners may receive wages and thus, have money to spend on tobacco products. Other prisoners rely on impoverished families and friends to provide money for tobacco products [16]. Tobacco products are bartered among prisoners and employees and function as a form of prison currency [47, 56]. Because of the high cost of cigarettes in prison, many prisoners purchase loose tobacco that they roll into non-filtered cigarettes [16, 17]. Thus, smoking inside a correctional environment may present higher risk for tobacco-related diseases than smoking in the community.

In contrast to the enormous literature focusing on smoking prevalence, prevention, cessation, and policies in other populations, smoking among prisoners remains virtually ignored, despite the enormous human, health, and economic costs [2, 16]. Only three published studies have examined smoking interventions for

prisoners [17, 25, 58]. All three suggest that prisoners are interested in smoking cessation and able to achieve smoking abstinence, despite pressures within the correctional environment to continue smoking. In the largest study to date of smoking cessation in a correctional setting, Cropsey and colleagues conducted a randomized controlled trial of a combined nicotine replacement and 10-week group smoking cessation intervention for female prisoners. Sustained cessation rates were comparable to cessation rates following smoking cessation interventions in the community [17].

Psychiatric Disorders

According to a recent Report to Congress by the National Commission on Correctional Healthcare and National Institute on Justice on the health status of soon-to-be released inmates, rates of psychiatric disorders in United States prisons and jails dramatically exceed general population rates [55]. A meta-analysis of 62 studies from 12 western countries estimated that one in seven prisoners has a psychotic or major depressive disorder [27]. Prevalence estimates for psychiatric disorders among state *prison* inmates are schizophrenia (2–4%), major depression (13–19%), bipolar disorder (2–5%), dysthymia (8–14%), anxiety disorder (22–30%), and posttraumatic stress disorder (6–12%). Prevalence estimates for psychiatric disorders among *jail* inmates are similar: schizophrenia (1%), major depression (8–15%), bipolar disorder (1–3%), dysthymia (2–5%), anxiety disorder (14–20%) and post-traumatic stress disorder (4–9%) [86]. Approximately 50% of female inmates suffer from mental illness [22]. A national study estimated rates of mental illness ranging from 3 to 23% for probationers and 1–11% for parolees [7]. Finally, 6% of male and 15% of female jail inmates have acute psychiatric symptoms in need of treatment at time of initial booking [72, 73].

Inmates with comorbid substance use and mental health problems report more numerous and serious past year and lifetime medical conditions and consume more medical services during incarceration and in the community [38]—underscoring the importance of psychiatric treatment in correctional settings. With the number of prisoners with serious psychiatric disorders exceeding the number of patients in psychiatric hospitals, jails and prisons have become "America's new mental hospitals" (p. 1612) [74]. For many individuals with severe mental illness, most psychiatric care is provided in jails and prisons [45]. The high prevalence of psychiatric disorders in correctional populations is due, in part, to deinstitutionalization of mentally ill persons, lack of access to community mental health services [49] and the criminalization of the mentally ill [45]. Unfortunately, most prisoners with psychiatric and substance use disorders do not receive adequate care during incarceration [27]. Although data are limited, most prisons and jails fail to conform to community standards for screening and treatment of mental disorders [55, 85]. For example, 83% of jails offer screening, 60% offer mental health evaluations, 42% provide psychiatric medications, 43% offer crisis intervention, and 72% offer access to inpatient psychiatric treatment [61]. Jails and prisons differ in the type and range of mental health services; jails may provide management of acute symptoms and suicide prevention, while prisons may offer a range of services including long-term support and treatment. Medical and psychiatric treatment in criminal justice systems varies from state to state; some contract with independent companies to provide psychiatric and medical services for their populations. Often facilities offer specialized services such psychiatric or sex offender treatment units [87] although little is known about the types and effectiveness of treatment programs offered.

HIV/AIDS and Sexually Transmitted Infections

The HIV/AIDS epidemic in the United States coincided with a sharp rise in incarceration

related to the "war on drugs," mandatory minimum sentencing, and "truth in sentencing" legislation in the 1980s and 1990s. As a result, many substance-abusing individuals at high risk for HIV/AIDS are also at high risk for criminal justice involvement. In 1997, 16% of individuals with AIDS and 22–31% of individuals with HIV passed through a United States correctional facility [35]. Between 1989 and 1999, 32.9% of positive HIV tests in Rhode Island came from the state correctional institution [21]. Between 1995 and 2004, the percentage of known HIV+ prisoners decreased from 2.3 to 1.9% of the prison population. Despite that decline, the rate of confirmed AIDS in state and federal prisons was three times higher than in the overall United States population—0.49% for prisoners and 0.14% for the United States population [78].

Offenders have histories of high-risk sexual behavior and high rates of sexually transmitted infections [39, 40]. High-risk sexual behavior includes inconsistent condom use with multiple sexual partners, history of sexually transmitted infections, exchanging sex for money or drugs, and engaging in sexual intercourse with an injection drug user or under the influence of drugs or alcohol [15, 52]. Rates of chlamydia and gonorrhea are 18–50 times higher in adult prisoners compared with adults in the general population [10]. Left untreated, chlamydia and gonorrhea may result in infertility, pelvic inflammatory disease, cervicitis, and ectopic pregnancy [10]. Rates of syphilis are also high among correctional populations; with 3.7% of male and 5.2% of female inmates testing positive for syphilis, compared with less than 0.001% of adults in the general population [10]. High rates of untreated sexually transmitted infections enhance risk for HIV transmission or infection [10]—suggesting the importance of addressing high-risk sexual behavior in the context of drug and alcohol abuse among criminal justice populations.

Other Infectious Diseases

Active or latent tuberculosis infections are higher among correctional populations than the general population, with 20–25% of prisoners testing positive for tuberculosis compared with 0.0048% of the general population [3, 11, 12]. Multi-drug-resistant tuberculosis has become epidemic in prison institutions around the world, where high rates of HIV facilitate transmission of multi-drug-resistant tuberculosis [89]. About one-third of prisoners test positive for hepatitis C, compared with general population rates of 2% [9]. The convergence of high rates of sexually transmitted infections, hepatitis C, HIV/AIDS, and tuberculosis among prisoners is not a coincidence; these diseases act synergistically in their infection rates and disease progression, making them more challenging to treat [89] and highlighting the importance of addressing them in the context of alcohol and drug abuse among correctional populations.

Pharmacotherapies for Substance Use

A review of the literature shows a dearth of research on pharmacological treatments for substance abuse among criminal justice populations, particularly in the United States [20]. Providing effective treatment for opioid dependence decreases relapse to active substance use upon release from prison and prevents recidivism [23]. Despite this, very few correctional facilities provide methadone or other detoxification or maintenance for opioid-dependent prisoners [19, 43, 51]. A recent study demonstrated that initiating methadone maintenance therapy for prisoners with histories of opioid dependence prior to release facilitated entry into community treatment [43]. However, a primary disadvantage of methadone maintenance therapy is that the individual has to be treated at a methadone maintenance clinic after release from prison and waiting lists for such treatments in the community are long [51], providing the opportunity for a recently released offender to "fall between the cracks" and miss the opportunity for immediate entry into methadone maintenance therapy upon release from prison.

An alternative treatment, oral naltrexone, an opiate antagonist, has been available for 20 years but has not been widely used, primarily due to problems with medication compliance. One review noted that fewer than 20% of recipients continued to take oral naltrexone 4 months after treatment was initiated [57]. Depot naltrexone has recently received Food and Drug Administration approval for use in treating alcohol dependence, but does not have an indication for treating opioid dependence and is unlikely to be adopted by criminal justice authorities until Food and Drug Administration approval is obtained. However, studies are under way to investigate the use of depot naltrexone with individuals in community corrections, which may provide another option for pharmacotherapy for individuals under criminal justice supervision in the community.

Buprenorphine, a thebaine derivative, is a mu opioid partial agonist with a pharmacological profile that makes it attractive as a pharmacotherapy for the treatment of opioid dependence. Buprenorphine, like other full mu agonists, produces opioid-associated subjective and physiological effects, but its maximal effects are less than those of a full agonist such as morphine [6]. This property contributes to its utility in the treatment of opioid dependence in that buprenorphine is effective in preventing the onset of the opioid abstinence syndrome in opioid-dependent individuals. With escalating doses, buprenorphine produces less effect than full mu agonists and exhibits a "ceiling" effect at which further dose increases produce no additional effects [88]. In addition, buprenorphine has high affinity for the mu receptor, a property that produces blockade of the effects of full mu agonists, should these be administered during buprenorphine maintenance.

The safety of buprenorphine in non-tolerant individuals (such as those exiting a controlled environment) was demonstrated by Walsh and colleagues [88], where a plateau on subjective and respiratory dose-effects resulted in sublingual doses up to 32 mg (2–4 times the recommended treatment dose) being well tolerated. Thus, the ceiling effect associated with buprenorphine administration provides a wide margin of safety. Buprenorphine has fewer restrictions on its use for treatment of opioid addiction and provides an attractive alternative to methadone. In comparison with methadone and oral naltrexone, buprenorphine treatment demonstrated lower overall mortality related to its use [29]. Thus, buprenorphine appears to have advantages over other opioid therapies, including better acceptance and compliance, a favorable safety profile, and the ability to deliver the medication by prescription in a general clinic practice after release from prison. A recent review concluded that the efficacy of buprenorphine has been firmly established for treatment of opioid dependence [48]. A cost-effectiveness study embedded in a randomized controlled trial of buprenorphine versus methadone concluded that buprenorphine is no more expensive than methadone maintenance therapy [24]. Buprenorphine has not been widely investigated with a corrections population, and adoption of this medication by criminal justice administrators has been non-existent, despite the well-demonstrated efficacy of buprenorphine in non-criminal justice populations.

Community Corrections

The community corrections population has quadrupled over the past 25 years (1.12 million in 1980 to 6 million in 2006) [70, 79] and comprises the largest segment of the criminal justice population. The increase in criminal justice sanctions has been attributed to a change in United States policy in the 1980s to "get tough on crime" and led to the "war on drugs" that continues today, with drug-related arrests skyrocketing over the past 35 years (322,300 drug arrests in 1970 to 1.65 mil in 2005) [79]; driving under the influence continues to be the largest arrest category in the United States, with over 1.8 million arrests a year [79].

Probation and Parole

At the end of 2006, there were over 6 million offenders on probation or parole in the

United States (about 5,237,000 on probation and 798,200 on parole). Over half of these offenders have orders for substance abuse treatment services in the community, and providing care to these offenders is a challenge given the dearth of treatment services available in the community. For example, a recent survey of correctional agencies in the United States found that less than 10% of the offender population can participate in treatment services on a daily basis, due to the size of the population, and the lack of availability of treatment services for offenders [67]. The majority of treatment services available to offenders are drug and alcohol education (53.1%), group counseling for less than 4 h a week (47.1%), substance abuse counseling 5 or more hours a week (21.2%), and therapeutic community or residential services (3.7%) (see Table 1). Even more revealing is that the most commonly offered services do not incorporate evidence based treatment strategies such as cognitive behavioral therapy, motivational interviewing, and therapeutic communities [67].

Over the last three decades, different strategies have been used to address the large percentage of offenders that are in need of treatment services. Most community correctional agencies use referrals to existing programs and services in the community to provide treatment for offenders. The referral process, generally referred to as the brokerage model, relies upon the probation/parole officer giving a referral to the offender for a public health clinic(s) or a specific program. The success of the model relies on the offender obtaining services. Other variations to bridge the correctional and drug treatment systems have evolved over the past two decades to provide more direct access to treatment services by offenders. These variations include the Treatment Alternatives to Street Crime (now called Treatment Accountability for Safer Communities), drug treatment courts, "break the cycle" or seamless systems of care, or on-site treatment services [1, 65, 71, 91]. Studies vary considerably on these different mechanisms but generally research demonstrates that more offenders have access to treatment services and increased participation in treatment services when these options are available [66, 71].

Another model is to train the probation/parole officer in a new role which involves engaging

Table 1 Substance abuse treatment services in community supervision agencies

			Specialized facilities		Generic prisons	
Type of service	% with service	Estimated # of offenders	% of ADP (median)	% of programs >90 days	% of ADP (median)	% of programs >90 days
Drug/alcohol education	53.1	190,906	7.7	78	8.6	56.9
Substance abuse group counseling: up to 4 h/week	47.1	141,263	4.8	90.9	3.3	62.8
Substance abuse group counseling: 5–25 h/week	21.2	37,090	1	87.9	2.7	92.9
Substance abuse group counseling: 26+ h/week	1.5	2,449	<1	71.8	1.1	24.2
Therapeutic community—segregated	3.7	17,579	27	24.3	2.6	77.2
Therapeutic community—non-segregated	3.4	9,815	100	0	6.6	86.8
Relapse prevention groups	34.3	43,740	<1	91.5	1.3	57.4
Case management	7.1	93,088	1.9	100	18	88.4

Note: % with service refers to the percentage of facilities that indicated that they offer the service
Estimated # of offenders is a national estimate of the sum of the number of offenders in the service on an average day
% of ADP refers to the percentage of the facilities' population that is involved in the service on an average day
Reprinted from Taxman et al. [69]

the offender in the change process [71] by utilizing clinical skills such as motivational interviewing and addressing the offender's ambivalence towards involvement in treatment services. Studies of this approach have demonstrated that the altered role of the probation officer reduces technical violations compared with traditional intensive supervision programs where the parole officer's focus is solely on monitoring the offender after release [28, 71].

Drug Court

The drug court, a post-adjudication sentencing program, was first established in 1989 and designed to reduce criminal involvement among drug-addicted offenders. By 2007 there were over 890 drug courts operating in the United States [82]. The theory that led to the formation of drug courts is that many drug-addicted offenders engage in criminal behavior as a means to acquire drugs; therefore, to reduce crime among drug-addicted offenders, the addiction must be treated [32]. The basic components of most drug courts include assessment of substance abuse disorder, assimilation of substance abuse treatment and criminal justice supervision through case management and weekly status hearings with judicial oversight, a continuum of care in which offenders have access to multiple services, frequent drug and alcohol screening, and continuous interactions between the offender and the criminal justice system (e.g., judges, case managers, etc.) [91]. Drug treatment courts have revolutionized treatment for the criminal justice offender in that they provide a mechanism to ensure that monitoring, supervision, and treatment are intertwined. However, only about 3% of substance-abusing offenders have access to drug treatment courts [67].

A number of studies have been conducted to determine the effectiveness of drug courts; findings are generally positive but mixed. Several studies have shown that participants in drug courts show diminished drug use and criminal activity and higher treatment retention rates compared with offenders in traditional treatment settings [32, 33, 67, 91]. Belenko [5] reviewed evaluations of 37 drug courts nationwide and found that 47% of participants graduated successfully and that drug use and recidivism were low while clients were enrolled in drug court. However, most studies did not include long term follow-up data, making post-program outcomes unclear [5]. An empirical study of drug treatment courts found that treatment participation (29–88%) and program graduation rates (29–50%) varied considerably [64].

A recent meta-analysis by Wilson, Mitchell, and Mackenzie revealed that while individuals graduating from drug court have significantly lower arrest rates than non-participants, most drug court participants did not attend the minimum number of required treatment sessions and more than half were not given the minimum number of drug tests [91]. Taxman and colleagues report treatment participation varied from 35% to 80% across drug courts [64]. In addition, none of the programs reviewed by Wilson and colleagues was based on a formal theory of the causes of addiction and most were using a "mixed bag" of therapeutic approaches without focusing on any one treatment method [66, 81]. For example, some programs used 12-step approaches, which require addicts to turn over their addiction to a higher power in conjunction with cognitive-behavioral therapy, which focuses on thoughts and feelings and emphasizes learning new skills to change addictive behaviors. Unfortunately, these two therapeutic approaches are incompatible in their views on the origins of addiction. In addition, while cognitive-behavioral therapy is widely considered one of the best approaches for treating substance abuse, it was used in only about 22% of therapy sessions [64].

There also appears to be a dearth in family involvement and minority or culture-specific treatment in drug courts, all of which are important treatment components [81]. Many researchers have suggested that the lack of evidence- and theory-based practices in substance abuse treatment contributes significantly to rates of relapse and recidivism among

offenders receiving treatment through drug courts [81]. Overall, it appears that the longer an offender is in treatment, the greater their chances are of succeeding in a drug court program—a finding consistent with research on all substance abuse treatment programs [59, 67].

Treatment Accountability for Safer Communities

Treatment Accountability for Safer Communities was developed in 1972 as a strategy to provide case management to bridge the gap between the criminal justice system and community substance abuse treatment. Treatment Accountability for Safer Communities models operate under the assumptions that drug addiction is prevalent among offenders, that there is a cycle of crime, incarceration, release, and relapse among drug-dependent individuals, and that this cycle provides frequent opportunities for treatment interventions [41]. Most Treatment Accountability for Safer Communities programs provide screening for program eligibility, assessment of treatment needs, referrals for treatment outside of Treatment Accountability for Safer Communities, and client-centered case management. Many programs emphasize a continuum of care and provide regular drug screens and correspondence with the criminal justice system regarding the client's progress. Treatment Accountability for Safer Communities currently operates in almost 40 states and about 100 organizations use the Treatment Accountability for Safer Communities model.

Anglin and colleagues assessed Treatment Accountability for Safer Communities programs at five sites in the United States across three domains: service delivery, drug use, and recidivism. Compared with individuals receiving the standard strategy of referral to community treatment services, offenders participating in Treatment Accountability for Safer Communities had access to significantly more services at four of the five sites (drug counseling, urinalysis, and/or AIDS/HIV education). At three of the five sites, drug use decreased for Treatment Accountability for Safer Communities participants. However, there were no significant differences in recidivism (as assessed by re-arrest rates) among control and Treatment Accountability for Safer Communities groups. In fact, at two of the sites there were indications that Treatment Accountability for Safer Communities participants were more likely to be re-arrested than control group participants. More positive findings occurred in sites where the Treatment Accountability for Safer Communities services included group counseling and offenders did not have to go to another agency to acquire the needed treatment clinical services. Similar findings for intensive supervision programs (i.e., the probation officer monitors the offender through more frequent contact) suggest that increased monitoring leads to easier detection of criminal behavior among participants. Thus, the increase in arrests among Treatment Accountability for Safer Communities participants can be seen as a success from a viewpoint of community safety, even though it increases technical violations and re-incarcerations [1]. Other researchers have postulated that the case management approach taken by Treatment Accountability for Safer Communities programs does not decrease recidivism because it does not lead to increased participation in substance abuse treatment, treatment is usually of a short duration, and there are often no provisions in place for non-compliance (e.g., positive drug tests or missed treatment sessions) [68].

A more recent study revealed that jurisdictions with Treatment Accountability for Safer Communities had increased use of motivational interviewing, continuum of care policies, and services for offenders with co-occurring disorders [93]. Additionally, the survey found that Treatment Accountability for Safer Communities administrators were stronger supporters of training initiatives likely to enhance cooperation among criminal justice organizations. A general survey of treatment services offered in correctional settings found that innovations tended to be

clustered. Treatment Accountability for Safer Communities organizations are more likely to offer this clustering of innovative practices than program and parole agencies [37]. This finding allows a better understanding of implementation issues based on how organizations such as Treatment Accountability for Safer Communities, jails, and community correctional agencies affect the treatment delivery system. Overall, the survey findings suggest that communities that have Treatment Accountability for Safer Communities or Treatment Accountability for Safer Communities-like organizations have made greater gains in improving service delivery for offenders in measurable ways, but that there is also considerable room for improvement in access to services and treatment and supervision outcomes.

Institutional Corrections

The availability of substance abuse treatment in correctional environments has decreased in the past two decades. In 1991, one-third of inmates who reported using drugs in the month prior to arrest received substance abuse treatment; in 1997, only 15% received treatment [54]. A recent survey of drug treatment services in the correctional setting found that less than 10% of the eligible inmate population receive drug treatment services in prison and that offenders in specialized treatment programs such as segregated therapeutic communities are more likely to be offered treatment services that are consistent with evidence-based practices [67]. Substance abuse treatment programs for inmates during and after incarceration are effective in reducing drug use and subsequent recidivism [4, 31, 60]. About one-quarter of inmates who participated in therapeutic community substance abuse treatment in prison and after release returned to prison compared with 75% of prisoners who did not receive treatment or who received treatment in prison but no treatment after release [50, 60]. The Washington State Institute for Public Policy noted that drug treatment in prison yields a benefit of $1.91 and $2.69 for every dollar invested in treatment. Drug treatment outside prison yielded a benefit of $8.87 for every dollar spent on treatment [83]. Thus, substance abuse treatment programs in and out of prison are successful in reducing substance abuse and recidivism and are cost effective [36].

Prisons and Jails

Despite the potential benefits associated with delivery of drug treatment in correctional facilities, drug treatment is increasingly unavailable for drug-dependent offenders during incarceration and the services provided are often not of sufficient duration or intensity and do not incorporate evidence-based practices. The National Criminal Justice Treatment Practices survey provided data on the availability of different types and intensities of drug treatment services offered in prisons and jails in the United States (see Tables 2 and 3) [69]. Substance abuse education and awareness is offered in 74% of prisons and 61% of jails and, as such, is the most prevalent form of drug treatment service provided. Group substance abuse counseling ($\leq$4 h/week) is available in 55% of prisons and 60% of jails; group counseling 5–25 h/week is available in 46% of prisons and 23% of jails; and group counseling $\geq$26 h/week is available in 11% of prisons and 1% of jails. Counseling programs within prisons and jails incorporate various combinations of 12-step work, cognitive-behavioral skills training, life skills training, and drug education [53], although less than 20% of sessions use cognitive or cognitive behavioral therapies [69]. Segregated therapeutic communities are available in 20% of prisons and 26% of jails; 45% of prisons and 51% of jails provide access to relapse prevention groups [69].

Although therapeutic communities are available in only a minority of prisons and jails in the United States, the aim of therapeutic communities goes beyond abstinence from drugs to complete lifestyle change for individuals involved in the therapeutic community, including

Table 2 Prevalence of substance abuse services in prisons

Type of service	% with service	Estimated # of offenders	Specialized facilities		Generic prisons	
			% of ADP (median)	% of programs >90 days	% of ADP (median)	% of programs >90 days
Drug/alcohol education	74.1	75,543	8.8	92.1	9	65.3
Substance abuse group counseling: up to 4 h/week	54.6	34,509	76.9	73.9	10	58
Substance abuse group counseling: 5–25 h/week	46	52,293	8.8	92.9	8	72.9
Substance abuse group counseling: 26+ h/week	11.2	12,182	11.3	78.9	18.6	24.3
Therapeutic community—segregated	19.5	34,776	8.8	84.3	15.5	74.8
Therapeutic community—non-segregated	9.2	10,710	5.7	91.6	14.4	66
Relapse prevention groups	44.5	39,493	13	74.3	3.8	62
Case management	6.9	10,761	100	91.1	9.1	40.7

Note: % with service refers to the percentage of facilities that indicated that they offer the service
Estimated # of offenders is a national estimate of the sum of the number of offenders in the service on an average day
% of ADP refers to the percentage of the facilities' population that is involved in the service on an average day
Reprinted from Taxman et al. [69]

Table 3 Substance abuse services in jails

Type of service	% with service	Estimated # of offenders in service	% of ADP (median) for general facilities	% of programs >90 days for general facilities
Drug/alcohol education	61.3	47,237	4.5	19.9
Substance abuse group counseling: up to 4 h/week	59.8	39,943	7.4	48.1
Substance abuse group counseling: 5–25 h/week	23.1	16,471	10.8	8.9
Substance abuse group Counseling: 26+ h/week	1.1	1,185	3.4	92.3
Therapeutic community—segregated	26.2	11,889	3	97.9
Therapeutic community—non-segregated	<1	282	4.3	75.4
Relapse prevention groups	50.7	20,173	3	93.6
Case management or treatment accountability for safer communities	22.8	15,235	7.7	89.8

Note: % with service refers to the percentage of facilities that indicated that they offer the service
Estimated # of offenders in service is a national estimate of the sum of the number of offenders in the service on an average day
% of ADP refers to the percentage of the facilities' population that is involved in the service on an average day
Reprinted from Taxman et al. [69]

development of prosocial attitudes and values and elimination of antisocial behaviors and attitudes. Therapeutic community members live with one another, ideally segregated from the general correctional population, and take responsibility for recovery through individual and group counseling, peer pressure, confrontation, and incentives and sanctions [53, 90].

Despite the apparent availability of drug treatment services in prisons and jails, less than 10% of prison and jail inmates have daily access to drug treatment services [69]. One way of assessing the quality and appropriateness of services offered is to examine the proportion of prisons and jails that use evidence-based practices in their drug treatment programs. Fewer than 60% of available evidence-based practices were used in treatment programs for drug-involved adult offenders, suggesting that services available for drug-involved offenders in prisons and jails may be far from optimal [28]. Interestingly, clusters of evidence-based practices tend to occur together, suggesting that some facilities may have overcome resource and philosophical barriers to the adoption of evidence-based practices—once one evidence-based practice is adopted, others may be adopted in the same setting with less difficulty [37].

The effectiveness of drug treatment programs offered in prisons and jails can be evaluated in terms of reductions in post-release drug use and in post-release reoffending. A meta-analysis of 66 published and unpublished evaluations of incarceration-based drug treatment programs [53] provided support for the effectiveness of therapeutic communities in reducing post-release drug use and reoffending. In contrast, other incarceration-based residential substance abuse treatment programs and group counseling programs reduced re-offending but were less effective in reducing drug use after release.

Conclusion

Research reviewed for this chapter documents the relationship between drug and alcohol abuse and dependence and criminal justice involvement, the relationship between drug and alcohol relapse and re-arrest and recidivism, the need for greater availability of drug and alcohol treatment within the criminal justice system, the need for strengthening treatment services by the inclusion of evidence-based practices and alternative forms of service delivery (such as drug courts and Treatment Accountability for Safer Communities or Treatment Accountability for Safer Communities-like programs), the need for a coordinated system of care that bridges the gap between incarceration and return to the community, the need to introduce pharmacotherapy for addictions into drug treatment for criminal justice populations, and the urgent need for research into effective models of service delivery.

On one hand, it is possible to look with horror at the system of drug treatment available for individuals under criminal justice supervision in the United States – as rates of incarceration and recidivism increase and comorbid conditions such as psychiatric disorders and infectious diseases become more prevalent, resources available to provide drug treatment become increasingly scarce. On the other hand, the association between criminal behavior and drug and alcohol abuse suggests a way out of the repeating cycle of drug abuse, criminal activity, incarceration, release, relapse, and re-arrest. Drug treatment reduces drug use and relapse and may reduce re-offense and re-arrest. Research is urgently needed to improve both access to and quality of drug treatment services for individuals under criminal justice supervision.

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Adolescent Neurocognitive Development and School-Based Drug Abuse Prevention and Treatment

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Contents

Introduction

Schools are an efficient and convenient choice of setting for intervention programs targeting adolescents. Schools provide access to a large number of adolescents in a learning environment in which adolescents are more likely to be receptive toward instructions involved in an intervention. Moreover, monitoring fidelity of program implementation and assessing program effectiveness in a school setting are relatively easy [67]. In addition, the typical 4-year structure of school systems is conducive to tracking down students in order to obtain long-term follow-up data.

Prevention programming attempts to reach adolescents prior to the expected occurrence of certain problematic behavior, such as drug abuse. The central focus of prevention is on the antecedents of problem behavior. Program participants are taught how to anticipate the impacts of these antecedents (e.g., such as desiring to feel good, cognitive exposure to drug-related cues, social influence, or cultural norms) and to counteract their potential impacts with instruction of protective cognitions, behaviors, or access to protective social units (e.g., drug-free communities). Among these strategies are "selective" or "indicated" approaches that attempt to prevent individuals who are either currently at-risk for drug use behavior, by virtue of their membership in certain segments of the population, or who are already demonstrating early signs of drug use behavior, from developing clinically diagnosed drug use disorders [45]. Some researchers tend to refer both indicated and selective programs as "targeted" programs [70].

Cessation (treatment) programs are designed to assist in stopping drug use, given that youth were either not exposed or did not respond to prevention efforts. Cessation programs provide participants with strategies to cope with psychological dependence (emotional reliance) on and physiological withdrawal from a drug

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_44,

(e.g., what types of withdrawal symptoms to expect, how long one will experience these symptoms, and how to cope with these symptoms without relapsing). Cessation programs focus on stopping a current behavior from continuing to arrest ongoing consequences and permit recovery of health. The goal may also involve teaching one how to live with permanent changes (e.g., drug-related injury).

In the school setting, prevention efforts are generally delivered school-wide (i.e., universal prevention), whereas cessation programs are usually delivered outside of the classroom (e.g., with student assistance programs, in clinics, or perhaps involving the school nurse, possibly involving self-help support groups which meet during lunchtime or after school). Exposure to early prevention programming could potentially provide proactive interference against later drug-facilitative-type information, resulting in protection against drug misuse. These prevention efforts may inhibit, delay, or halt addiction, which is what makes cessation so difficult. For older adolescents who are caught up in cycles of drug misuse or abuse, prevention programming could help minimize the time spent in a using cycle.

A recent focus of adolescent school-based drug abuse prevention and cessation programming involves applying models of neurobiology/neuropsychology as potential influences on program outcomes. This chapter will provide a brief overview on the application of neuroscience to adolescent development, indicate current school-based prevention and cessation strategies that may impact neuroscience-relevant adolescent functioning, and suggest new directions for the development and implementation of drug use prevention and cessation programs.

Brief Overview: Neuroscience and Adolescents

Adolescent vulnerability to substance use has been associated with the protracted morphological development of the neural systems responsible for self-control and regulation, in conjunction with a heightened tendency to seek novel experiences (e.g., [7, 66]). The regions of the human brain linked to self-control and self-regulation are not fully developed until late adolescence. However, an increase in novelty-seeking behavior is evident when children transition into early adolescence. Thus, increases in risk-taking and sensation-seeking tendencies among adolescents seem to precede the development of self-regulatory competencies [66].

Several animal as well as human studies suggest that novelty-seeking behavior increases rapidly during adolescence [7], which has been attributed to the changes that occur in the pro-motivational dopamine systems during this stage in ontological development [7]. The level of dopamine turnover among adolescents is likely to be higher than among children and adults [7, 64]. Dopamine in the ventral striatum, which includes the nucleus accumbens, is believed to modulate the conversion of thoughts and emotions into motivated actions [30]. Dopamine release in the nucleus accumbens appears to filter and gate the motivational signals received from the cortical and limbic systems that are to be processed by the downstream motor systems [7, 30].

Several motivational stimuli have been associated with dopamine stimulation in the nucleus accumbens, including the drugs of misuse and agents of natural reward (e.g., food, sex). Further, novel experiences tend to cause higher levels of dopamine stimulation compared with previously learned behaviors that have expected outcomes [7]. Hence, the same mesolimbic dopamine systems appear to mediate both drug- and novelty-seeking behaviors [1]. Conversely, concentrations of inhibitory motivation neurotransmitters such as serotonin appear to be lower in adolescent cerebrospinal fluid, which has been associated with higher impulsivity [7]. A greater tendency to "act" along with decreased inhibitory tendencies for self-destructive action could contribute to drug use experimentation.

Adolescents' vulnerability to drug use due to developmental changes in the dopaminergic

system is further exacerbated by the relatively underdeveloped prefrontal cortex. Brain structure and function undergo significant changes throughout adolescence, notably in the forebrain regions which comprise the prefrontal cortex. The prefrontal cortex is one of the last cortical structures to reach full ontogenetic development and may not achieve complete maturation until the third decade of a person's life [15]. This region of the brain is responsible for the spatiotemporal organization of goal-directed actions, which involve the carrying out of relevant actions in response to internal (e.g., memory) or external (e.g., environmental context) cues [15, 29]. In other words, the principal function of the prefrontal cortex is to perform executive function. Executive function represents a complex set of interrelated functions that make the temporal organization of goal-directed behavior, language, and reasoning possible [15]. Methodologically, brain researchers find it difficult to separate the interrelated components of the executive system into discrete units (e.g., attention, working memory, decision-making) and localize them to specific areas of the prefrontal cortex [15]. For example, the functional contribution of a specific prefrontal cortex area is difficult to measure after a discrete lesion, for such a lesion is likely to functionally affect the entire executive system [15]. Nonetheless, researchers have linked deficiencies in executive function to abnormalities related to attention, working memory, long-term memory retrieval, planning, temporal integration of memory and goal, decision-making, monitoring, and inhibitory control [15].

Ability to exert sustained attention or manipulate the focus of one's attention is necessary to formulate a goal-directed thought or bring an action to completion. In turn, one needs to control distracting or interfering urges, both internal (e.g., thoughts, memory, instinctual) and external (e.g., environmental), in order to maintain sustained attention [15]. Working memory refers to the ability to retain information and utilize the information to execute a related action. Like most executive functions, working memory and sustained attention are interrelated and are essential for task perseverance. Further, execution of actions involves foresight and planning. Planning represents the ability to utilize information obtained from selective retrieval of long-term memory, such as memory of past actions, for the anticipation of future events. Planning provides a conceptual scheme for the execution of a goal-directed behavior, and based on the anticipation of consequences, lays out the order of prospective actions. Individuals often have to choose among competing actions. The executive function of decision-making involves choosing an action after rationally evaluating the potential risks and rewards associated with its outcomes. Successful execution of goal-directed behaviors also depends largely on the ability to self-monitor. Monitoring enables one to assess the discrepancies between one's actions and one's goals, thus creating feedback which allows one to correct subsequent actions.

Inhibitory control involves controlling an impulse by inhibiting a response. According to Barkley [2], response inhibition involves three processes: (1) inhibition of the prepotent response (i.e., a response linked in associational memory to immediate reinforcement), (2) stopping of an ongoing response in order to delay the final decision to respond, and (3) protecting this decision-making time interval from being interfered with by other competing stimuli and responses (i.e., interference control). Primary response inhibition partially aids the functioning of working memory, regulation of motivation, verbal internalization, and behavioral analyses.

Hence, executive functions make the self-regulation of thoughts, emotion, and behavior possible. Conversely, deficiencies in executive function may result in poor impulse control, poor judgment, and disinhibited behavior [2]. Among adolescents, poor executive functioning has been consistently associated with higher rates of drug use (e.g., [22, 38, 73, 84]. Further, early adolescent deficiencies in executive function have been found to predict later drug use disorders [17, 71]. For example, Habeych et al. [24] found that attenuated amplitude of the P300 wave, an indicator of executive cognitive function, in late childhood predicted substance use disorders in late adolescent males.

Research suggests that executive function develops in sophistication at the same rate as the structural maturation of the prefrontal cortex; and age-related social and cognitive maturation during adolescence may be attributed to the concomitant structural changes in the brain [15, 66]. For example, improvements in planning and decision-making have been linked with the structural developments in the dorsolateral and ventrolateral prefrontal cortex, respectively [66]. Most notable developmental changes in the forebrain region have been observed as changes in grey and white matter volumes. Recent neuroimaging studies suggest that there occurs a continuous increase in the brain white matter volume during adolescence [19, 49]. For example, a significant growth is noticed in the posterior corpus callosum, the collection of over 200 million nerve-fibers that allow communication between right and left hemispheres of the brain [19, 49]. In addition, the grey matter volume, which increases substantially during childhood, appears to decrease during adolescence in certain cortical structures (e.g., the prefrontal cortex [18]).

Reduction in cortical gray matter volume might occur due to increased intra-cortical myelination and/or due to synaptic pruning [49]. Increased myelination of neurons results in a more efficient propagation of action potentials. Synaptic pruning involves selective removal of synapses that "do not efficiently transmit information pertaining to accumulating experience" [7]. Synaptic pruning appears to serve a number of functions that facilitate cognitive development. For example, the process appears to stabilize the firing patterns of cortical neurons, which in turn is thought to enhance working memory performance [7]. In general, both myelination and synaptic pruning are believed to enhance the efficiency of cortical information processing as well as the connectivity between cortical and subcortical regions [7, 49, 64, 66].

Thus, since adolescent prefrontal cortex is not yet fully developed, the associated executive functions are expected to be inadequately developed. As a result, adolescents tend to have lower regulatory competence, which makes them highly susceptible to drug use risk factors such as rash impulsiveness and poor decision-making [72]. For example, adolescents tend to be poor judges of the harmful consequences of drug use, yield easily to peer pressure, and seek immediate gratification [72]. Therefore, it is not surprising that most adult drug users are likely to have initiated drug use in the period between early to mid-adolescence, before the brain regions associated with self-regulation are optimally developed [72].

In summary, evidence suggests that the developmental upsurge in novelty seeking coupled with suboptimal brain development makes adolescents vulnerable to drug use. Thus, to some extent, adolescent experimentation with drugs appears to be a normative behavior [72]. However, it should be noted that individual differences exist among adolescents with respect to both novelty seeking and executive functioning; some adolescents are always at a higher risk for developing substance use disorders than others [1, 72].

Negative Consequences of Drug Use on Teen Cognitive Function

Early onset of drug use, escalation of use, and possible dependence might subject adolescents to the risks of developing mental health disorders and experiencing social, academic, and legal consequences. The developing adolescent brain appears to be highly vulnerable to the neurotoxic effects of drugs, including those of licit drugs such as tobacco and alcohol and the so-called "soft" drugs such as marijuana. Prolonged exposure to drugs during adolescence may result in neuropsychological deficiencies and structural brain damage, especially in areas associated with memory and executive functions [32, 33]. Brown et al. [6] have reported that compared with a matched group of healthy youth, alcohol-dependent young adolescents (in the third week of abstinence) were found to perform poorly on verbal and visuospatial tasks, suggesting that

protracted exposure to alcohol might have enduring adverse effects on the brain's functional ability involving memory and information processing. In fact, magnetic resonance imaging results indicate that youth with alcohol use disorders tend to show smaller hippocampal and white matter volumes [8, 10, 43] and smaller prefrontal cortices [10]. De Bellis et al. [8] further found that the total hippocampal volume among adolescents with alcohol use disorder increased with the age of onset and decreased with the duration of disorder.

Although, taken together, the relatively limited extant neuroimaging studies fail to conclude whether chronic marijuana use is related to structural abnormalities in the brain (for review, see [53]), some of the findings (e.g., [82]) suggest a relationship between age of first onset and decreased total brain volume. Further, it appears that early marijuana use initiators (e.g., before the age of 17) tend to show significant later cognitive deficits (e.g., indicated by verbal IQ; visual scanning tasks) in comparison with non-users and late-onset users [12, 51]. Nicotine-dependent adolescents have been suggested to perform normally on working memory tasks following nicotine intake but poorly while on withdrawal [25, 26]. One neuroimaging study indicated that despite poor task performance, nicotine-dependent adolescents on withdrawal exhibited increased activities in the prefrontal cortex regions (e.g., dorsolateral prefrontal cortex) associated with working memory [26]. As an optimal level of dopamine action is essential for normal working memory functioning, the adverse effects of tobacco use cessation on working memory suggests that regular nicotine use causes abnormal adaptations of the dopaminergic circuitries [26]. In fact, research on rodents has shown that the normal development of catecholaminergic systems during adolescence might be disrupted by protracted exposure to nicotine [74–76]. These studies have linked adolescent nicotine exposure with hippocampal damage and impairments in the midbrain catecholaminergic systems that play important roles in mood regulation and addiction development [74–76].

By adversely affecting the normal development of the cortical and limbic brain structures associated with risk and reward calibration, decision-making, and inhibitory control, drug use not only exacerbates the loss-of-control due to incentive-sensitization [56] but also undermines the cognitive ability to stop using drugs voluntarily [85]. Evidence suggests that drug addiction might be related to impairments in ventromedial prefrontal and anterior cingulate cortices, brain regions associated with decision-making and inhibitory control [85]. Further, acute withdrawal of drug use seems to affect the anterior cingulate cortex, consequently weakening inhibitory control [85].

However, it should be noted that most of the research linking adolescent drug use, drug use withdrawal, and neuropsychological deficiencies have been cross-sectional, which makes any conclusion on their causal relationships open for debate [85]. Nonetheless, it seems that deficient neuropsychological functioning and adolescent drug use share a reciprocal relationship. For example, neuropsychological deficiencies in preteen years tend to predict drug use disorders (e.g., [73]), and, similarly, early drug use onset or abuse seems also to predict neuropsychological deficiencies [85]. Such bidirectional relationships imply that adolescents with impaired neuropsychological functioning face the additional risk of drug use-mediated further neuropsychological deterioration [85].

Thus, there appears to be at least three important reasons why prevention or treatment targeting adolescent drug misuse should address motivation, decision-making, and inhibitory control. First, adolescents normally tend to show suboptimal development of regulatory competence [9, 66]. Second, this regulatory competence is likely to be markedly lower among drug-misusing adolescents due to possible impairments in certain brain regions such as the prefrontal cortex, anterior cingulate cortex, and hippocampus [8, 10, 85]. Poor regulatory competence may not only make it difficult for these high-risk adolescents to stop using drugs but also cause them to relapse easily in case of temporary

successful cessation [85]. Third, adolescents at high risk for using drugs or developing drug use disorders are already likely to rank low on neurobehavioral inhibition [73], which might additionally indicate that their executive functions have trait-based deficiencies [2]. Thus, drug-abusing adolescents and adolescents at risk for developing drug dependence would benefit greatly from supplemental programming that promotes adaptive coping, impulse control, problem solving, and self-monitoring.

Brain Development and School-Based Drug Use Prevention and Treatment

It has become increasingly important for prevention researchers to take into account the findings made in neuroscience to guide their approach in designing drug use prevention programs for youth. In particular, researchers are interested in knowing whether developmental neurobiological and neurocognitive variables moderate and/or mediate prevention effects [20, 54]. Currently, the research attempting to answer these questions seems to be at a preliminary stage [20]. For example, there is some evidence that adolescents' neurocognitive skills moderate their response to preventive intervention materials. In a study dealing with social competency skills training, adolescents with poor executive cognitive abilities were less likely to respond positively to the prevention curriculum [13, 14]. Hence, not all youth may be equally able to process prevention messages and instructions, and program materials may need to be individualized to address differential neurocognitive skills.

Alternatively, prevention or treatment programs may aim to enhance adolescent neurocognitive skills in order to counteract drug use behavior. Recent evidence suggests that practice in tasks requiring regulatory skills may enhance one's executive functioning and this alteration appears to correspond to practice-induced structural changes in the brain (e.g., [27, 45]). Hence, one might argue that repeated practice of skills and tasks demanding the use of executive functions (e.g., attention control, working memory) during childhood and adolescence, when cortical structures are likely to be most malleable, may assist the age-related development of executive functions, and in turn protect adolescents from engaging in risky behaviors.

Need for Tailoring Prevention and Treatment Programs

To promote program efficacy, prevention and treatment programming may need to be tailored to participants' personality characteristics. For example, outcomes may be enhanced a great deal if programs are designed to permit maximum processing of information by sensation-seeking recipients with neurocognitive processing that prefers presentations of rapidly changing stimuli [50]. As noted by Bardo et al. [1], novelty exposure tends to activate the same neural substrates that mediate the rewarding effects of drugs of abuse. The reinforcing effects of drugs play a key role in promoting continued drug use behavior, especially among those more susceptible to drug effects (e.g., sensation-seeking or novelty-seeking individuals). Initial positive or neutral physical responses to drugs may encourage subsequent use, whereas initial aversive physical reactions may discourage subsequent use behavior. One suggestion for prevention is to consider that at-risk youth (e.g., sensation-seeking youth) may process information differently than lower risk youth, and therefore prevention materials should be tailored accordingly.

Given the evidence that individuals higher in sensation seeking may have a neurobiologically based need for stimulation, it seems reasonable to assume that they need drug abuse prevention messages that are novel and exciting enough to grab their attention and pique their curiosity (e.g., see [50]). In fact, Palmgreen et al. [48] found that high-sensation-seeking value-type public service announcements may have influenced higher sensation seekers' drug

intake for several months following a media campaign. Fast-paced, novel, and stimulating media-type programs that grab or increase adolescents' attention and learning may more effectively influence sensation-seeking individuals with lower baseline dopamine turnover [48].

Staiger et al. [65] have recently stated the need for tailoring drug abuse treatment programs with respect to three specific personality-based drug use risk factors, namely reward sensitivity, behavior disinhibition (or rash impulsivity), and anxiety proneness. For example, contingency management could be used as a possible tactic for someone with high levels of reward sensitivity, as to replace drug-related reward with a prosocial alternative [65]. Similarly, treatment strategies such as meditation and mindfulness-based practices could be used to promote attention control and relaxation in order to address impulsiveness and anxiety proneness, respectively [65].

Current School-Based Prevention Practices and Executive Functions

School-based programs designed for young children often focus on improving social-emotional competence (e.g., [21, 61, 62]). Temperament characteristics such as emotionality predict adolescent problem behavior, including drug use behavior [80]. Wills and colleagues [79, 81] argue that a person's childhood temperament characteristics and socialization affect his or her ability to self-regulate during adolescence, and in turn, his or her drug use behavior [79, 81]. "Promoting Alternative Thinking Strategies" is a school-based prevention program which attempts to assist young children in social and emotional learning through the teaching and practice of executive function skills [21]. The Promoting Alternative Thinking Strategies curriculum is based on the affective-behavioral-cognitive-dynamic model of development [20, 21]. The assumption underlying the affective-behavioral-cognitive-dynamic model is that due to delayed development of the neurocircuitry connecting cortical and limbic structures children's cognitive and linguistic development tends to be inadequate when required to regulate complex emotional experiences. Thus, children appear to have difficulty verbally internalizing emotional experience and managing related behavioral response. The Promoting Alternative Thinking Strategies curriculum uses the concepts of vertical control and horizontal communication to assist children's age-related neurocognitive development. Vertical control refers to the exertion of control by higher-order cognitive processes on the lower-order limbic impulses, and horizontal communication refers to mediated communication between the two hemispheres of the brain, a process integral to the internal verbalization of affect [20, 55].

Results demonstrate that Promoting Alternative Thinking Strategies can improve vertical control and horizontal communication. Vertical control is addressed though the combined use of curriculum lessons and the Control Signals Poster which teach strategies for self-control such as "self-talk" that facilitate inhibitory control and planning [20]. The control signals poster uses a traffic-signal to guide goal-directed behaviors (e.g., red light signaling to stop and calm down, yellow light to slow down and think, and green light to try out the plan [55]). Horizontal communication is addressed through the identification and labeling of emotions and feelings through the combined use of curricular lessons and Feeling Face cards, which include color-coded facial images of affective states [55].

A Promoting Alternative Thinking Strategies trial involving 7–9 year olds recently found that the curriculum was effective in reducing externalizing and internalizing behaviors at 1-year follow-up, that Promoting Alternative Thinking Strategies had significant positive effects on verbal fluency and inhibitory control nine month posttest, that both inhibitory control and verbal fluency partially mediated internalizing behaviors, and that inhibitory control partially mediated the program effects on externalizing behaviors [55].

Another example of a program for young children that focuses on social and emotional learning is the "I Can Problem Solve" program [61, 62]. This program has been implemented on preschooler through 6th graders and provides children with language and critical thinking skills that help them successfully resolve interpersonal problems with peers and adults through effective decision-making. The program is recommended to be implemented as a daily 20-min classroom session for 15 months. All sessions are designed to foster interpersonal cognitive problem solving through dialogues, games, and group discussions that involve the use of words, pictures, puppets, and role playing. For example, students are taught to identify words that are precursors to understanding behavioral consequences and problem solving, and teacher-initiated interpersonal cognitive problem-solving dialogue is used to solve actual interpersonal problems among children. The program has been successful in reducing impulsivity and social inhibition (e.g., fear and timidity of others), which are related to the development of drug use and mental health disorders [62].

Although it is common for prevention programs to include cognitive-behavioral skills training as a major component (e.g., "life skills training") [4, 5], executive function variables are not often directly measured as mediators of program effects [55]. However, in essence, such studies attempt to enhance the rate and quality of age-related cortical development. Several developmentally tailored life skills training trials have been successfully implemented in elementary, middle, and high schools to develop social and personal skills among youth [58]. The skills-building component of the program focuses on developing regulatory competence among youth necessary to counteract the social influences of drug use through training on, for example, coping and anxiety management (e.g., vertical control), and effective communication and assertiveness (e.g., horizontal communication) [58].

Recently, mindfulness-based interventions have emerged as having promising implications for executive function enhancement. Mindfulness refers to attaining a mental state in which attention is sustainably focused on the non-judgmental awareness of thoughts and sensations passing through one at the given moment. Interestingly, mindfulness-based programs are also starting to be practiced children and adolescent populations. An investigation carried out by the Garrison Institute [16] on the mindfulness practices of kindergarten to 12th grade students found that nearly 20 school and community-based organizations have established mindfulness programs, and several more use elements of mindfulness as part of other social and educational programs.

Mindfulness-based interventions typically use a simple sitting technique that teaches participants to focus on the breath, image, or mantra for as little as 10 min per session. In a sample of 194 1st–3rd graders, Napoli et al. [44] found that a mindfulness intervention increased selective attention as measured by a visual task. Moreover, several studies have replicated evidence that mindfulness can decrease externalizing and problem behaviors in adolescents [3, 31, 60].

Studies are just beginning to examine the effects of mindfulness on neurocognitive variables. A randomized control trial of school-based "mindful awareness practices" involving 44 4–5 year olds found that children in the treatment condition showed significant increases in executive functioning as indicated by improved working memory and planning skills [59]. The treatment program consisted of implementing a 30-min session, twice a week, over 8 weeks. Interestingly, further analyses of the program effects suggested that mindful awareness practices may have stronger effects on children with executive function difficulties.

Clearly, further studies are required to better understand the potential protective effects of mindfulness-based interventions on adolescent drug use. However, preliminary evidence seem promising, to the extent that some of the known outcomes of mindfulness-based interventions such as increased self-awareness, emotional intelligence, and lowered externalizing

problems are known to be protective against adolescent drug use behavior [3, 16, 31, 44, 60].

It appears that prevention programming would benefit additionally from the inclusion of a motivation component. Sussman et al. [70] evaluated 29 evidence-based, targeted drug abuse prevention programs for their effects on drug use or other problem behavior among high-risk youth. Eighteen of these programs involved school as a setting in some way. Of the 18, 12 involved some motivation aspect, generally motivation enhancement, but sometimes they included extrinsic reinforcement strategies (i.e., reinforcement by manipulating environmental consequences of behavior such as by being paid contingent on performance). Sixteen of the 18 programs provided skills training, and 11 programs provided instruction in decision-making.

Taken together, these programs appear to define a type of programming referred to as the Motivation-Skills-Decision-making Model [70]. According to this model, targeted programming needs to: (1) motivate the at-risk recipients, who might have higher reward sensitivity [65] to not desire to misuse drugs, (2) teach skills to enhance regulatory competence (e.g., self-control strategies [37]) and form prosocial bonds; and (3) facilitate decision-making and goal-directed behaviors. The Motivation-Skills-Decision-making Model tends to appear in a majority of the 18 programs; however, all three components were included together in only 5 of the programs.

The Reconnecting Youth program was one of the five programs and was implemented to youth at risk for school dropout [11]. The program involved 90 sessions within a comprehensive high school class, delivered generally over one semester, with small student groups and highly trained teachers. Instruction included use of group support and providing life skills training (norm setting, self-esteem enhancement, mood management, communication skills, self-monitoring, monitoring goals, school bonding and social activities), with feedback to parents. Program goals were achieved through use of a quasi-experimental design, showing effects for school performance (18% improvement in grades), drug use (54% decrease in hard drug use), and suicide risk (32% decline in perceived stress). This program involved all three components of the Motivation-Skills-Decision-making Model, except that motivation was provided through peer group support, not through provision in motivational enhancement strategies. In essence, these targeted programs for high-risk populations could be interpreted as modifying phenotypical expressions of suboptimal neurobiological development. However, future integrative research will be needed to examine the reality of this speculation.

Schools as a Modality for Implementation of Cessation Programming

School-based interventions have been recognized as one of the most effective community-based means of delivering drug use treatment services to adolescents [77]. Empirical evidence indicates that most school-based drug use treatment programs tend to yield treatment outcomes that are, in terms of success, similar to outcomes of programs targeting adults [77]. Treatment services in schools can be delivered either through school clinics (i.e., clinics located within schools), classroom-level interventions, or a combination of both [68, 77].

Traditionally, treatment services have been delivered to youth drug users by trained health professions in clinics located outside schools, such as in hospitals and universities [77]. In regard to adolescents, school-based treatment delivery options seem to have clear advantages over the traditional modes of service delivery, in terms of both identifying the need for treatment and access to treatment [77]. Adolescents are not only less likely to recognize their own drug use problems but also less likely to make an effort to seek treatment services voluntarily [77]. Hence, unless concerned adults guide them to treatment facilities, which is less likely to happen if the problems have not yet become serious,

most adolescents requiring treatment might not receive any treatment at all. Moreover, visiting clinics situated in institutions other than schools might exact potentially deterring efforts from adults and adolescents alike, such as spending money and one's free time, and making appointments [77]. Ethnic minorities and individuals of lower socioeconomic status in particular might fail to take advantage of treatment opportunities offered outside schools [77].

In a review of 66 adolescent tobacco use cessation programs, Sussman [68] found that 28 (i.e., 43% of the studies) of the programs used school-based clinics to deliver services and 9 programs used classroom-based programming, while the remaining involved system-wide efforts (e.g., mass-media campaigns, policy, or statewide), computer-based self-help, medical or recovery clinics, and family-based interventions. The review suggested that a school clinic is located within school premises and generally delivers services to students in non-classroom sessions that usually address groups of 5 to 15 students during school-hours [68]. On the other hand, classroom-based programs make use of course curricula to deliver services in classroom settings [68]. These programs often combine prevention and cessation components together [68]. Although school clinics are supposed to address subjects' individual needs and thus be more effective, among the studies reviewed by Sussman [68], classroom-based programs showed higher quit rates (i.e., 17%) compared with school clinics (12%). In fact, classroom-based programs showed the highest rates of cessation among all channels of program delivery [68].

However, it seems unclear whether school clinics and classroom-based treatment programs function similarly for alcohol or illicit drug use problems. Most of the Motivation-Skills-Decision-making Model-based classroom programs that combine prevention and treatment objectives seem to target all drug use [68]. However, school-based interventions that only target alcohol or illicit drug use disorders seem to rely more on problem identification, referral (e.g., referring problem users or suspected users to outside facilities for treatment or screening) or group counseling (e.g., Student Assistance Programs) [77]. Moreover, the efficaciousness of these interventions has not been rigorously researched [78].

Treatment Strategies and Executive Function Skills

As with prevention programming, treatment programming for adolescent drug users is likely to benefit a great deal from motivational enhancement and skills training. Preparedness to change one's drug-using behavior (e.g., motivation) and drug use outcome expectancies are considered to be important cognitive mediators of drug abuse treatment [83]. Treatment efforts are successful when drug abusers are receptive toward treatment, understand the risks of abusing drugs, and identify the benefits of stopping [83]. In other words, treatment efforts are more likely to be successful when subjects are adequately motivated to change their behaviors.

However, compared with adult drug abusers, adolescent abusers might be less motivated to change their behaviors and less likely to accept that they have drug abuse problems [63]. For example, a study on high school alcohol users found 49% of the sample at the "precontemplation" stage [52] of behavior change [39]. Hence, treatment programs targeting adolescents need to be able to motivate them to seek treatment and comply by treatment protocol [46]. A large number of adolescents with less serious problems miss treatment opportunities because of lack of motivation [46]. In other words, motivation is a prerequisite for the success of other treatment strategies, such as cognitive-behavioral skills training, which includes self-control, planning, self-monitoring, and decision-making treatment strategies.

Smith and Anderson [63] argue that much of adolescent alcohol-related problem behaviors

can be explained in terms of an interplay between personality factors such as behavioral disinhibition and learned or acquired pro-alcohol outcome expectancies. According to their model, over time, disinhibited adolescents learn to yield more readily to positive outcome expectancies of alcohol than negative [63]. Teaching adolescents cognitive skills such as self-instruction [36] to allocate attention on negative consequences of drug use rather than positive would be one way to treat biased outcome expectancies [63]. For example, an intervention could train adolescent drug users on mentally reviewing and countering the positive consequences of drug use with negative ones [63]. Another treatment strategy that Smith and Anderson [63] recommend deals with restructuring memory associations such as replacing incentives associated with drug use in memory with deterrents. For example, metamemory techniques can be used to train adolescents on selectively retrieving negative experiences of past drug use episodes when confronted with a new drug use situation [34, 63]. Treatment components should also include additional cognitive-behavioral strategies, particularly those dealing with self-control, stress management, and coping, which are especially important in helping individuals sustain through recovery. For example, meditation and mindfulness techniques, which are not commonly used in adolescent drug use treatment, can be implemented to improve attention and stress management [27] and reduce withdrawal-related symptoms.

Interventions based on motivational interviewing combine motivational enhancement with cognitive-behavioral therapy [46]. Brief motivational interviewing interventions have been found to be effective in reducing drug use among adults and young adults. Sussman's [68] review of youth tobacco use cessation programs found that most school-related programs tend to use cognitive-behavioral strategies compared with very few that use motivational enhancement, even though programs that use motivational enhancement tend to have higher quit rates.

Motivation Enhancement and Motivational Interviewing

Motivation enhancement techniques serve to clarify desire for change and reduce ambivalence toward change. This may include, but is not restricted to, a specific strategy such as motivational interviewing [40]. Motivation enhancement helps participants to clarify their direction of change and increases their willingness to change. Motivation enhancement may also include use of response-contingent reinforcement which reinforces quit-behavior with the chance for extrinsic rewards such as money or prizes [68]. In one of the largest controlled field trials of a school-based teen smoking cessation program that uses various motivating activities (e.g., games, talk-shows), Sussman et al. [69] found 17% adolescents who received the treatment to have stopped smoking at 3-month follow-up compared with 8% of the control adolescents. The clinic curriculum, of Project EX, consisted of eight sessions spread over 6 weeks [69]. The motivation component in the first session was represented by a talk show where family and friends confront smokers about their habits. In session three, adolescent smokers were involved in a game which intended to teach them about the negative effects on one's body of the harmful substances in tobacco [69].

Motivational interviewing is a type of brief intervention (i.e., comprising of one to five sessions), based on the theoretical principles of stages of change model (the transtheoretical model) [52], client-centered therapy [57], and cognitive behavioral therapy. As advocated by the client-centered therapy, motivational-interviewing attempts to motivate individuals to change their health risk behaviors through a non-judgmental and non-confrontational form of counseling [40]. In order to assist individuals to take action and maintain the behavior change, motivational interviewing programs usually intend to help individuals toward building self-regulatory skills that are essential in coping with stress and solving personal as well as interpersonal problems [46].

As a treatment and harm-reduction technique, motivational interviewing has a relatively long history of effectiveness among alcohol-dependent adults [46]. More recently, researchers have begun to apply the technique on adolescent drug users too (e.g., [41]). In a systematic review of motivation interviewing trials on adolescents and emerging adults, Grenard et al. [23] located 17 treatment studies that dealt with alcohol use, tobacco use, multiple drug use, and injury-related outcomes. These interventions, five of which reported successful outcomes, were set in hospital outpatient clinics and emergency rooms (e.g., a youth visiting an emergency room after a drinking-related incident), colleges and universities, psychiatric hospitals, and other outpatient clinics. Evidently, most interventions tended to target adolescents with relatively serious drug use problems and none of them were school-based. Further, majority of the studies (i.e., 9 out of 17) dealt with alcohol use only [23].

Providing one-to-one motivational interviewing sessions in school-based settings might be a daunting effort but certainly not impossible. Methods used by alcohol abuse interventions among young adults in college settings (e.g., [35]) could perhaps be applied to adolescents in high schools. For example, drug-using adolescents could be screened and referred to school clinics, where they would be assisted by trained motivational interviewers [42]. Another possible way of utilizing motivational interviewing in school-based prevention or treatment practices is to combine it with a longer intervention. In an ongoing school-based intervention study Sussman and colleagues are testing the effects of adding telephone-based motivational interviewing component to an existing teen drug abuse prevention curriculum. Motivational interviewing has a prospect of proving effective in treating adolescent drug abuse in a school setting.

Conclusions and Future Directions

Table 1 lists examples of strategies that could possibly be used to alter children or adolescents' executive functioning with the aim of preventing or treating drug abuse. Novel techniques that might help assist age-related development of executive functioning are being increasingly tested (e.g., [28, 47]) and seem to have relevance to school-based prevention and cessation programming. To implement these strategies, school-based drug use prevention and cessation programming should consider important findings from the field of neuroscience. First, programs should be tailored to meet the appropriate developmental stage of youth considering both age and the special needs of certain subgroups (e.g., students raised in poverty or abuse). Treatments that require a certain level

Table 1 Potential intervention strategies to improve adolescent executive function skills

Executive functions	Strategies
Attention	Attentional control skills instruction (e.g., self-instruction strategies to help shift attention); mindfulness training
Memory	Training on metamemory (e.g., selective memory retrieval)
Working memory	Task practice (e.g., backward digit span task); mindfulness training
Inhibitory control	Self-control skills instruction (e.g. practice "control signals poster"; self-instruction; delay of gratification strategies)
Planning	Self-regulation skills instruction (e.g., making action plans; practice "control signals poster"); motivational interviewing
Decision-making	Social and emotional problem-solving skills instruction (e.g., dialoguing; internal verbalization of speech); motivational interviewing
Monitoring	Self-regulation skills instruction (e.g., practice behavioral and emotional analyses; "Feeling Face cards"; life skills training)

of emotional and cognitive processing should make sure that the psycho-physiological skills have been developed by participants. Second, the neurocognitive mediators acting between the intervention and drug outcome need to be carefully measured. Third, the social environment must be considered since resources, support systems, and messages delivered in the intervention may not be available in the general community (i.e., lack of community or family support not to use drugs, lack of financial resources to quit smoking such as the nicotine replacement patch). Thus it is important to assist youth to develop executive functioning skills to plan and obtain resources from their environment (identify treatment centers, plan transportation, consider options of treatment centers). Lastly, much more research is needed in order to substantiate and improve the application of neuropsychological models to school-based drug use prevention and research.

Acknowledgment This paper was supported by grants from the National Institute on Drug Abuse (#s DA13814, DA016090, DA020138 and P50 DA16094).

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The Therapeutic Community for Drug Abuse Treatment: A Journey Yet Unfolding in the Recovery Movement

David A. Deitch and Liliane Drago

Contents

Origins

It is wrong to assume that there has always been a specific and widely accepted understanding of what is meant by a "therapeutic community." The designation has an ancient pedigree and an historic association with diseases of appetite and the concept of mutual help. By the late twentieth century, it had come to identify a specific mode of treatment for substance misuse, addiction, and other behavioral disorders based on the power of the treatment community to change attitudes and behavior through mutual help and a regimen of structured activities and expectations. This is a regimen designed to promote compassion and responsibility, foster self-awareness, enable social learning, and make possible the acquisition of social capital.

At the dawn of the Christian era, in 25 A.D., Philo Judaeus wrote, "They are called communitae therapeutrides . . . because they profess an art . . . more excellent than in general use . . . for medicine only heals the bodies but [these] heal the souls which are under the mastery of terrible . . . incurable diseases of pleasures and appetites" [21]. (Curiously, the term "appetitive" became a neurobehavioral declaration regarding addictive behavior in the late twentieth and early twenty first centuries—as supported by neuroimaging techniques that became available in the late twentieth century.) Thus, it appears that the struggle with uncontrolled appetite behavior was a challenge then, as it is now, and the ancients embraced an approach not unlike the therapeutic communities of today [11].

We can presume that Philo, writing in Alexandria early in the first century, was describing the early Essene communities, where according to the Qumran Community rules of order and duty, life was meant to conform to the following principles: concern for the state of our soul and our physical survival; search for meaning

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_45,

(transcending truths); challenge and admonish with love; be invasive—accountable to the community; public disclosure of acts, fears, hopes, guilt; public expiation for wrongs done; banishment is possible—done with concern for survival; and leadership by elders—by models.

These same principles have been present in mutual help communities from early monastic splinter groups to the much later Methodist congregations that espoused a "return to first principles" and morphed into the early Oxford movement [48]. It may well be that combining two sets of rules—one imposing rigid moral and behavioral standards and the other promoting humanizing compassion and forgiveness—is why these principles have so often and so successfully been brought to bear on delinquent or deviant behavior, problems of social maladaptation, and finally on addictive behavior and other problems of appetite.

This can be seen in the spread of religiously based mutual help societies in Western Europe during the seventeenth and eighteenth centuries. Responding to the widespread overuse of alcohol, they launched temperance efforts in Europe which spread to America. Many of these early attempts at "appetite control" included temporary residential support and "pledges" of abstinence [48]. Key principles embraced by these mutual help groups included disclosure (confession), admonition, commitment, and conversion of others. By the 1800s, the spread of these principles had influenced development of the Washingtonian and numerous other small groups.

Before World War II, however, the term therapeutic community recurs only once, when it was applied to the care of orphans in eighteenth century Russia. It was next revived in wartime England at Northfield Hospital, a facility dedicated to the treatment of traumatized British troops. There, two psychiatric innovators, Maxwell Jones and Tom Maine, sought to reapportion authority and decision making between staff and patients [1, 7].

They began referring to the "democratic therapy" they introduced at Northfield Hospital as a "therapeutic community," designed to reverse the dynamics of the traditional psychiatric hospital, which many had come to believe infantilized patients, exacerbating their disability, and rendering them incapable of functioning outside the hospital environment. Patients in Northfield psychiatric units became the active decision makers, taking on increasing responsibility for ward management. Early discussions among these pioneers resulted in five basic assumptions: two-way communication at all levels; decision making at all levels; shared leadership; consensus in decision making, and social learning by social interaction with emphasis on the "here and now" [26].

The horizontal, open system of communication, based on those five principles, was itself assumed to result in healing. It did, in fact, produce marked improvement among community members, and such success made the need for individualized treatment plans seem unnecessary (a notion that would later become doctrine in American drug treatment therapeutic communities). Maxwell Jones went on to become a teacher of this method in Europe and the United States throughout the 1950s and 1960s, influencing younger psychiatrists, particularly at state psychiatric hospitals in Washington, Oregon, New Mexico, and other Southwestern states [27]. However, not until the late 1970s did Jones become aware of and engaged with the American drug treatment therapeutic community movement [40].

The drug treatment therapeutic community was not introduced by any of the nurses or psychiatrists who, inspired by Jones, sought to develop similar treatment models. Its origin is attributed to a group that emerged in Venice Beach, California, in 1958, when an Alcoholics Anonymous member, Charles E. (Chuck) Dederich, started an organization he called Synanon, embodying mutual help principles of Alcoholics Anonymous and characterized by hierarchical structure, a semi-open communication system, and small group interactions focusing on behavior change.

Not unlike other charismatic and gifted figures, Dederich brought his own background—corporate, Midwestern, and

Depression-influenced—to the organization he founded. As is often the case when strong leading theoreticians mount efforts designed to alter human behavior, the organization took on the personality of its founder. Imitation of the leader—in dress, language, and general demeanor—became a defining characteristic of Synanon and an influence on subsequent therapeutic communities.

Dederich launched Synanon by breaking away from the Alcoholics Anonymous group he had been attending. Within the tradition of Alcoholics Anonymous anyone can pick up the "Big Book" and start his own meeting. When Dederich and the few members who followed him started their meeting in Venice Beach in 1958, the community was loaded with "alkies", "pill-heads", and a few "junkies". These people, living on the edge of society, in the pleasant, hospitable, Southern California beach community, were sleeping on the beach, begging for money, making drug deals, and essentially staying intoxicated with the drug of their choice or whatever else they could get. It was a setting ripe for an evangelical salvation-oriented mission.

With the help of a dedicated few, Dederich and his followers obtained funds to open a "club" and, in a tradition easily traced back 200 years, encouraged folks to drop in for conversation in hopes of gaining sobriety. Dederich began holding long meetings in which his innate verbal talents and wide range of interests—from corporate structures to Zen and Transcendental philosophies—drew growing audiences and proved a powerful magnet for membership.

Hearing of these meetings, the availability of food and rumors of easy sex, a few heroin users recently released from the California prison system dropped in. Contrary to their expectations, they were immediately confronted by a loud, bombastic host, who assured them they were welcome, but only if they were willing to help out. "There's no free lunch," Dederich told them, and this proved an attractive challenge to some, since it was such a departure from the traditional social work style they anticipated [3].

A nascent community came into being made up of Dederich's Alcoholics Anonymous cadre, former prisoners, quasi-homeless addicts from the beach, and an upscale contingent of musicians and other artists. Core members from outside the area began moving in, renting the readily available small cabin rooms along Venice Beach. Later in that first year, the group acquired an armory on the beach in Santa Monica, which gave members a chance to live together, pool their funds, share meals, and begin to "hustle" in the community, soliciting donations of cash, foodstuffs, and other living supplies. It also challenged Dederich to organize, preside over, and control community life.

A large man, highly verbose and partially deaf, Dederich spoke at length and high volume. He loved to argue and debate, inspiring heated confrontation among members. These confrontations became a common style of interaction within the group, valued for the relief that many members claimed such abrasive exchanges brought them. Soon formalized, this mechanism was first called "The Synanon" after the name of their organization. By 1964 "The Synanon" began to be referred to as the "game" [3].

It is from the Synanon "game" that the therapeutic community "encounter" evolved. What Dederich added to the fundamental Alcoholics Anonymous mechanism of self-disclosure was the muscle of confrontation. Alcoholics Anonymous rejects both invasiveness and cross-talking. While no one at an Alcoholics Anonymous meeting interrupts, questions, or challenges a speaker, the "game" encouraged this kind of spirited exchange.

As the "game" developed, so did the ethical demands of mutual responsibility. Although "no drug use" was an early requirement of the group, many members continued to use. A troubling question arose: "What then is the responsibility of others in the group? Are they obliged to expose their drug-using fellow members?"

The issue came to a head at what later became known as the "Night of the Big Cop-Out", when a number of drug users were "outed" and others "copped to" their use. At this point, the role of the community as monitor was established along with the principle of expulsion from the group for drug use [3].

As a daily schedule took shape, work tasks necessary to operation of the community were assigned and a schedule of daily seminars established to broaden the intellectual horizon and knowledge base of members. A distinct corporate-like hierarchy was formed, with a top-down structure based on coercion ("our way or the highway") and leadership determined and rewarded by Dederich. The early rewards included special living quarters, special food, access to vehicles, and the ability to acquire girlfriends or boyfriends and sleep with them. (The euphemisms were "courting" and "steady dating").

Early on Synanon began organizing the process of drug treatment into a series of phases. Phase One was live in and work in; Phase Two, work out and live in; and Phase Three, live out, work out, and maintain membership. But very soon, by 1960, Phase One had grown from 2 to 6 months in response to relapse among members in Phases Two and Three [19]. By 1962, during a period of rapid membership growth, Phase One was extended to at least 1 year. Nevertheless, relapse continued to occur in Phases Two and Three. As a result, the work out and live out phases were entirely eliminated in 1964, with Dederich rationalizing that "Our members remain healthy and drug free while with us—so that we are obviously a healthier community than is the greater society" [14]. At this point, the effort once labeled by *Life Magazine* as a "Miracle on the Beach" began its drift into increasingly wilder utopian community fantasies and ultimately into a cult capable of criminal behavior (pleading "no contest" to charges of soliciting an assault and conspiracy to murder).

Early Expansion

Not surprisingly, and consistent with the experience of other psychosocial movements, there were breakaways from Synanon by 1964. These breakaways, while troubled by the Synanon's flaws, still took with them a deep belief in the essential elements of a treatment model that had made it possible for them to achieve and sustain abstinence. They also, however, carried with them a vision of treatment as "redemption" and the Synanon belief that they had the right and the only right answer. Theirs was a point of view that perceived addiction, if not as a moral weakness and sin, then as a disorder of character [3]. Thus, they were not only entitled to, but charged with, correcting such flaws by whatever means necessary within the limits of the law.

It was at this moment that new opportunities were created by growing demand for a response to the seemingly intractable problem of addiction to heroin and other illicit drugs. By the early 1960s, heroin use was expanding, particularly in urban America. The accompanying increase in crime brought to the surface public frustration with the failure of stern anti-addiction measures to effect change. Longer and longer minimum mandatory sentences for drug law offenses and civil commitment of addicts for treatment with lengthy stays in federal hospitals did not produce abstinence outcomes.

The notion that abstinence might not be a rational expectation had surfaced back in the early 1950s when Victor Vogel, M.D., who then oversaw addiction treatment at the United States Public Health Hospital at Lexington, Kentucky, wrote that "If treatment results are compared with those in other chronic or recurrent diseases such as TB… arthritis… hypertension … diabetes … or cancer—results in this field (drug treatment) are good" [36]. But this early glimpse of addiction as a chronic disease was ignored. Both the public and the afflicted either hoped for or wanted an answer called "cure." Synanon had promised such a miracle and so did the first spin-off, Daytop Lodge in New York.

Daytop Lodge was a research project based on Synanon. It was supervised by Brooklyn's Chief of Probation Joseph Shelly and his lead psychologist Alex Bassin. The acronym stood for Drug Addicts Treated on Probation. The population consisted of 35 male felons who accepted treatment at Daytop under probation supervision rather than prison sentences [42]. This marked a serious departure from the mutual help

members involved in volitional recovery. Money in the past was begged or provided as charity. Now it was underwritten by government and administered by a criminal justice agency. It should be noted that this was the first step in what came to be known as therapeutic community institutionalization, and a new term, "ex-addict" came into use. The project had a shaky start with a rapid turnover of leadership. In October 1964, under a new and more experienced leadership team and with increased financial support from New York City, the program was reorganized, and Daytop Lodge morphed into Daytop Village.

Probation was no longer a requirement for admission, and the program now accepted women. A board of directors was formed, chaired by co-founder Monsignor William B. O'Brien, a Bronx priest with strong ties to the New York archdiocese [41]. Alex Bassin joined the board. Daniel Casriel, M.D., a psychiatrist who had written the first book about Synanon, So Fair a House, was now psychiatric director and David Deitch clinical and program leader [5]. Soon, a growing number of candidates sought admission and by the end of 1965, there were 100 "members/residents" in a larger facility [12].

In 1966, New York City's mayor, John V. Lindsay, recruited Efren Ramirez, M.D., a psychiatrist from San Juan, Puerto Rico, to coordinate the City's narcotic treatment programs as commissioner of the city's new Addiction Services Agency. Dr. Ramirez had already developed systems of community engagement, protracted client induction processes and treatment approaches similar to those of Daytop Village ("Daytop"). Ramirez developed a close working relationship with the program, and Daytop staff became a resource for him as he set out to expand the City's response to a growing heroin epidemic. It was Ramirez, trained in the Max Jones model, who persuaded Daytop, which had been calling itself a "humanizing community," to adopt the term "therapeutic community" to better describe its approach.

Dr. Ramirez was soon joined by Mitchell S. Rosenthal, M.D., a psychiatrist who had developed an alcohol and drug treatment hospital unit at the Oak Knoll Naval Hospital in Oakland, California. There, he had introduced many of structural and group characteristics he had observed at a Synanon facility in San Francisco. Ultimately, Ramirez made him deputy commissioner for rehabilitation.

Commissioner Ramirez was also reaching out to other young psychiatrists in hopes of expanding addiction treatment. He created a weekly get-together of Deitch, Rosenthal, and a young psychiatrist still in residency training, Judy Densen-Gerber Baden. These meetings provided the impetus for an explosive growth of the model in New York City. Rosenthal developed Phoenix House, and Judy Densen-Gerber created Odyssey House [18]. Daytop lent staff to each of these projects, and help also came from other former Synanon members [41].

In short order, these projects spun off other new starts: Samaritan Village and Project Return in New York City; Gaudenzia in Philadelphia; Village South in Miami; and Gateway in Chicago. All of them shared many similar beliefs, hierarchical structures, group activities, and goals.

There was also a significant role in the expansion of the therapeutic community played by the young psychiatrists who finished their training and served in the United States Public Health Service. The earliest concentrations of addiction treatment were located at the United States Narcotic Farm in Lexington, Kentucky, run jointly by the Public Health Service and the United States Prison Service, and a similar facility in Fort Worth, Texas. These facilities accepted voluntary admissions as well as addicts convicted in federal territories or found guilty of federal offenses [2].

Three of these psychiatrists emerged as leaders in addiction research and treatment. Jerry Jaffe, who was to become the first White House director of the Special Action Office for Drug Abuse Prevention, currently referred to as the Office of National Drug Control Policy, became familiar with therapeutic community methods at Daytop while at Albert Einstein Hospital in at New York City. Recruited by the Department of Psychiatry at the University of Chicago to serve as the director of drug abuse treatment

programs for the State of Illinois, he subsequently recruited two Daytop staff members who helped him to further develop Illinois' first therapeutic community, Gateway Foundation. In order to secure a facility for Gateway, Jaffe took a lien against his own home so that the therapeutic community model would be part of the broad array of programs, from outpatient detoxification through methadone maintenance, he created in Chicago.

A second United States Public Health Service psychiatrist, Herbert D. Kleber, had his introduction to addictions at the Lexington Hospital and went on to the Department of Psychiatry at Yale's medical school. There, he recruited Daytop staff to develop a separate Daytop Connecticut in New Haven. Kleber was subsequently tapped to become the Office of National Drug Control Policy's first deputy director for demand reduction. Another United States Public Health Service Hospital psychiatrist, Fred Glaser, helped bring the therapeutic community program Gaudenzia to Philadelphia while teaching at Temple University.

This rapid spread of therapeutic communities was made possible by program members seeking a cure and communities in search of new and better ways to confront addiction. Unlike the Alcoholics Anonymous movement which holds that "members are in recovery not recovered," the therapeutic communities believed that cure was possible [12]. This belief was reinforced when peers were seen to succeed. Use of the term "ex-addict" grew, and the expansion of the therapeutic community was now fueled not only by former Synanon members, but by "graduates" of these new and exciting programs.

Proliferation of the therapeutic community was carried on a wave of optimism characteristic of the era—a period of seemingly infinite possibilities, before the war in Vietnam clouded the political landscape. The climate of the times made possible the spread of therapeutic community doctrine by outsiders, for here was a treatment model with no academic provenance or research history that essentially invented itself. Pioneering psychiatrists who embraced the model did not come from the medical or mental health mainstream, and few of those first-generation program leaders had any professional credentials at all. What they did have was an ideology. The concept of "giving to get"—the notion of helping others to facilitate one's own recovery—was a philosophical cornerstone, as was the belief that healing was possible only when one was part of something greater and more important than oneself. The men and women who staffed the early therapeutic communities strived to submerge their separate identities. To them, the golden word was "we." Many of these early staffers—formerly gone astray, isolated and addicted themselves—needed that merged identity to heal themselves before they could help others heal.

As Deitch wrote many years later [51], "These outsiders ... created humanizing communities that espoused dignity of all people, equality between races and sexes, nonviolence and peace, heightened consciousness and spirituality, and action as the road to personal and social change. These first-generation ideologists committed themselves to a way of life that provided health, safety, caring, and honesty—sometimes brutal honesty. They censured deception, cheating, and gain at others' expense. The original version of these early crusaders—a vision that still holds true today—was a commitment to live and act as agents of positive social transformation. We believed that what goes around comes around."

The Formative Years

Admissions

The mind set of first-generation United States therapeutic communities was shaped by the realities of the heroin epidemics of the 1950s and 1960s and the lack of much in the way of alternative treatment resources. Candidates for admission were not then greeted with open arms—admission, it was felt, had to be earned. One had to prove oneself ready for treatment. In some programs this meant demonstrating that one had "hit bottom."

Therapeutic community membership was then, as it is now, deemed to be voluntary. But few candidates at any time have sought admission without some form of suasion, generally from family, employers, or the legal system. The pressure on addicts to seek therapeutic community treatment was particularly strong in the 1960s, when there was great threat of arrest or civil commitment, particularly in New York, which held the greatest concentration of first-generation therapeutic communities.

Admission to most therapeutic community programs then generally involved heavy doses of dissonance. These ranged from the demand that applicants demonstrate commitment by daily telephone calls to the program and long waits in the interviewee chair. Interviews could be conducted by three or four program members who would challenge the applicants' candor, belittle their claims of sincerity, and demand they drop their drug user's "street" facade and adopt new language and behavior [50]. Clearly, this type of challenge and the levels of dissonance discouraged many applicants and prompted others to leave soon after admission, feeling both angry and confused or compromised. For those who stayed, however, many would subsequently claim that the dissonance experience left them more invested in the process that followed.

The Role of Family

Then as now, the pressure that brought many applicants to treatment came from their families. This posed something of a problem for the therapeutic communities, which wanted to keep families engaged but distant. They needed families to understand that they were vulnerable to manipulation and exploitation and must to learn to resist pleas for help from their addicted children—particularly for money.

A favored practice for dealing with families that remained committed to their addicted children was bringing a group of families together to discuss their concerns and answer their questions. These sessions led to the creation of an education program that dealt not only with therapeutic community goals, structure, and methods but also with the stages and nature of addiction. This practice was, in many ways, an innovation that was adapted by other groups to help family members deal with such other disorders as mental illness, autism, and alcoholism.

Families were taught, as were their loved ones in the program, the concept of "responsible concern," the notion that when you care about someone, you must set limits on their behavior, which may, at times, mean denying them money, shelter, and other benefits that might "enable" addicts to keep using without facing the natural consequences of their behavior. This later evolved into the "tough love" philosophy, one that would become a central theme to a self-help movement for parents and others intimately involved with addicts and others with problem behavior.

Eventually, many therapeutic communities formed small groups for family members, where the staff would lead discussions about their attitudes, behaviors, and values. This was considered a way to explore conflicts that potentially abetted their loved one's drug use. The preferred means of encouraging frank discussion was the encounter group which aimed at revealing differences between stated goals or needs and actual behavior. The intensity of interaction at these family groups, however, did not rise to the level practiced in the treatment community, and there was little acceptance or use of harsh confrontation [21].

The Hierarchy of Roles

Once admitted to the residential setting, the new member was introduced to the community's elaborate and hierarchical structure, much of which remains as a cornerstone in the American therapeutic communities to this day. Rank and status were based on work assignment, and newcomers were assigned to what was considered a "bottom" function, such as cleaning the toilets or washing dishes. These jobs were meant

to make clear to the client his position at the bottom in status, and the need to do the job well in order to gain status and move up in the hierarchy (which was often called "growing up"). But work was only one element on which moving up was based. Attitude, change, and commitment to the treatment community were also considered. The theme constantly reinforced by leaders to those beneath them was "You can have my job;" "You can be in charge," but "You must earn it!"

Each of these work assignments was real and necessary to the actual functioning of the community. Facilities needed to be cleaned, food prepared and cooked, cars oiled, gassed, and repaired, walls painted, and rooms renovated. Household needs had to be met, and effort was made to solicit contributions of everything from milk to gasoline from the greater community.

All donations were accepted: used clothing; slightly stale bread; fruit and vegetables; old dishes; and cookware. It was all needed. There were also cash gifts and, by incorporating as non-profit organizations, therapeutic communities were able to add the inducement of a tax deduction to the selling points of personal recovery and self-reliance.

Much also had to be done to run what was, in reality, a small business—write the letters; answer the phones; make agendas; ensure positive behavior, coordinate between departments, and represent the therapeutic community in the outside world. Each task was the responsibility of a specific department. Each department had its place within the hierarchy, and one's status depended upon one's role within the department and the department's place within the community. One gained status first by moving up within a department and then by moving on to a department with a more complex or demanding function.

Over time, each member, depending on his investment in treatment (judged to be doing well by peers and elders) was promoted upward. The promotions were done with drama and praise and were part of the reward system. Each promotion was discussed internally and was used as an example to guests and visitors to show how the therapeutic community structure rewarded one with increasing amounts of responsibility for areas of work, productiveness, and oversight of others.

During this time, youth and adults were mixed together, as were genders. All were treated with the same methods, expectations, and accountability demands. There was then no consciousness of a need for formal education for this predominantly adult population, and vocational training was "on the job," in the classic apprenticeship tradition. The need for supervision and oversight within the departments and within the community created an interesting tension between trust and scrutiny.

The Interactive Healing Life

Group processes were then and still are the lifeblood of the therapeutic community. Every day, every member, staff or client, and even steady visitors and friends, became involved in one group process or another [12].

The community began the day with a morning community meeting where concerns were expressed, and problems were solved. These meetings always began with a prayer or a statement of the program philosophy. Each therapeutic community group strove to be unique, creating its own language and terms to describe shared activities common to all other therapeutic community groups. Program philosophies became a critical means of identification and morale building. Many were created by the members themselves and reflect the spirit of the times and the intense need for affiliation, membership, and family. Indeed, the greeting, "Good morning, family," permeated most American therapeutic communities and (at least until the mid-1970s) most therapeutic communities outside the United States.

During these early formative years, the problems that came up at morning meetings often dealt with issues of survival, such as getting food for the table. Others were more mundane, like dealing with laundry, announcing

visitors that day, or welcoming new members. Some were personal disclosures, making the community aware of some member's personal distress. These morning meeting public disclosures were greeted with "reach-outs," expressions of concern and support from others. There were "pull-ups" for tasks left undone and also "push-ups", applause and recognition for tasks accomplished. These activities generated positive feelings—laughter and energy to start the day. The meetings usually ended with mutual hugs.

Intellectual Exchange

There was usually a break in the workday in mid-afternoon for lunch followed by the "daily seminar". Participation was mandatory for all, including the leadership. The goal of the seminar was to broaden the intellectual vista of community members. It was an opportunity to make them familiar with ideas and concepts that they had perhaps never heard of before. Everyone became a tutor or mentor, reading up on subjects so it could be brought to the group. There, members were encouraged, cajoled, and sometimes coerced into taking part in discussion of matters that ranged across vast subject areas. Philosophy was discussed, along with science, and literature. Sessions might focus on the works of Nietzsche or Freud or the writing of Hemingway or Faulkner. The seminar was an important part of daily life, not only for its content, but as a means of helping members learn to conceptualize and verbalize.

Small Group Interventions

Generally, every evening was reserved for small group process. These sessions were at first called "encounters," although some used the language of Synanon and called them the "game". One dimension of the encounter was its formation, for the makeup of each group was usually decided by elders in the program drawing on information they had received from various members. No less than twice weekly, when the call went out "encounter-time," every member experienced a moment of tension and anxiety. One never knew until that moment who might be in their group and how they might be perceived or challenged about their behavior, attitude, or social contribution to learning to live drug free. Encounters involved challenge, and often exaggerated elaboration of a person's behavior would be used to elicit truth, the admission of error, and acceptance of corrective action [6].

In 1968, the psychologist O. Horbart Mowrer, who visited Daytop frequently and was certainly in the behavioral therapy camp, made a unique contribution to the encounter group by adding a new aspect—promise-making. Members would now make a commitment to another (or many others) in the group to change or adapt some specific behavior. One did not necessarily have to believe in the need for or use of this behavior, one merely had to practice it. Subsequently, such phrases as "act as if" or "go through a motion" became a commonplace part of early therapeutic community life.

Also in 1964, Deitch and Casriel began experimenting with groups lasting 18–30 h. This was not a physically impractical notion at a time when all community members, including the directors, paid staff, and program elders, all lived either in the same facility or one close by. Therapy was an ongoing process, 24 h a day, and interactive dialogues were primary aspects of community life [6].

These long-lasting groups became known as marathons, and a set of methods and procedures slowly evolved. The staff who selected marathon participants would consider how the process could be the most useful for the member. However, common to all was the expectation of going deep toward the past, toward unresolved guilt and unrevealed strengths to discover, in the process, that one could be vulnerable in the face of fears and, by doing so, gain strength. The format began with autobiography, particularly aimed at early feelings of fear, shame, and defenses that became self-defeating [6].

As hours passed and intimacy grew, an atmosphere of caring emerged with expressions of compassion, and attempts at resolution became key. This experience was heightened by the combination of sleep deprivation, limited external stimuli, and selected stimuli to provoke moods (usually music, mirrors, drawing supplies, and occasional props such as photographs). Usually, by 24 h, all had experienced a sense of catharsis and acceptance by the others over conflicts, guilt, and regrets.

This marathon session would be followed by a break during which each participant was asked to be alone and reflect on the experience. They were usually escorted by a non-participating member who had experience with the process to a quiet, private space to sleep, eat, and think. After this 6-h break, participants reconvened for feedback. This process became very carefully regulated after the first few years, with the participants asking for feedback being given a scribe to record those portions of the feedback they requested. After feedback the members would talk about their "commitments" to the group.

Considering the regressive possibilities of this type of group, there was a safety net provided by the fact that they all lived together in a larger community of others equally committed to being there for each other. Most often, this experience resulted in peaks of love and compassion and group bonding. At this point a follow-up plan could be developed to monitor the keeping of commitments made during the marathon [6].

These marathons and shorter versions, with fixed targets of inquiry known as probes, ultimately morphed into a static group that met weekly and where the emphasis was on maintaining the intimacy created by the marathon or probe for further deep work. By 1979, static groups were created for members regardless of marathon participation.

The General Meeting: A Response to Crisis and Bad Behaviors

Unlike the daily morning meeting, when one heard the announcement "general meeting" therapeutic community members immediately headed for the meeting space knowing something big or bad had happened. Here, unlike at traditional meetings, the chairs were not arranged in a circle, but rather in a classroom format, with the front reserved for standing elders who had a message to deliver. These meetings did not occur often. When they did occur, it had to do with a serious threat (usually by a member's behavior) to the community's two principal taboos—no violence or even the threat of violence, and no drugs or alcohol. (Cigarettes were used by all members, and smoking was considered normative.) Such violations usually called for banishment of the offender. The meeting was to bring focus to the event, generate anger toward the offender, challenge the offender's right to remain, and vent fury at the threat to the community. The decision about whether an offender stayed or was banished was made as a result of the group's assessment of the offender's display of regret, seeking of forgiveness, and pleas to stay. Such a visible display and catharsis for the entire community was considered necessary for safety and the community's drug-free goals [4].

Public acts of contrition also permeated normal daily life. Signs were hung around member's necks describing their failures to be honest, their propensity for manipulation, or some other set of behaviors requiring a high level of focus and embarrassment to the person. These signs were often quite creative and developed for a specific individual and the particular offense. Others signs for more common offenses were used routinely and could be kept in a closet until needed [12].

Treatment Duration

All of the New York therapeutic communities and many others maintained a phase system with an average prescribed length of stay, in order to complete all phases, of two to two-and-a-half years. The early therapeutic communities believed in a full character makeover and the creation of a new pro-social role in society. Indeed,

such roles were made possible by becoming "change agents" and taking on careerist roles of therapeutic community staff which were in high demand [11].

Understandably, considering the length of prescribed stay, the problem of sexual needs and interaction was always present. Many attempts were made to resolve this dilemma. At first, permission to have sex was given if the heterosexual couple were behaving well in their community life, presented as stable in courting, and had been in treatment long enough to presume greater stability. This approach varied from program to program and often within the same programs.

The tradition at that time was to insist on couples' education groups, followed by encounter groups for couples meant to explore feelings and conflicts. When such couples demonstrated that the relationship was not compromising their positive treatment engagement, they were permitted a designated space and privacy for a given time period. This ranged from 2 h for beginners to an overnight visit for residents who had been in treatment for a considerable time.

By the early 1970s, the controversy and complexity of permitting, condoning, monitoring safety, public relations, and couples' conflict resolution soon gave way to exhaustion and brought about an official end to this era. Henceforth, sexual identity and romance could be discussed, but sanctioned sexual interactions were no longer permitted. The admonishment "You are here to get better; those other aspects are off the table and impede your personal recovery" eliminated the conversation but not the problem. However, sexual interactions between staff and clients continue to plague the recovery and mental health communities to this day.

The Therapeutic Community's Coming of Age

Therapeutic community treatment spread throughout country as well as to Europe and the Philippines (where there were new heroin epidemics). Expansion to Europe followed the visits of medical and psychiatric professionals to New York, then a hub of heroin use and treatment. Daytop (and later Phoenix House and Odyssey House) had a tradition of welcoming overseas visitors and enjoyed displaying their accomplishments. By 1970, this exposure had led Dr. Griffith Edwards, a leading addiction specialist in Britain, to sponsor Phoenix House London. Daytop sent staff to Sweden (1972) and Canada (1973). In 1972 Community Emiliehoefe in the Netherlands began shifting from a democratic (Jones) therapeutic community model to a United States model therapeutic community. In 1976, the first world federation conference of therapeutic communities took place in Sweden. There was to be continued growth in Europe, where expansion, which had initially involved the American therapeutic communities, was soon undertaken by the Europeans themselves [32].

In the United States, a national conference was organized by the National Institute on Drug Abuse and a very newly formed Therapeutic Communities of America in January 1976. Prominent among participants were the New York City therapeutic communities, but also represented were therapeutic communities from Florida, Canada, Pennsylvania, New Jersey, Washington, DC, Illinois, Washington, California, Ohio, Arizona, Rhode Island, Maryland, and Wisconsin [40].

However, the majority of the incorporators of the Therapeutic Communities of America remained in steady stable roles as chief executive officers, and their organizations grew in numbers of people treated and locations throughout the United States.

A key finding of the 1976 conference was that ". . . the therapeutic community is now determined to succeed in the public arena. In part this choice is a reflex to survive, but the therapeutic community is aware that it is an evolving institution!" Certainly there was prescient truth of what continues to this day. In 1974 there were 15,000 people in therapeutic community treatment . . . and major new drug-taking trends of type, method, and user populations [40].

The proceedings of the 1976 conference were sensitive to vulnerabilities of the past, noting that

"the communities are still dependent upon the emergent sanctioned leader. Despite an ostensible peer dynamic, individual therapeutic communities and the therapeutic community movement as a whole are very hierarchical in their internal process particularly in the selection, cultivation, and acceptance of their leaders. . ." [40]. This, however, proved no bar to expansion. Although the majority of the incorporators of the Therapeutic Communities of America remained in steady stable roles as chief executive officers, their organizations thrived, growing in size and spreading to new locations throughout the country.

Therapeutic Community Research

The 1976 conference proceedings also called for more research on both process and outcomes. Three major outcomes "researchers"—George DeLeon hired by Phoenix House [16], followed a few years later by Vincent Biase, hired by Daytop and Sherry Holland hired by Gateway—began to publish a set of promising outcome studies attesting to efficacy of the therapeutic community model.

The most prolific outcome spokesman for the therapeutic community movement was George DeLeon, who completed a series of 5-year follow-ups that revealed an important term for the entire drug abuse field. Time in program showed that any dose of drug treatment—regardless of type—of less than 3 months' duration did not appear helpful.

By 1984, DeLeon had published five papers, first describing the socio-demographics of New York Phoenix House therapeutic community members, then the signs or types of pathology and differences between men and women at Phoenix House. But it was the 1984 paper on a study of effectiveness which found that therapeutic community graduates had significant improvements in areas of drug use, criminality, and employment, which became the rallying point used by all therapeutic communities. These positive outcomes, with observable effect beginning after 90 days of treatment, were found to increase with the amount of time spent in treatment. The success rate at 2 years' post-treatment was approximately 90% for graduates (members who both completed residential care and achieved 6 months or more of aftercare in good status), 50% for completers, and 25% for dropouts who remain more than 6 months and less than 1 year [15]. The relationship between time in program and post-treatment success was found by other researchers as well [23, 43].

While there were critics then as even now, all of DeLeon's publications gave the entire field a sense of accomplishment, a right to brag (sometimes boast) that this was a model that produced drug-free cures, and regardless of cure, helped reclaim lives.

Early Therapeutic Community Studies

Outcome research by De Leon and others continued to demonstrate the value of therapeutic community treatment. In 1988, in another study at Phoenix House, DeLeon found that over 75% of Phoenix House graduates were both drug and crime free 5–7 years after completing treatment. In contrast, dropouts in DeLeon's sample were 31% drug and crime free, and only 25% of individuals who received less than 1 year of treatment were drug and crime free.

Following the Drug Abuse Reporting Program studies [43], a series of national studies in the 1990s with large samples of clients continued to demonstrate the efficacy of therapeutic community treatment. In the Treatment Outcomes Prospective Study, it was found that the longer clients spent in therapeutic communities, the less likely they were to use heroin, cocaine, marijuana, and psychotherapeutic drugs, and the more likely they were to be employed full-time and to have committed no predatory crimes during the follow-up year [9].

In four large-scale follow-up studies interviewing samples of more than 1,000 clients—the California Drug and Alcohol Treatment

Assessment [20], the Services Research Outcomes Study, the National Treatment Improvement Evaluation Study and the Drug Abuse Treatment Outcomes Study [44]—long-term therapeutic community treatment was found to produce greater reductions in marijuana, cocaine, and crack use 1 year after treatment than any other modality. Heroin use was reduced nearly as much as by methadone maintenance. Similar effects were shown for reductions in arrests and in drug selling. The Drug Abuse Treatment Outcomes Study also reported that full-time employment following long-term residential treatment was more than 250% greater than for any other modality. The National Treatment Improvement Evaluation Study found employment among former participants in long-term residential treatment nearly 200% the rate for any other treatment modality.

Dropout rates early in therapeutic community treatment are high, but similar to those across all substance abuse treatment modalities [15, 43, 23]. In his early studies, DeLeon reported completion rates from 10 to 20%, and 1-year retention was from 15 to 30%, with the highest dropout within the first 30 days. In the mid-1980s, DeLeon and psychologist Steven Schwartz reported 12-month retention rates ranging from 4 to 21% at seven therapeutic communities, with the dropout rate highest in the first 14 days and declining thereafter.

The Treatment of Adolescents and Findings

The Drug Abuse Reporting Program and Treatment Outcomes Prospective studies of the effectiveness of the therapeutic community when adolescents were treated with adults in the same programs yielded mixed but disappointing results on the reduction of substance abuse, particularly alcohol and marijuana. Positive outcomes were found on employment and criminal involvement. Retention of adolescents was similar to that found for adults, as was the time-in-program correlation with post-treatment improvement.

However, as the 1970s witnessed an explosion in adolescent drug use and a significant decrease in the average age of onset of drug dependency, calls were being made to treat adolescents separately from adults. Therapeutic communities developed adolescent day and outpatient programs, as well as residential therapeutic communities for teens only [13]. The regimens of these programs were designed to be responsive to the developmental tasks of adolescents.

Many of the programs incorporated educational programs. In the case of some of the larger residential therapeutic communities, these were at times annexes of local high schools that offered a full range of academic courses and services.

School attendance and homework took the traditional place of job functions in the therapeutic community regimen for adolescents, with job assignments relegated to after-school hours and weekends, similar to the balance of work and school responsibilities of most adolescents in the community at large [17].

Recreation was also more prominent in the therapeutic community regimens of adolescent facilities compared to those for adults, predicated on the notion that teens needed a physical outlet for their energies that otherwise would be channeled into misbehavior and that they needed to find ways of amusing themselves that did not involve the use of intoxicants.

Work with the adolescent population also necessitated working with their families. At Phoenix House, the use of multi-family therapy was pioneered with adolescent clients and their families [28]. This treatment approach capitalized on the strengths of group therapy, helping parents and other family members reduce their sense of shame and guilt with the help of similar peers, and built upon the merits of the therapeutic community by creating a sense of belonging, social support, and collective identification. Subsequently, multiple studies have demonstrated improved outcomes for clients whose families are included in the treatment process and have demonstrated support for the use group approaches for families [28].

In a RAND study by Andrew Morral et al., teens randomly assigned to a therapeutic community residential program and other types of residential settings were compared [38]. The adolescents who were in the therapeutic community program had superior outcomes on measures of drug use, criminal activity, and measures of psychological dysfunction. These findings were substantiated in a study of adolescents in six different therapeutic communities, whose members were found to have significant reductions in alcohol, marijuana, and other illicit drug use, as well as criminal and other deviant behavior [25].

The holistic therapeutic community approach for adolescents proved especially useful, with its emphasis on the broader range of developmental tasks instead of exclusive focus on drug taking, given that some drug and alcohol use and risk taking behavior is normative for young people in their late teens and early twenties. If abstinence is achieved in the months they are in the treatment setting, and gains are made in educational achievement and psychosocial development and functioning, adolescents may well reap significant and valuable therapeutic benefit, avoiding the high likelihood of intransigent addiction known to be the trajectory for youngsters who initiate substance abuse in early adolescence [17].

To the Twenty First Century

Responding to two decades of remarkable advances in our understanding of the addicted brain, therapeutic communities slowly modified the early treatment methods that were predicated upon a view of addicts as they presented in the 1950s. As is true for most diseases, it was the grossest manifestations of addiction that first came to the attention of therapeutic community workers. This reflected more than the severity of their drug involvement. Because of the illegal nature of heroin (opiate) abuse, most addicts of the 1950s were stereotyped, marginalized, and imprisoned with all kinds of other criminals. As a result, they developed the competencies necessary to survive as outsiders. They may have wished they wanted to quit, but they continued to use because they had very little, if any, other identity.

The heroin epidemic continued through the 1960s, but with the 1970s came widespread misuse of such other drugs as amphetamines, hallucinogens, and cocaine, and a new and more diverse population of drug users. They came from all social strata and had a broader range of education and economic resources.

The image of the addict as an end-stage user with concomitant social and psychological disorders began to change with the emergence of the 1970s users, predominantly white and middle class, and included numbers of college age users of hallucinogens.

While the 1960s had seen an expansion of methadone maintenance and therapeutic community treatment for heroin addiction, a new model of treatment, neither residential nor pharmacological, was developed for the drug abusers of the 1970s. The introduction of ambulatory care, labeled "outpatient drug-free" [44], swelled the ranks of behavioral healthcare professionals engaged in the treatment of drug misuse. They were quite unlike the men and women who provided most Alcoholics Anonymous and therapeutic community-based treatments, whose role was as much a commitment as a calling and who themselves suffered from the disorder, learned the lore of the model that had helped them, and presented the same with zeal and deep belief.

The outpatient drug-free community drew psychologists, social workers, and others from the helping professions. This new work force brought with it standards of practice based on the delivery of care during set hours and in discreet units of either individual counseling or group therapy. This was quite different from what was being practiced in the therapeutic community and 12-step world of full-time recovery engagement and constant involvement (albeit with sloppy boundaries). It was, however, this "professional" model that soon came to influence all of drug treatment, particularly that which was funded directly or indirectly by government.

Changing Therapeutic Community Practices

As federal and state substance abuse agencies were created in 1969 in response to President Nixon's "War on Drugs," the influence of new regulatory demands and the increased demand for practices that closely resembled hospital and medical clinics markedly changed therapeutic community practices.

Basic to the therapeutic community was the concept of clients and staff belonging to a single community in which therapy was an ongoing process, interactive dialogues were a primary aspect of community life, and counselors were fully engaged in this process, regardless of the time it took. Imposition of a strict 40-h work week in which at least 10 h was needed for paperwork (case notes, group notes, counseling notes, treatment plans, and revisions) played havoc with this concept.

Regulation and credentialization raised therapeutic community costs. The early therapeutic communities, built upon adult care paradigms, utilized a client (resident) workforce to perform all the many tasks necessary to maintain the community—food services, cleaning and repairs, auto maintenance, escort service, and administrative chores. Residents, as they rose in the hierarchy, also undertook supervisory functions. Moreover, the early therapeutic community was also predicated on a long-term care model which gave the population a substantial group of more mature members who were actualizing recovery skills in their daily lives. Regulations now barred residents from certain tasks. Since counselors now spent substantially less time with clients and there were fewer senior residents (the "elders" of the early years) to serve as role models and monitors, staff needs increased. Whereas once a ratio of one counselor for 20 or even 30 residents was sufficient, regulations now called for ratios closer to 1:15.

Funding sources responded to increased costs with demands for shorter lengths of stay, and therapeutic community programs attempted to control expenditures by creating economies of scale, developing treatment settings capable of housing a client population in excess of—often far in excess of—150 residents. While these settings were often able to reduce fixed costs for food and building supplies, they created issues of clinical management that also limited the time and quality of client interactions. One must consider Bill White's admonition regarding threats to viability: "The twin threats of professionalism (preoccupation with power or status) and commercialism (preoccupation with money or property) have often proved fatal to advocacy movements" [49].

The nature of therapeutic community treatment also reflected a changing treatment population. This was due, in part, to the criminal justice system's widespread acceptance of treatment as an alternative to incarceration for most nonviolent drug law offenders. The courts, probation, and parole authorities became, for most therapeutic community programs in the United States, a major if not the sole source of referrals.

The therapeutic community client base had, over the decades, come to display a rising level of pathology as seen in multi-generational use of drugs, with new court referrals often reflecting three or four generations of family use. These clients were quite different from addicts of the 1950s, who were most often adults, usually the first in their families to use drugs, and who accepted the view that something was wrong with them because of their drug use. This view eroded in the 1980s as a growing number of addicts came to reject the social view of drug-taking as deviant. They considered their drug-taking normative and the laws as deviant and blindly prejudiced against them. Unlike the burned-out residents of the past, who arrived exhausted by their jail experiences and addiction lifestyle, these court referrals arrived resenting their mandated treatment. Rather than viewing treatment staff as helpers who cared deeply about them, they tended to view program staff as "jailers".

Added to the forces reshaping therapeutic community treatment was the competition for clients. The days when therapeutic communities were "the only game in town" and clients

needed to demonstrate their commitment to be admitted were long gone. Since few addicts were now eager to submit to the therapeutic community's demanding regimen, the programs became increasingly reliant on court referrals, who lacked any real choice.

At this point a further challenge emerged from academics and federal researchers who challenged therapeutic community claims of effectiveness. The landmark, long-term, follow-up studies of George DeLeon and others that had demonstrated the pivotal role of time in program were faulted for lacking random assignment and the control groups that make up the gold standard of experimental design. These critical voices reinforced a jaundiced view of therapeutic communities taken by a number of academically trained professionals entering the field, who not only challenged the utility of the therapeutic community, but raised as an issue the potential harmfulness of therapeutic community practices [37]. This came at a time when many researchers, particularly those studying the treatment of other life-threatening disorders, were adopting new and more rigorous experimental design [39]. The call for more credible studies and more evidence-supported practices extended throughout the field of medicine and behavioral health.

Buffeted by these forces therapeutic community credibility began to wane. Some therapeutic communities faced these doubts by digging in their heels and becoming more rigid and orthodox. Others began to modify methods and incorporate new clinical practices into the therapeutic community regimen. However, the stereotype of shame-based, attack therapy which humiliated its members, screamed and yelled at them, and broke them down to build them back up was kept alive by those who questioned the validity of the therapeutic communities. Although the overwhelming majority of therapeutic communities had long ago abandoned such primitive practices, the field was demoralized in the late 1980s by its failure to shake off the stereotypes.

In 1992, however, a new and more favorable light was cast on therapeutic communities with the publication of studies that documented the effectiveness of therapeutic communities in prison settings to reduce recidivism and/or increase the length of time between release and re-incarceration. New York's Stay'n Out program led the way [47]. Then, the prison therapeutic community was tried in Delaware with similar promising outcomes. Evaluations of the Key/Crest program found that significantly more of the clients who completed the in-prison program and the transitional aftercare program remained arrest free during the follow-up (55%) than an untreated comparison group (29%) [35]. Those who also had received outpatient aftercare following the transitional residential treatment had the best outcomes, with 69% being arrest free after 3 years. Results for relapse to drug use were similar, reported for 17% of those who completed the in-prison therapeutic community only, 27% who had both the in-prison treatment and transitional residential treatment, and 35% who also had outpatient aftercare remaining drug free during the follow-up, compared to only 5% of the comparison group [35]. Five-year outcomes were similar [24]. Recidivism rates were significantly lower for those who went through both Key and Crest or through Crest. Participation in the in-prison therapeutic community treatment alone did not appear to significantly improve 5-year outcomes, although it was associated with higher rates of aftercare use.

The federal government's Substance Abuse and Mental Health Services Administration subsequently sponsored a treatment project in two of California's prisons, and, by 1992, Texas had adopted prison therapeutic communities as the state's primary means of halting an ever-growing demand for prison construction [31]. California followed Texas and, by 2000, close to 8,500 therapeutic community treatment slots existed in California's prisons. In each state, outcome data supported the financial investment in prison-based therapeutic community as a means of reducing rates of recidivism and extending the length of time former inmates remained out of prison [30].

In the Amity program at the R.J. Donovan prison in California, follow-up studies found 3

years post-parole that only 27% of those who received both in-prison and aftercare treatment were reincarcerated during the follow-up interval, compared to 75% of those in the comparison group, 79% of those who completed only the in-prison treatment, and 82% of those who were in-prison treatment dropouts [46].

Evaluation of the Kyle/New Vision program in Texas demonstrated that completion of 3 months of residential aftercare in a transitional therapeutic community followed by up to another year of supervised outpatient aftercare was the strongest predictor of remaining arrest free for 2 years following release from prison, and aftercare completion was strongly associated with parolee satisfaction with these programs [22]. Three-year follow-up studies showed that in-prison treatment followed by aftercare was most effective for high-risk, high-need offenders [34].

The research showed that positive outcomes would only be sustained if prison therapeutic community treatment was followed by transitional care in the community. Therapeutic communities have been shown to be effective within a prison environment and significantly reduce recidivism. Positive outcomes improve significantly when in-custody treatment is followed by community-based treatment [31, 35, 46].

Also gaining traction in the 1990s were drug courts [8], offering coerced and highly monitored treatment in the community in lieu of prison or jail. As the nation increasingly came to realize that the treatment of addicted offenders—whether in prison or mandated by the courts—was reducing the social cost of crime and promoting health [34], the therapeutic community approach was re-evaluated and its reputation substantially restored [45].

Further studies of prison therapeutic communities, showing substantial variations in outcome, highlighted the need for therapeutic community clinicians to better understand aspects of criminality [33]. Most treatment providers had then presumed that criminal acts were a result of addiction, although, for 30–50% of this population, criminal activity preceded drug misuse. What was becoming clear was the need to recognize and respond to individual client differences [29].

This perception was widespread—and not only in prison therapeutic communities. Programs throughout the country recognized the need for differentiated care and turned to a variety of validated assessment instruments as the basis for differential diagnoses and individual treatment plans. Disorders were becoming more recognized, particularly depression and anxiety, and in women the presence of trauma and post-traumatic stress disorder. Such data demonstrated even further the need for a mix of methods, approaches, intensities, and time in treatment [52]. Increasingly therapeutic communities both in prison and in the community have come to recognize the need for and benefit of adopting other evidence-based approaches, although the resulting changes have been met with varying degrees of enthusiasm, readiness, and workforce willingness.

The therapeutic community has undergone an extraordinary evolution over the years. Yet some troubling issues are being resolved only now, in this first decade of the twenty first century. Many have long been aware that the therapeutic community treatment model was, in large measure, based on male paradigms. But only with today's greater gender sensitivities have those in the field finally come to realize that, because of the staggering amount of trauma visited upon women, some traditional therapeutic community practices (particularly the mixed gender encounter groups) [37] can have profound iatrogenic effects on women [10].

What the therapeutic community has proven during its evolution is that a system once rigid and orthodox is capable of extraordinary flexibility and adaptability. This can be seen in the use of medications, lengths of stay, settings (residential or outpatient), trans-disciplinary staffs, and the adaption of evidence-based practices and validated assessment instruments. But what makes the therapeutic community unique is not simply the power of the community as a treatment force but the uses to which this force is put.

When therapeutic community practitioners speak of treating "the whole person" they have

in mind all the dimensions of the individual—the emotional and psychological, the physical, the social and vocational, as well as the intellectual, ethical, and spiritual. For each of these dimensions, there are discreet goals and means of employing the elements of mutual help to identify strengths, remedy deficits, build competencies, and foster the capacity for continued growth. It is an ultimately enabling mechanism, for therapeutic community treatment is not an end in itself. It is a bridge to recovery and a life path that makes recovery manageable, sustainable, and, yes, enjoyable too.

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Substance Use-Focused Self-Help Groups: Processes and Outcomes

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Contents

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Introduction

Twelve-step self-help groups, often also called mutual help or support groups, are an important component of the system of informal care for individuals with substance use disorders. Individuals make more visits to self-help groups for help with their own or family members' substance use and psychiatric problems than to all mental health professionals combined. About 9% of adults in the United States have been to an Alcoholics Anonymous meeting at some time in their life, and almost 80% of adults who seek help for alcohol dependence participate in Alcoholics Anonymous [14]. Moreover, many substance use disorder treatment service providers have adopted 12-step principles in treatment, and the majority of them refer clients to self-help groups.

Self-help groups offer a forum wherein members can express their feelings in a safe, structured setting, improve communication and

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_46,

interpersonal skills, better understand the reasons for their substance abuse, learn self-control, and identify new activities and life goals. Accordingly, the American Psychiatric Association [1] and several other professional and health care organizations recommend referrals to self-help groups as an adjunct to the treatment of individuals with substance use disorders.

Major Types of Substance Use-Focused Self-Help Groups

The majority of the literature on self-help groups that address substance abuse focuses on traditional 12-step groups. The most prevalent traditional 12-step groups are Alcoholics Anonymous, Narcotics Anonymous, and Cocaine Anonymous; other important substance-use-focused self-help groups include Secular Organizations for Sobriety, Self-Management and Recovery Training, and Moderation Management. These groups are briefly described next; Women for Sobriety and Double Trouble in Recovery are described in the sections on women and individuals with substance use and psychiatric disorders.

Alcoholics Anonymous

Alcoholics Anonymous is a fellowship whose primary purpose is to help individuals with alcohol-related problems maintain sobriety. It is structured around the Twelve Steps (e.g., admission of powerlessness over alcohol, belief in a higher power) and Twelve Traditions (e.g., an emphasis on common welfare and recognition that personal recovery depends on Alcoholics Anonymous unity). (See www.aa.org/pdf/products/p-42_abriefguidetoaa.pdf for the Twelve Steps and Twelve Traditions.) Other key aspects of Alcoholics Anonymous involve open and closed group meetings and literature that describes Alcoholics Anonymous, shares its tenets, and provides guidance to recovering individuals. Estimated Alcoholics Anonymous membership is about 1,200,000 members and 52,000 groups in the United States and more than 2,000,000 members and 105,000 groups worldwide; about 35% of the members are women (see www.aa.org).

Narcotics Anonymous and Cocaine Anonymous

Narcotics Anonymous is a fellowship of recovering individuals with drug use disorders. Narcotics Anonymous grew out of Alcoholics Anonymous and is similar to Alcoholics Anonymous in that it provides a structured support network in which members share information about overcoming addiction and living productive, drug-free lives through adherence to the Twelve Steps and Twelve Traditions. Narcotics Anonymous encourages complete abstinence from all drugs, including alcohol, but, like Alcoholics Anonymous, accepts the use of prescribed medications for psychiatric and medical disorders. Narcotics Anonymous has about 44,000 weekly meetings in more than 120 countries worldwide; about 70% of the members are Caucasian and 45% are women (see www.na.org).

Cocaine Anonymous is a fellowship open to individuals who want to stop using cocaine, including "crack" cocaine and other mind-altering substances. Cocaine Anonymous' program of recovery was adapted from Alcoholics Anonymous and, like Alcoholics Anonymous, uses the 12-step recovery method. There are an estimated 30,000 members and more than 2,000 groups (see www.ca.org).

Secular Organizations for Sobriety

Secular Organizations for Sobriety provides support for individuals who seek to achieve and maintain sobriety, a forum to express

thoughts and feelings about recovery, and a non-religious or secular approach that does not depend on the Twelve Steps or Twelve Traditions. Members are expected to acknowledge their addiction and take responsibility for achieving and maintaining sobriety. Members tend to be well-educated individuals who have been in professional treatment and have attended and continue to attend Alcoholics Anonymous. The majority of the members are men (see www.secularsobriety.org).

Self-Management and Recovery Training

Self-Management and Recovery Training espouses a rational treatment orientation and focuses on teaching individuals new coping skills and more logical ways of thinking and acting. It emphasizes practical methods of changing maladaptive behavior rather than a 12-step or spiritual approach. Self-Management and Recovery Training's 4-point program includes: (1) building and maintaining motivation to abstain, (2) learning how to cope with urges, (3) managing thoughts, feelings, and behavior, and (4) balancing momentary and enduring satisfactions (see www.smartrecovery.org).

Moderation Management

Moderation Management construes problem drinking as a habit that can be controlled by applying principles of cognitive-behavioral treatment in the context of a network of supportive peers. Moderation Management provides an alternative to the spiritually oriented disease model of traditional 12-step self-help groups and to an abstinence goal; it allows members a choice of abstinence or moderate drinking goals. Moderation Management members tend to emphasize the value of self-control, insight, personal responsibility and choice, and rationality. Most Moderation Management members are Caucasian; they tend to be married, college educated, and employed, and more than half are women (see www.moderation.com).

Participation in Self-Help Groups and Substance Use Outcomes

Individuals with substance use disorders who participate in 12-step self-help groups, especially Alcoholics Anonymous and Narcotics Anonymous tend to experience better alcohol and drug use outcomes than do individuals who do not participate in these groups. The most common index of participation has been attendance at group meetings; however, recent attention has focused on aspects of involvement, such as reading 12-step literature, working the steps, obtaining a sponsor, and doing service work.

Attendance and Substance Use Outcomes

People who attend Alcoholics Anonymous in the first few weeks or months after treatment tend to experience good short-term substance use outcomes. For example, Project MATCH was a large clinical trial that compared 12-step facilitation, cognitive-behavioral, and motivational enhancement treatment for individuals with alcohol use disorders. Participants who attended Alcoholics Anonymous more often in each of the 3-month intervals after treatment were more likely to maintain abstinence from alcohol in that interval. In addition, more frequent Alcoholics Anonymous attendance in the first 3 months after treatment was related to a higher likelihood of abstinence and fewer alcohol-related consequences in the subsequent 3 months; these findings held for participants in each of the three types of treatment [59].

Comparable findings were obtained in two projects conducted among individuals with substance use disorders who were treated in residential programs. Among individuals in hospital-based programs, those who participated in 12-step self-help groups in the 3 months prior to a 1-year follow-up were more likely to be abstinent, in remission, and free of dependence symptoms. Clients who attended more group meetings experienced better outcomes than did clients who attended fewer meetings [48]. Among individuals in community-based programs, those who attended more 12-step self-help group meetings in the 3 months prior to a 1-year follow-up were more likely to be abstinent at follow-up [43].

Individuals who continue to attend self-help groups for a longer interval are more likely to maintain abstinence than are individuals who stop attending. In a 5-year follow-up of individuals with alcohol use disorders who entered treatment, Kaskutas and colleagues [23] identified four types of Alcoholics Anonymous careers: (1) a low Alcoholics Anonymous group mainly attended Alcoholics Anonymous in the year after treatment entry; (2 and 3) medium and high Alcoholics Anonymous groups had stable attendance for 3 years after treatment entry (about 60 meetings per year for the medium group and more than 200 meetings per year for the high group), and (4) a declining Alcoholics Anonymous group attended an average of almost 200 meetings at first but dropped to about six meetings by year 5. Consistent with these attendance patterns, at year 5, the low Alcoholics Anonymous group had a 43% rate of 30-day abstinence, compared with 73% for the medium group, 79% for the high group, and 61% for the declining group.

Another prospective study of individuals with alcohol use disorders showed that a longer duration of attendance in Alcoholics Anonymous in the first year after help-seeking was associated with a higher likelihood of 1-year, 8-year, and 16-year abstinence. These findings were based on better outcomes for individuals who attended Alcoholics Anonymous for 17 weeks or more. Individuals who attended Alcoholics Anonymous for 1–16 weeks had no better outcomes than non-attendees did. Moreover, after controlling for the duration of Alcoholics Anonymous attendance in year 1, the duration of attendance in years 2–3 and 4–8 was related to a higher likelihood of 16-year abstinence [39, 41].

Involvement and Substance Use Outcomes

Attendance is an important indicator of participation, but it may not adequately reflect an individual's level of group involvement, as shown by such indices as acceptance of 12-step ideology, having a spiritual awakening, giving Alcoholics Anonymous talks, socializing with Alcoholics Anonymous members, becoming a sponsor, and self-identification as a group member. These aspects of group involvement may be associated with substance use outcomes independent of the duration and frequency of attendance per se.

In support of this idea, individuals who held stronger beliefs in 12-step ideology were more likely to be abstinent independent of their 12-step group attendance [18]. In the National Institute on Drug Abuse Collaborative Cocaine Treatment Study, individuals who increased their 12-step involvement in the first 3 months of treatment had better cocaine and other drug use outcomes in the next 3 months. Individuals who regularly engaged in 12-step activities but attended meetings inconsistently had better drug use outcomes than did individuals who attended consistently but did not regularly engage in 12-step activities [62].

Caldwell and Cutter [8] identified a group of individuals who showed substantial attendance at meetings but mixed involvement in Alcoholics Anonymous practices. These individuals were likely to have a sponsor, admitted powerlessness, and worked the steps; however, they were less enthusiastic about the concept of a "higher power" and Alcoholics Anonymous literature and were less involved with other Alcoholics Anonymous members. They also had high relapse rates. Individuals who attend

self-help groups but are unable to embrace key aspects of the program appear to be less likely to benefit from it.

Participation and Outcomes Other than Substance Use

Participation in self-help groups is associated primarily with better substance use outcomes; however, it has also been linked with more self-efficacy and spirituality and less distress, better social support and functioning, and enhanced coping skills and community participation.

Participation in self-help groups has been associated with stronger self-efficacy for abstinence, less distress and depression, and fewer psychiatric symptoms [39, 41, 43, 48]. Compared with individuals who had not worked all 12 steps, those who had worked all 12 steps had more self-esteem and social confidence and were more optimistic and trusting [53]. In addition, some studies have shown an association between participation in self-help groups and higher levels of spirituality and perceived meaning of life [30].

There is a relatively robust relationship between self-help group involvement and better social support and functioning. For example, individuals with alcohol use disorders who attended more Alcoholics Anonymous meetings over a 3-year interval had more friend-related support; individuals who attended Alcoholics Anonymous longer over 1-year and 8-year intervals also reported more support from friends [54]. Similarly, individuals who attended Narcotics Anonymous once a week or more had more friends than did individuals who did not attend Narcotics Anonymous or attended infrequently [13].

In a review of this area, Groh and colleagues [19] concluded that more involvement in Alcoholics Anonymous was associated with larger friendship networks, primarily due to acquiring an Alcoholics Anonymous sponsor and the development of new 12-step friends. Involvement in Alcoholics Anonymous was also linked to more specific support for abstinence from friends and to higher quality friendships and more general support. Importantly, the strength of affiliation among Alcoholics Anonymous members may be comparable to or even stronger than feelings for close friends and family members.

Affiliation with 12-step self-help groups tends to promote more reliance on approach coping and behaviorally oriented substance use coping processes. For example, Snow and colleagues [52] found that individuals who were more involved in Alcoholics Anonymous were more likely to rely on coping responses aimed toward reducing substance use, such as spending time with non-drinking friends, talking to someone about their drinking problems, rewarding themselves for trying to stop drinking, and becoming more aware of social efforts to help people stop drinking. In addition, individuals who attend Alcoholics Anonymous for longer intervals tend to rely more on approach coping and less on avoidance coping [54].

There has been speculation that the admonition against public self-identification as a member of Alcoholics Anonymous or Narcotics Anonymous may discourage participation in community activities. However, many long-term Alcoholics Anonymous/Narcotics Anonymous members are active in established neighborhood organizations and civic groups, such as homeless coalitions and parent-teacher associations [29]. Similarly, Alcoholics Anonymous participation has been associated with community helping activities, such as mentoring youngsters or doing volunteer work among alcoholic individuals in recovery [65].

Connections Between Self-Help Groups and Treatment

Many individuals who enter professional treatment also participate in self-help groups; in fact, 50–80% of individuals in substance use disorder treatment also participate in self-help groups, and 60–80% of Alcoholics Anonymous

members have participated in treatment [34]. These two sources of help could contribute independently to better outcomes, or they could either bolster or detract from each other.

Participation in Treatment and Self-Help Groups

In general, individuals who enter treatment are more likely to participate in self-help groups than are individuals who do not enter treatment. Compared with help-seeking individuals who entered only Alcoholics Anonymous, individuals who entered both treatment and Alcoholics Anonymous participated as much or more in Alcoholics Anonymous in the subsequent 15 years. Individuals who stayed in treatment longer in the first year after seeking help subsequently showed more sustained participation in Alcoholics Anonymous. More extended treatment later in individuals' help-seeking careers was not associated with subsequent participation in Alcoholics Anonymous, which suggests that treatment providers' referrals to Alcoholics Anonymous have more influence in the context of an initial treatment episode [40].

Moreover, individuals who participate in self-help groups are more likely to enter and complete treatment. Clients with drug use disorders who attended self-help groups weekly before treatment stayed in treatment longer and were more likely to complete treatment. In turn, clients who stayed in treatment longer subsequently were more likely to attend Alcoholics Anonymous at least weekly [17]. In a study of individuals with alcohol use disorders, those who participated in both treatment and Alcoholics Anonymous attended more treatment sessions and more Alcoholics Anonymous meetings than did those who participated only in treatment or only in Alcoholics Anonymous [57].

Several studies have shown a more specific link, in that individuals who participate in 12-step treatment, which introduces clients to 12-step philosophy and encourages them to join a group, are more likely to affiliate with self-help groups than are individuals who participate in treatment that is not oriented toward 12-step principles. In Project MATCH, participants in 12-step facilitation treatment were more likely to attend and affiliate with Alcoholics Anonymous than were those in cognitive-behavioral treatment or motivational enhancement treatment [59]. Similarly, in another multisite study, participants in 12-step facilitation programs affiliated more with 12-step self-help groups after treatment than did those who were treated in cognitive-behavioral treatment programs [20].

A supportive and spiritually oriented treatment environment can enhance participation in 12-step activities. In this vein, clients in more supportive treatment environments increased more in 12-step involvement during treatment; that is, they were more likely to acquire a sponsor and 12-step friends and to read 12-step literature. Moreover, when clients who had a high risk of dropping out of self-help groups after treatment were treated in a more supportive environment, their risk of dropout declined [27].

These findings suggest that referral and alliance processes contribute to an association between participation in treatment and subsequent participation in self-help groups. A positive treatment alliance may enhance clients' motivation for recovery and underlie the impact of counselors' recommendations to attend self-help groups. Treatment that highlights the value of 12-step self-help groups in recovery encourages more self-help group involvement than treatment that does not highlight this value.

Treatment, Self-Help Groups, and Substance Use Outcomes

Participation in treatment and participation in self-help groups have independent effects on substance use outcomes that tend to augment each other. In this vein, individuals who participated more intensively in self-help groups after

treatment experienced better substance use outcomes even after controlling for the effects of treatment completion and continuing care [16]. This finding has been obtained in follow-ups of individuals discharged from hospital-based and community-based residential care [43, 48].

More importantly, participation in each of these two modalities of help can independently contribute to better outcomes. In a nationwide sample of alcohol-dependent individuals, those who participated in 12-step self-help groups in addition to professional treatment were more than twice as likely to achieve an abstinent recovery as were individuals who obtained professional treatment alone [14]. Similarly, among clients with drug use disorders, longer episodes of treatment and weekly or more frequent self-help group attendance during and after treatment were each independently associated with 6-month abstinence [17].

Participation in self-help groups may compensate for the lack of services provided in treatment. Among dually diagnosed participants in residential programs, the benefits of 12-step self-help group attendance depended on the intensity of treatment services. More 12-step self-help group attendance during treatment was associated with better alcohol and drug outcomes at discharge only among individuals treated in low-service-intensity programs. More 12-step self-help group attendance after discharge from treatment was associated with better psychiatric and family/social functioning at 1 year only among individuals receiving low-service-intensity care [56].

Treatment Orientation and Self-Help Group Outcomes

Twelve-step facilitation treatment may enhance the effectiveness of 12-step self-help groups. Humphreys and colleagues [20] identified a stronger relationship between 12-step self-help group participation and better substance use outcomes among clients from 12-step facilitation treatment programs than among those from cognitive-behavioral treatment or eclectic programs. Post-treatment self-help group involvement partially explained the higher rates of abstinence among individuals from 12-step programs than among those from cognitive-behavioral treatment programs.

In Project MATCH, clients who had networks supportive of drinking at baseline and were assigned to 12-step facilitation treatment had better drinking outcomes at a 3-year follow-up than comparable clients in cognitive-behavioral treatment or motivational enhancement treatment. Treatment assignment did not affect drinking outcomes for clients with networks unsupportive of drinking. In part, this matching effect occurred because 12-step facilitation clients were more involved in Alcoholics Anonymous after treatment than were clients in either cognitive-behavioral treatment or motivational enhancement, and because more Alcoholics Anonymous involvement led to a higher percentage of abstinent days and fewer drinks per drinking day [33].

Essentially comparable findings were obtained in the National Institute on Drug Abuse Collaborative Cocaine Treatment study. Participants in individual drug counseling, which emphasized 12-step principles, were more likely to adopt 12-step beliefs and engage in 12-step behaviors than were those in supportive-expressive therapy, cognitive therapy, or group drug counseling, which placed less emphasis on 12-step ideology. These individuals also experienced better end-of-treatment substance use outcomes; changes in participants' 12-step beliefs and behaviors explained part of this effect [12].

Personal Factors, Participation, and Self-Help Group Outcomes

In an attempt to identify individuals who may be especially well-suited for participation in self-help groups, researchers have considered

a range of personal factors, including severity and impairment related to substance use, and disease model beliefs and religious/spiritual orientation. Studies also have examined the suitability of self-help groups for individuals with substance use and psychiatric disorders, women, older adults, and members of racial and ethnic minority groups.

Severity and Impairment

In general, individuals who are heavier substance users, are more dependent on substances, have more substance-related problems, and lack control over substance use are more likely to affiliate with self-help groups. More impaired clients are more likely to continue self-help group attendance and less likely to drop out after treatment [10]. Compared with Type A alcoholic individuals in 12-step treatment, Type B alcoholics, who have more severe alcohol-related problems, were more likely to attend Alcoholics Anonymous in the 12 months after treatment. Moreover, the less impaired Type A individuals were more than twice as likely to stop attending Alcoholics Anonymous after treatment [58].

Compared with individuals with less severe substance use problems, those with more severe problems may benefit more from self-help group involvement. Morgenstern and colleagues [45] found that individuals with more severe substance use and psychosocial problems who had high levels of self-help group affiliation had better 6-month substance use outcomes; outcomes were poor when group affiliation was low. For those who had less severe problems, levels of self-help group affiliation were not related to outcomes.

Disease Model Beliefs and Religious/Spiritual Orientation

Individuals whose beliefs are more consonant with the 12-step orientation are more likely to affiliate with 12-step self-help groups. More specifically, people who believe in the disease model of substance use, have an abstinence goal, and see themselves as alcoholics or addicts tend to become more involved in self-help groups after discharge from acute treatment and are less likely to drop out [27].

Many individuals see a positive role for an emphasis on spirituality in self-help groups and focus on spirituality as a source of: (a) personal strength and self-protection (e.g., help in maintaining abstinence, reducing craving, and facing mortality) and (b) altruism and protection of others (e.g., not sharing drug paraphernalia or engaging in unsafe sexual practices) [2]. Individuals with stronger religious beliefs are more likely to attend and become involved in 12-step self-help groups during and after treatment. In contrast, less religious individuals, including those who profess atheistic and agnostic beliefs, are less likely to attend and more likely to drop out of 12-step self-help groups. Nevertheless, when they do become involved in self-help groups, less religious individuals appear to obtain as much or more benefit from them as more religious individuals do [24, 27].

More generally, individuals whose religious/spiritual beliefs better match those of their primary self-help group tend to participate more in that group. More religious individuals are more likely to participate in 12-step than in other types of self-help groups; in contrast, religiosity does not seem to be associated with participation in Self-Management and Recovery Training but is associated with less participation in Secular Organizations for Sobriety. Matching an individual's spiritual/religious beliefs to those of a self-help group may increase the individual's participation in the group and perhaps indirectly increase the likelihood of continued sobriety [5].

Individuals who profess a stronger religious/spiritual orientation may be better able to accept their craving and, therefore, become more involved in 12-step self-help groups. Consistent with this view, clients who professed stronger spiritual/religious beliefs at intake to treatment improved more in acceptance-based responding between baseline and a 1-year follow-up.

These individuals became more aware of and able to acknowledge internal experiences, such as cravings and distress, and were able to rely more on adaptive coping responses to confront and manage these experiences. In turn, enhanced acceptance-based responding at a 1-year follow-up predicted increased subsequent self-help group involvement. Thus, together with treatment, spirituality/religiosity may promote self-regulation skills that contribute to 12-step self-help group affiliation [9].

Individuals with Substance Use and Psychiatric Disorders

A high proportion of individuals with substance use disorders have co-occurring psychiatric disorders. With the exception of clients with psychotic disorders, these dually diagnosed individuals are as likely to attend 12-step self-help groups as are those with only substance use disorders. In general, individuals with dual diagnoses appear to benefit from substance-use-focused 12-step self-help groups as much as do those with only substance use disorders [43, 48].

A few studies have focused on participants with specific psychiatric disorders, especially post-traumatic stress disorder and major depression. Individuals with substance use disorders and post-traumatic stress disorder participated as much in 12-step self-help groups after treatment as did those with only substance use disorders. The dually diagnosed individuals who participated more in self-help groups were more likely to be abstinent and experienced less distress; they also were more likely to maintain stable remission over a 2-year follow-up [49].

The situation may be different for clients who have substance use disorders and co-occurring major depression. Compared with individuals with only substance use disorders, those who also had major depression were less likely to become involved in 12-step self-help groups after treatment. At a 2-year follow-up, the association between self-help group involvement and abstinence was stronger for clients who had only substance use disorders than for those who also had major depression. These participants did not benefit as much from contact with a sponsor, 12-step friends, reading 12-step literature, and working the steps. Depressed individuals may have interpersonal problems that make it harder to develop friendships and to acquire and relate to a sponsor; thus, they may need more support and guidance to become involved in and benefit from 12-step self-help groups [26].

Traditional 12-step self-help groups may have some limitations for dually diagnosed individuals, who may be less able to bond with other members who do not share the experiences associated with psychiatric problems. Some group members may have ambivalent or negative attitudes about the use of medications to prevent relapse or alter mood. In addition, some dually diagnosed individuals may be alienated by 12-step philosophy, the emphasis on denial, and an apparent lack of empathy for individuals with psychiatric problems.

Given these issues, some dually diagnosed individuals may do better in dual-focused 12-step self-help groups, such as Double Trouble in Recovery. Double Trouble in Recovery is a 12-step fellowship adapted from the 12-step method of Alcoholics Anonymous; it is designed to meet the needs of individuals who have both substance use and psychiatric disorders. Double Trouble in Recovery specifically addresses the problems and benefits associated with psychiatric medications. It has amended steps 1 and 12 of the 12 steps to include mental disorders so that, for example, step 1 is: "We admitted we were powerless over mental disorders and substance abuse—that our lives had become unmanageable" (see www.doubletroubleinrecovery.org).

Individuals who experience more psychiatric symptoms and more severe consequences of drug use are more likely to maintain attendance in Double Trouble in Recovery. With respect to outcomes, Double Trouble in Recovery members who engaged more in reciprocal learning and assuming a helping role were more likely to be abstinent at a 1-year follow-up. A 2-year follow-up showed that individuals who affiliated

more strongly with Double Trouble in Recovery improved more in self-efficacy for recovery, leisure time activities, feelings of well-being, and social relationships [35, 37].

In a subsequent study, a cohort of dually diagnosed individuals who did not have Double Trouble in Recovery available during treatment was compared with a cohort exposed to it after Double Trouble in Recovery meetings were instituted in the treatment program. Compared with the pre-Double Trouble in Recovery cohort, the post-Double Trouble in Recovery cohort had significantly fewer days of alcohol and drug use, more frequently attended traditional 12-step group meetings outside the program, and adhered more to their psychiatric medications at a 6-month follow-up [36].

Women

Women with alcohol or drug use disorders are at least as likely as men to attend and affiliate with self-help groups. Compared with men, women may be more likely to read Alcoholics Anonymous literature, call an Alcoholics Anonymous member for help, and experience a spiritual awakening. In a study of individuals with alcohol use disorders, women were more likely than men to attend Alcoholics Anonymous and went to more Alcoholics Anonymous meetings in the first year after initiating help-seeking. More extended participation in Alcoholics Anonymous was associated with a higher likelihood of 1-year remission for both women and men; however, the positive association between a longer duration of Alcoholics Anonymous attendance and stable remission was stronger for women [42, 55].

Compared with men, women may be more in tune with 12-step philosophy, which involves acceptance of powerlessness over the abused substance and dependence on a higher power to attain sobriety. Self-help groups are non-hierarchical and non-authoritarian and foster recovery in a relational, mutually enhancing, and safe context, which may especially appeal to women. In addition, compared with men, women may be more comfortable in self-help groups such as Alcoholics Anonymous because they are more interdependent with other people, more likely to gain self-esteem from developing and maintaining close relationships, and more at ease with emotional self-disclosure [51].

Even though many women attend and benefit from Alcoholics Anonymous or Narcotics Anonymous, the emphasis in these groups on powerlessness, humility, and surrender alienates some women, who express discomfort with face-to-face self-disclosure in group meetings populated mostly by men. Alcoholics Anonymous may be especially problematic for women who drink for reasons associated with sexuality and gender roles. Many women report feeling that they do not fit in at Alcoholics Anonymous, and that they find it to be too negative, dislike the primary focus on the past, and feel that interchanges in Alcoholics Anonymous are dominated primarily by men.

These issues led to the development of Women for Sobriety, which provides an alternative for women who prefer an emphasis on improving self-esteem, independence, and personal responsibility rather than powerlessness, humility, and surrender. Women for Sobriety shares Alcoholics Anonymous' focus on meditation and spirituality but espouses the idea that sobriety is dependent on taking personal responsibility for one's behavior rather than on a higher power. Women for Sobriety seems to be especially attractive to well-educated, middle-aged, and middle- and upper-class women, many of whom, nevertheless, continue to attend Alcoholics Anonymous (see www.womenforsobriety.org).

In contrast to Alcoholics Anonymous, Women for Sobriety is based on the idea that women need a positive program that reinforces optimistic thinking about their abilities and independence, reduces their guilt, and enhances their coping skills. Many women report that they attend Women for Sobriety for support and nurturance, a safe environment, sharing about women's issues, and the positive emphasis on self-esteem. In this respect, there is an association between longer membership in Women for Sobriety and higher self-esteem [22].

Older Adults

Late-middle-aged and older adults participate in and benefit from 12-step self-help groups. In two studies, older clients (55+ years of age) with substance use disorders were matched with younger (aged 21–39) and middle-aged (aged 40–59) clients on the basis of race, education, marital status, and dual diagnosis status. These three groups of participants attended a comparable number of self-help group meetings during residential treatment and were equally likely to attend self-help groups in the first 2 years after treatment and to have a sponsor. Overall, individuals who attended more group meetings and those who obtained a sponsor in the first year experienced better 1-year alcohol and psychological distress outcomes. Participants who attended more meetings and had a sponsor in the second year reported less alcohol consumption at a 5-year follow-up. The three age groups did not differ in the associations between 12-step self-help group attendance and these outcomes [32].

In a similar study of clients in community residential care, the three age-matched groups showed comparable self-help group attendance during treatment and in the year after entering treatment. A comparable percentage had a sponsor. Overall, clients who attended more self-help group meetings and those who had a sponsor a year after entering treatment had better alcohol-related and psychological distress outcomes at 1-year and 4-year follow-ups. Again, the three age groups did not differ in the associations between 12-step self-help group involvement and these outcomes [31].

Race and Ethnicity

Compared with Caucasian clients, African-American clients may be more likely to attend self-help groups as part of treatment and to increase their affiliation during treatment; in addition, they appear to be less likely to drop out of self-help groups after treatment [28]. Certain characteristics of 12-step self-help groups may especially appeal to African-American clients, including the fact that meetings are widely available and open to anyone, have a strong social and spiritual component, and are free of charge. African-American clients seem to be more likely to identify as Alcoholics Anonymous members, experience a spiritual awakening in Alcoholics Anonymous, and do service at Alcoholics Anonymous meetings. In contrast, Caucasian clients are more likely to read 12-step literature and have a sponsor [25, 44].

In order to meet their unique recovery needs, African-Americans appear to integrate cultural factors and a unique language and perspective in the process of affiliation with Alcoholics Anonymous. According to Durant [15], African-Americans are more likely to associate their problems with racism and economic disadvantage than with alcohol abuse; they are less likely to accept the disease concept of alcoholism. Nevertheless, they are able to contrast the negative aspects of drinking with the positive aspects of abstinence, to respond to modeling and support from mentors and sponsors, to modify the moral aspects of Alcoholics Anonymous to meet their spiritual needs, and to adapt the Alcoholics Anonymous world view to better fit their racial and cultural background.

Compared with non-Hispanic white individuals, Hispanic individuals may be less likely to attend Alcoholics Anonymous after treatment, perhaps because they tend to turn to their existing support system. However, attendance at Alcoholics Anonymous appears to be similarly associated with decreased alcohol consumption among both Hispanics and non-Hispanic whites [4].

In Project MATCH, Hispanic individuals attended Alcoholics Anonymous less often after 12-step treatment than non-Hispanic white participants did. Nevertheless, as judged by self-identification as an Alcoholics Anonymous member, having an Alcoholics Anonymous sponsor, experiencing a spiritual awakening, and celebrating an Alcoholics Anonymous birthday, they were as committed to Alcoholics Anonymous as were non-Hispanic whites. Thus,

Hispanics' lower Alcoholics Anonymous attendance does not necessarily mean that they are less favorably inclined toward Alcoholics Anonymous. However, Hispanic clients who were more involved in specific Alcoholics Anonymous practices were not more likely to achieve abstinence [3].

Active Ingredients of Self-Help Groups

The effectiveness of self-help groups in curtailing substance use is based largely on four key ingredients: (1) abstinence-specific and general support that emphasizes the value of identification with abstinence-oriented role models and strong bonds with family, friends, work, and religion, (2) the goal direction and structure of a consistent belief system that espouses a substance-free lifestyle, (3) involvement in rewarding activities that do not involve substance use, and (4) an emphasis on bolstering members' self-efficacy and coping skills and helping others overcome substance use problems [38].

These critical factors appear to be common change factors that underlie long-term recovery from substance abuse. A recent survey of self-help groups, including traditional 12-step groups, Self-Management and Recovery Training, Secular Organizations for Sobriety, and Women for Sobriety, supported the idea of common change factors. It showed that active involvement in a support group was associated with a higher likelihood of long-term remission irrespective of the particular group to which the individual belonged [5].

Abstinence-Specific and General Support

Self-help groups are an important source of abstinence-specific and general support, and may be especially effective in counteracting the influence of substance users in a social network. Self-help groups provide modeling of substance use refusal skills, ideas about how to avoid relapse-inducing situations, practical advice for staying sober, and helpful hints about how to address the panoply of everyday life problems. Individuals who continue to attend Alcoholics Anonymous more regularly after treatment are more likely to have social network members who support cutting down or quitting substance use than are individuals who attend Alcoholics Anonymous less regularly. In fact, the increase in friends' abstinence-oriented and general support associated with involvement in self-help groups explains part of their positive influence on remission [21, 61].

According to Bond, Kaskutas, and Weisner [7], individuals who have fewer heavy drinkers in their social network and more people who encourage the reduction of drinking, as well as more Alcoholics Anonymous-based support for reducing drinking, are more likely to initiate and maintain abstinence; the number of Alcoholics Anonymous-based social network members who support reduced drinking explains part of Alcoholics Anonymous' effect on abstinence. Involvement in Alcoholics Anonymous also may protect individuals from the potential negative influence of a "wet" social network [23].

Goal Direction and Structure

Self-help groups provide a context of goal direction and structure in the form of a shared ideology that enhances individuals' immersion into the group. The shared ideology, which is reinforced by explaining group beliefs in understandable terms, specifying changes needed to maintain sobriety, and providing the 12 steps as a guide for change, helps members negotiate the recovery process. Alcoholics Anonymous norms appear to result in more personal and intimate self-disclosures and less conflict in Alcoholics Anonymous groups than in non-Alcoholics Anonymous support groups [60, 63].

There also is a system of taking turns in Alcoholics Anonymous that exemplifies its egalitarian nature, non-differentiated roles of members, and low levels of conflict. In this vein, members acknowledge and identify with previous speakers' contributions and do not openly confront or challenge them, thereby maintaining solidarity, communicating acceptance, and reducing the potential for conflict. Alcoholics Anonymous members tell life stories aligned with Alcoholics Anonymous principles, which supports the development of shared identities characterized by dependence on Alcoholics Anonymous and relevance to the 12 steps [47].

The emphasis on spirituality is a key aspect of the goal direction in 12-step self-help groups. In this sense, Alcoholics Anonymous can be seen as a spiritual recovery movement that rewards compliance with its norms by engaging individuals in a social system that promotes new meaning in their lives. Among individuals in day hospital or residential treatment, increases in 12-step involvement from baseline to a 1-year follow-up predicted a higher likelihood of abstinence at follow-up. This relationship was partially explained by an increase in religious practices and spirituality. Thus, spiritual change may contribute to recovery within the context of self-help group involvement [64].

Involvement in Rewarding Activities

Another active ingredient of self-help groups involves their role in engaging members in rewarding substance-free social pursuits, such as home groups, parties, and community activities. Members who are more involved in group meetings and related activities, such as doing service and becoming a sponsor, are more likely to achieve and maintain abstinence [23]. Involvement in community groups predicted 1-year abstinence among drug-dependent individuals independent of attendance at Alcoholics Anonymous/Narcotics Anonymous and being a sponsor. By helping their members become more socially integrated, self-help groups increase the likelihood of sustained abstinence [11].

Self-help groups also provide members with an opportunity to help other individuals in need, which tends to increase the helper's sense of purpose and personal responsibility, rewards for remaining sober, and commitment to recovery [65]. In a prospective study based on data from Project MATCH, recovering individuals who became sponsors or were otherwise engaged in helping other alcoholics were less likely to relapse [50]. Similarly, compared with Double Trouble in Recovery members who were less involved in sharing at meetings and helping other members, those who were more involved in these activities were more likely to be abstinent at a 1-year follow-up [37].

Sponsors provide other members with support and direction, 12-step instruction, tips to help promote abstinence and improve relationships, and crisis intervention. Engaging in these helping activities can improve the sponsor's self-esteem and social standing, strengthen the sponsor's social network, and provide a model of successful commitment to live a sober lifestyle. Accordingly, self-help group members who become sponsors are more likely to maintain abstinence than those who do not [11].

Self-Efficacy and Coping

Affiliation with Alcoholics Anonymous tends to be associated with increases in members' self-efficacy and motivation for abstinence. For example, an analysis of data from Project MATCH showed that participation in Alcoholics Anonymous was positively related to self-efficacy to avoid drinking. Self-efficacy predicted a higher likelihood of abstinence and explained part of the association between participation in Alcoholics Anonymous and abstinence. In addition, Alcoholics Anonymous attendance at 6 months post-treatment predicted self-efficacy at 9 months, which predicted abstinence at 15 months. Self-efficacy to avoid drinking explained part of the effect of Alcoholics

Anonymous attendance on abstinence for both less severe (Type A) and more severe (Type B) alcoholic individuals [6, 10].

A study that assessed individuals in 12-step treatment during treatment and at 1- and 6-month follow-ups focused on several common change factors, including self-efficacy, commitment to abstinence, appraisal of harm due to substance use, and active cognitive and behavioral coping. More affiliation with Alcoholics Anonymous in the month after treatment was associated with increases in these change factors and with better 1- and 6-month substance use outcomes. In addition, these common change factors appeared to explain all of the effect of Alcoholics Anonymous affiliation on 6-month substance use outcomes [46].

Affiliation with 12-step self-help groups promotes more reliance on coping responses directed toward reducing substance use. Individuals who are more involved in Alcoholics Anonymous are more likely to rely on coping skills directed toward controlling substance use, such as spending time with non-drinking friends, seeking advice about how to resolve their drinking problems, and rewarding themselves for trying to stop drinking [52]. The active ingredients of self-help groups that foster improvement in coping skills likely include modeling of substance use refusal skills, ideas about how to manage relapse-inducing situations, and practical advice for coping with craving.

Participation in self-help groups is also associated with improvements in general coping skills—i.e., increases in approach coping and declines in avoidance coping [46]. Individuals who are more involved in 12-step groups tend to rely more on approach and less on avoidance coping; approach coping responses explained part of the effect of involvement in these groups on the reduction of substance use [21].

Conclusions

The active ingredients of self-help groups reviewed thus far tend to enhance motivation for recovery, self-efficacy to resist substance use, and effective coping skills. In this vein, increases in common change factors such as support, goal direction and structure, and involvement in rewarding activities are likely to result in increased motivation for recovery, self-efficacy to resist drinking, and approach coping.

Most generally, the finding that a longer duration of participation in self-help groups predicts better substance use outcomes indicates that self-help groups are most beneficial when they become a long-term supportive aspect of individuals' lives. Extended 12-step group engagement may initiate and maintain the personal and social changes needed to solidify stable remission, especially abstinence-specific and general support, goal direction and structure, involvement in rewarding substance-free activities, and enhanced self-efficacy and coping skills. Self-help groups represent an important part of the array of effective interventions than can change the enduring aspects of individuals' life contexts and increase the likelihood of a long-term course of recovery.

Acknowledgments Department of Veterans Affairs Health Services Research and Development Service funds and NIAAA grant AA15685 supported preparation of the manuscript. I thank Bernice Moos for help in reviewing the literature. The views expressed here are the author's and do not necessarily reflect the views of the Department of Veterans Affairs.

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Part VIII
Treatment and Application: Pharmacotherapy

Pharmacotherapy for Alcoholism and Some Related Psychiatric and Addictive Disorders: Scientific Basis and Clinical Findings

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Contents

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Introduction

Alcohol dependence is a common disorder. Globally and in the United States, alcohol dependence ranks 5th and 3rd, respectively, on the list of preventable causes of morbidity and mortality [294]. In 2000, the United States had 20,687 alcohol-related deaths, excluding accidents and homicides, with an overall estimated cost to the nation of about $185 billion [294].

In the 1980s, the lifetime prevalence of alcohol-related disorders was estimated to be 13.5% in the United States [255]. Later, the National Comorbidity Survey reported a higher lifetime prevalence of 23.5% [151]. It has been estimated that up to 24.3% of men and 48.5% of women with alcohol dependence have prominent depressive symptoms [152]. Furthermore, alcohol dependence increases the risk of depression up to fourfold [152, 251]. Depression in alcohol-dependent individuals increases the degree of morbidity [233, 239] and risk for suicide [82, 214]. Individuals with bipolar disorder have a high prevalence of 46% to develop an alcohol-related disorder; indeed, the odds of a bipolar disorder if a person has an alcohol-related disorder are 5.1 times greater than in an individual without an alcohol-related disorder [251]. Bipolar

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_47,

alcoholics are at increased risk of violent behavior [264], treatment non-adherence, high rates of hospitalization [278], and mortality. Anxiety-related disorders also occur frequently among alcohol-dependent individuals (with a prevalence rate of 19.4%), especially general anxiety disorder, social phobia, and post-traumatic stress disorder [251]. Up to 90% of alcohol-dependent individuals are smokers, and the heaviest drinkers tend to smoke the most [14]. In a sample size ranging from 80 to 1,142, surveys of alcohol-dependent inpatient and outpatient treatment participants showed an 86–97% smoking rate among males and an 82–90% rate among females [37, 69, 161, 302]. Smoking increases the health risks and associated morbidity and mortality of alcohol dependence greatly, and vice versa. Comorbid psychiatric disorder or smoking complicates the treatment of alcohol dependence and increases the level of public health concern.

Alcohol dependence is a chronic relapsing medical disorder [210]. Notwithstanding its psychological and social ramifications, once established, alcohol dependence is essentially a brain disorder that bears many of the characteristics of other medical relapsing disorders such as diabetes and hypertension. Indeed, without a pharmacological adjunct to psychosocial therapy, the clinical outcome is poor, with up to 70% of clients resuming drinking within 1 year [81, 287]. Comorbid psychiatric or smoking-related behavior with alcohol dependence would be expected to increase these rates of relapse.

Alcohol dependence is a treatable disorder when efficacious medicines are added to enhance the effects of psychosocial treatment. Advances in the neurosciences have facilitated the development of medicines that target neurotransmitter systems, which modulate activity in the cortico-mesolimbic dopamine pathway, the primary circuit by which alcohol's reinforcing effects associated with its abuse liability are expressed. Also, neuronal circuits in the extended amygdala modulate the expression of alcohol reinforcement in the cortico-mesolimbic dopamine pathway and increase the propensity for conditioned behaviors to trigger relapse ([159]; also see Chapter "Opportunities, Challenges, and Successes in the Development of Medicines for the Treatment of Addiction"). Additionally, it is now known that some alcoholics may possess a biological predisposition to the disease. These biologically vulnerable alcoholics can be expected to benefit from specific adjunctive medications targeted toward correcting or ameliorating their underlying abnormalities. Further, we are now better at controlling the "dose" of adjunctive psychosocial treatments, thereby optimizing the therapeutic response of the candidate medicines. Targeting medicinal treatments toward psychiatric or smoking-related disorders that are comorbid with alcohol dependence is complex because the neuronal targets are broadened, and the implications of altering their function are less well understood.

Recently, the treatment of alcohol dependence has been advanced by development of new models as well as broader therapeutic objectives. An important model is that with appropriate pharmacotherapy it is possible to initiate treatment for alcohol dependence while the individual is still drinking heavily and at the point of maximum crisis and help-seeking behavior [140]. To broaden access to treatment, effective but brief and standardized behavioral treatment has been developed to accompany medication delivery; thus, these medicines can now be provided more readily in the general practice setting [136, 245]. Finally, it is now better recognized that although abstinence remains the ultimate goal in treating alcohol-dependent individuals, reducing the frequency of heavy drinking has the major impact of decreasing alcohol-related consequences and improving quality of life [140].

In this review, we focus on the development of those medications for which there is clinical information and that have been designed to reduce the desire to drink, to promote abstinence, or both. Basically, of the numerous neurotransmitter systems that have been identified for the development of new medicines, the most

promising compounds appear to be those that modulate the function of opioids, glutamate with or without gamma-aminobutyric acid, and serotonin. Other putative therapeutic medications including direct modulators of dopamine function and enzyme inhibitors also shall be discussed. Each subsection of this chapter provides an overview of the basic science, clinical studies, and future directions for the development of specific promising medications from these neurobiological systems. Emphasis is made in places where the development of a particular medicine has advanced the development of a new treatment model or broadened therapeutic objectives. As appropriate, subsections are expanded or added where there is the discussion of a medication that has been tested for the treatment of alcohol dependence with a comorbid psychiatric disorder or smoking pertinent to this review. We conclude the chapter with remarks pertaining to current barriers to treatment and how they might be overcome.

Opioids: Mu Receptor Antagonist—Naltrexone

Basic Science and Human Laboratory Studies

The endogenous opioid system, particularly through its interactions with the cortico-mesolimbic dopamine system, is involved in the expression of alcohol's reinforcing effects [97, 108, 117, 130, 147, 177, 203] (Fig. 1). Obviously, opioid receptors also have interactions with other neurotransmitters, including those in the glutamate [172], gamma-aminobutyric acid [83], serotonin [202], cannabinoid [195] and perhaps glycine [252] systems, that contribute to its effects on ethanol intake.

Even though naltrexone has some affinity for the kappa-opioid receptor [250], its principal pharmacological effect on alcohol consumption

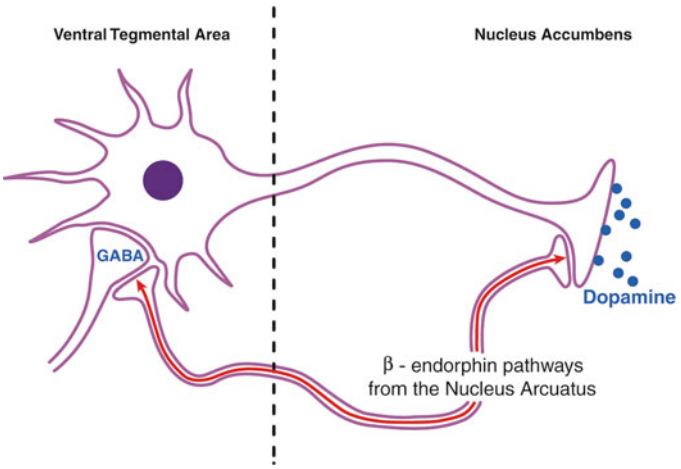

Fig. 1 Schematic representation of opioid interactions with the cortico-mesolimbic dopamine reward pathway. Functional activity of beta-endorphin pathways primarily originating from the nucleus arcuatus can lead to increased dopamine release in the nucleus accumbens via two mechanisms. First, beta-endorphins can disinhibit the tonic inhibition of gamma-aminobutyric acid (GABA) neurons on dopamine cells in the ventral tegmental area [108, 147, 203]. Second, beta-endorphins can stimulate dopamine cells in the nucleus accumbens directly. Both mechanisms may be important for alcohol reward. Alcohol stimulates beta-endorphin release in both the nucleus accumbens and ventral tegmental area [97]. Mu receptor antagonists such as naloxone and naltrexone block these central effects of beta-endorphins [97, 117]. Embellished from Gianoulakis [97]. Reprinted from Johnson and Ait-Daoud [130], with kind permission from Springer Science+Business Media

is through blockade of the mu-opioid receptor as mice that lack the mu-opioid receptor do not self-administer alcohol [254]. Further, alcohol intake increases beta-endorphin release in brain regions such as the nucleus accumbens [196, 197, 234], an effect that is blocked by naltrexone [315]. Mu receptor antagonists such as naltrexone and naloxone also suppress ethanol intake across a wide range of animal paradigms [8, 62, 84–86, 120, 150, 175, 262, 295, 298] cf. [17, 148, 258]. More recently, there also has been interest in elucidating the role of the hypothalamic-pituitary-adrenocortical axis in stress-induced ethanol consumption and sensitivity and how this might be influenced by naltrexone treatment [153, 308].

Ethanol has complex neurobiological interactions that affect the production, secretion, and binding of opioids to their receptors [119], thereby hinting at a fundamental mechanistic process linking the two. This relationship does, however, remain imperfectly understood. For example, animals bred for high ethanol preference exhibit an exaggerated reactive rise in beta-endorphin level following ethanol intake [98]. Yet, naltrexone's ability to suppress ethanol-associated increases in beta-endorphin level appears greater in animals bred for low rather than high preference for alcohol [315]. Indeed, from a group of animals in the beta-endorphin-deficient mutant mouse line—C57BL/6-Pomc1(tm1Low)—the highest ethanol consumption occurred in the heterozygotes (50% beta-endorphin deficient) and not the homozygotes (no beta-endorphin) or control group of sibling wild type mice from the same strain [105]. These findings do, however, suggest that molecular genetic differences that alter beta-endorphin expression, not simply its plasma levels, modulate the level of response to naltrexone. Nevertheless, there is growing evidence in humans that differences in the OPRM1 mu-opioid receptor gene are associated with differential therapeutic response to naltrexone—a theme that is explored in detail later in this review.

Human laboratory studies that have evaluated naltrexone's effects on alcohol-induced positive subjective mood and craving have yielded mixed results. Although it has been shown that naltrexone can reduce alcohol-induced positive subjective mood, albeit with increased sedation [288], and increase the latency to consume alcohol among social drinkers [61], others have reported no effect [67]. It does, however, appear that a positive familial loading for alcoholism might predict the potential anti-drinking and anti-craving effects of naltrexone in human laboratory studies. For example, King et al. [155] showed that social drinkers with a familial loading for alcoholism were more likely than those without it to exhibit a decrease in the stimulant effects of alcohol following naltrexone treatment. Nevertheless, they also reported concomitant negative mood exemplified by increased tension, fatigue, and confusion and decreased vigor, as well as notable adverse events such as nausea and vomiting following naltrexone. More recently, Krishnan-Sarin et al. [169] have shown that individuals with a family history of alcoholism, compared with their family history-negative counterparts, consumed less alcohol in a laboratory paradigm. Obviously, these results would lead to the speculation that a genetic explanation for differential response to naltrexone's effects on craving and alcohol consumption among alcohol-dependent individuals is being studied in the human laboratory. Nevertheless, even here, what has been demonstrated is that naltrexone increases the urge to drink among alcohol-dependent individuals who are aspartate (Asp) carriers of the OPRM1 gene but has no effect on their homozygote, i.e., asparagine-carrying, counterparts in a cue-reactivity laboratory paradigm [207]. Despite the dissimilarities between studies, including the subject's motivation toward seeking treatment, experimental set, setting, expectations, and paradigm, these results do appear to be in contrast with the report that naltrexone preferentially protected against relapse in Asp-carrying alcohol-dependent individuals [240]. The implications of these findings are discussed in the clinical subsection below.

In sum, basic science studies support the finding that naltrexone can reduce ethanol

drinking and related behaviors in animals. Naltrexone appears most effective in suppressing the expected ethanol-induced increase in beta-endorphin level among animals that exhibit an exaggerated beta-endorphin response. The pharmacogenetic construct for understanding preferential response to naltrexone is not well understood and is even contrary to expectations. Generally, human laboratory studies provide some support for naltrexone as a medication that can reduce craving for alcohol as well as its consumption; however, these effects appear to be more readily demonstrable among individuals with high familial loading for alcoholism. An initial pharmacogenetic exploration did not demonstrate that naltrexone's anti-drinking effect is greatest among non-treatment-seeking, alcohol-dependent individuals who carry the Asp variant of the OPRM1 gene.

Clinical Studies with Oral Naltrexone

In 1994, the Food and Drug Administration approved naltrexone for the treatment of alcohol dependence based on data from two relatively small (total $N = 167$) studies [235, 299]. In those studies, recently abstinent, alcohol-dependent individuals who received naltrexone (50 mg/day), compared with their counterparts who got placebo, were less likely to relapse during the treatment period of 12 weeks. Nevertheless, 5 months after treatment, the relapse rates for the naltrexone and placebo groups were similar. The anti-alcohol-craving effects that were ascribed to naltrexone were based on three findings. First, individuals with the highest level of baseline craving appeared to benefit the most from naltrexone [122]. Second, abstinent individuals who had received naltrexone had less of an impulse to initiate drinking [236]. Third, even among those who sampled alcohol, less pleasure was derived from the beverage [300]. These earlier studies were limited by the fact that only male veterans were tested in one of the studies [299], and either there was no biomarker used to corroborate the self-reported data [235] or when the liver enzyme gamma-glutamyl transferase was used as a biomarker the results were not contributory [299]—presumably due to the relative insensitivity of this measure to capture transient drinking patterns.

Notably, in two large meta-analytic studies [30, 283], naltrexone has been demonstrated to be efficacious at reducing the risk of relapse among recently abstinent, alcohol-dependent individuals. What has emerged an examination of these studies was that naltrexone's effect size was small, with a corresponding number needed to treat (i.e., the number of individuals who need to be treated to prevent relapse in a single individual) of 7. An important threat to demonstrating efficacy for naltrexone is not having quite high enough levels of medication compliance. Indeed, in a 3-month follow-up and systematic replication of their study, Volpicelli et al. [301] only found a significant effect of naltrexone treatment compared with placebo recipients if the pill-taking rate exceeded 90%; even here, the difference in the percentage of drinking days between the naltrexone and placebo groups was small—3 and 11%, respectively.

Perhaps because of this small effect size, some studies have failed to demonstrate naltrexone's efficacy in treating alcohol dependence. For instance, in the United Kingdom collaborative trial led by Chick et al., no overall difference was found between the naltrexone 50 mg/day and placebo groups on any of the endpoint measures; however, when individuals with less than 80% pill-taking compliance were excluded from the analysis, naltrexone was associated with a lower percentage of days drinking compared with placebo—12% vs. 20%, respectively [183, 184]. With naltrexone treatment, reduced pill-taking compliance is typically the result of adverse events such as nausea that can be reported as significant in up to 15% of trial participants [56]. Therefore, new technologies that aim to improve compliance by delivering naltrexone in depot form might possess a therapeutic advantage to the oral formulation. These technologies are discussed later in this section.

Importantly, the landmark COMBINE study ($N = 1383$) has served to underscore that naltrexone (100 mg/day) plus medication management to enhance compliance compared with placebo reduced the risk of a heavy drinking day (hazard ratio = 0.72; 97.5% CI = 0.53–0.98; $p = 0.02$) [10]. Uniquely, this study used a higher naltrexone dose (i.e., 100 mg/day vs. 50 mg/day), and the high compliance rate of pill taking—85.4%—improved clinical outcome.

Recently, it has been proposed that individuals with the Asp variant of the OPRM1 gene exhibited preferentially higher relapse prevention rates when receiving naltrexone treatment [240]. As described previously, a similar response to naltrexone treatment on cue-elicited craving was not observed among non-treatment-seeking, alcohol-dependent individuals in a human laboratory study [207]. Further, a recent clinical trial did not find a preferential effect of naltrexone treatment on any of the variants of the OPRM1 gene [92]. Notably, the functional importance of variation in the OPRMI gene is still being elucidated. Although earlier studies in transfected cells suggested that the OPRM1-Asp^{40} variant had a 3-fold higher affinity for beta-endorphin than OPRM1-Asn^{40}, which would suggest enhanced function [29], this has not been corroborated by others [16, 18]. Recent in vitro transfection studies have, however, suggested that the G118 allele might be associated with lower OPRM1 protein expression than the A118 allele [318]. A further complication to estimating the general clinical significance of the effects of the Asp^{40} allele on pharmacotherapeutic response to naltrexone is that its frequency can vary considerably between populations—from as low as 0.047 in African Americans to 0.154 in European Americans, and as high as 0.485 among those of Asian descent [91, 316]. More genetic studies are, therefore, needed to elucidate fully the mechanistic effects of the Asp^{40} allele, and to establish whether or not naltrexone response varies by variation at the OPRM1 gene.

Certain clinical characteristics have, however, been associated with good clinical response to naltrexone, and these include a family history of alcohol dependence [122, 156, 215] or strong cravings or urges for alcohol [215].

Naltrexone's utility compared with placebo as an add-on treatment in alcohol-dependent individuals with comorbid bipolar I or II disorder was investigated recently [269]. All individuals received their concomitant medications prescribed for bipolar disorder prior to study entry, along with standardized cognitive behavioral therapy designed for the treatment of bipolar disorder and substance use at scheduled intervals during treatment [263]. Naltrexone did not differ statistically from placebo on any outcome measure of drinking, and the attrition rate was high—48%.

Naltrexone's utility compared with placebo as a treatment for alcohol dependence and smoking cessation also has been studied recently [157]. In that placebo-controlled study, there was no overall effect of naltrexone on either the consumption of alcohol or smoking. In a subsequent subset analysis confined to heavy drinkers (defined as those with at least one heavy drinking episode during the 2-week pre-enrollment baseline period), there was an effect of naltrexone to reduce heavy drinking; however, again there was no effect on smoking. Interestingly, there was a significant negative association between quitting smoking and decreasing alcohol consumption, whereby greater success in stopping smoking was correlated with increased amounts of heavy drinking. These results do not provide strong support for the use of naltrexone as a medication for the simultaneous reduction or cessation of alcohol consumption and smoking among individuals comorbid for these conditions.

In sum, the majority of the data confirm that naltrexone is an efficacious medication for treating alcohol dependence. The therapeutic treatment effect size is, however, small, and poor pill-taking compliance can be associated with poor clinical outcome. There remains a dearth of published studies on the effects of different doses of naltrexone on drinking outcome. Further research is needed to establish whether naltrexone's therapeutic efficacy in treating alcohol dependence differs among individuals who

have variants of the OPRM1 gene. Alcohol-dependent individuals with a positive family history for the disease and individuals with strong cravings for alcohol appear to benefit the most from naltrexone treatment. Naltrexone does not appear to be a promising medication for the treatment of alcohol dependence with comorbid depression, or for the contemporaneous reduction or cessation of alcohol consumption and smoking.

Clinical Studies with Depot Naltrexone

Three extended-release formulations of naltrexone for deep intramuscular injection have been developed—Vivitrol® (Alkermes, Inc., Cambridge, MA, USA), Naltrel® (Drug Abuse Sciences, Inc., Paris, France), and Depotrex® (Biotek, Inc., Woburn, MA, USA). The premise for developing these depot formulations of naltrexone is three-fold. First, a well formulated depot preparation can maintain relatively constant plasma levels by producing a slow but regular release of naltrexone. Individuals who take oral naltrexone and have notable adverse events such as nausea that can lead to study discontinuation probably experience this phenomenon due to the rapid rise in plasma levels following initial doses of oral naltrexone. Hence, a depot formulation might be expected to decrease these initial adverse events if it provided a more gradual rise in naltrexone plasma levels. Second, by providing a monthly depot preparation, compliance with receiving the medication is optimized and should be greater than reliance on remembering to take tablets. Third, because plasma levels should remain relatively constant throughout the month following the administration of a depot preparation, there should be relatively greater exposure to the therapeutic dose, thereby facilitating good clinical outcome. Information pertaining to the three depot preparations of naltrexone that are being tested is provided below.

Vivitrex® or Vivitrol®

Vivitrex®, or Vivitrol® as it is known now, is naltrexone formulated into poly-(lactide-co-glycolide) [270], small-diameter (<100 μm), injectable microspheres that contain other proprietary active moieties, which lead to its extended-release properties lasting for several weeks [179]. In 2004, Johnson et al. [139] published the initial safety, tolerability, and efficacy trial of Vivitrex® for treating alcohol dependence. The design of the study was a 16-week randomized, placebo-controlled, double-blind clinical trial. Of the 25 alcohol-dependent individuals who participated in the trial, five of them got placebo and the remainder ($N = 20$) got 400 mg of Vivitrex®. Results of that trial showed the safety of Vivitrex®, with the most common adverse events being non-specific abdominal pain, nausea, pain at the injection site, and headaches. None of the placebo recipients dropped out due to adverse events; in contrast, two of those who got Vivitrex® discontinued for that reason. Due to the unbalanced design and small subject numbers, any inferences regarding efficacy had to be viewed quite cautiously. Nevertheless, there was a trend for those on Vivitrex®, compared with placebo, to have a lower percentage of heavy drinking days—11.7% vs. 25.3%. Later, in a large placebo-controlled, double-blind, randomized, multi-site, 24-week clinical trial, Garbutt et al. [90] showed that high-dose Vivitrex® (380 mg) recipients had a significantly lower percentage of heavy drinking days than those who got placebo (hazard ratio = 0.75; 95% CI = 0.60–0.94; $p = 0.02$). Recipients of low-dose Vivitrex® (190 mg) had outcomes similar to those who got placebo. The treatment response signal in the high-dose Vivitrex® recipients came from the male participants as the effect of both Vivitrex® doses was no different from that in women who took placebo (hazard ratio = 1.23; 95% CI = 0.85–1.78; $p = 0.28$). The lack of efficacy for Vivitrol® in women has been ascribed to greater subclinical affective symptoms, less of a family history of alcoholism (which is meant to

be associated with good clinical outcomes to naltrexone), more responsiveness to placebo, and more clinical heterogeneity in the sample. In contrast with the premise for developing depot preparations, the dropout rate of 14.1% in the high-dose Vivitrex® group was similar to that reported in studies with oral naltrexone. The chosen objective biomarker to corroborate the self-reported data—gamma-glutamyl transferase—did not show a difference between any of the Vivitrex® doses and the placebo group. The common reasons for study discontinuation were injection site reactions, headaches, and nausea. Serious adverse events were reported in two participants taking active medication that resulted in an interstitial pneumonia and an allergic-type eosinophilic pneumonia, both of which resolved after medical treatment. Thus, the evidence remains that Vivitrol® appears to be efficacious in preventing heavy drinking in men; however, it was approved by the Food and Drug Administration for treatment of both men and women based on the extant literature on naltrexone as a treatment for alcohol dependence. The expected advantage of Vivitrol® to increase compliance did not materialize quickly although this might become more manifest in generic treatment settings rather than a closely monitored clinical trial. The potential for hypersensitivity reactions to Vivitrol®, while small, does require post-marketing evaluation by the Food and Drug Administration.

Naltrel®

Naltrel® consists of naltrexone incorporated into microspheres of poly-(DL-lactide) polymer. These microspheres, stored in single-dose vials, are suspended in a diluent that contains carboxymethylcellulose, mannitol, polysorbate 80, and water for injection. The polylactide polymer is metabolized to water and carbon dioxide. Then, as the microspheres degrade, naltrexone is released. In 2004, Kranzler et al. [167] studied the safety and efficacy of Naltrel® in treating male and female alcohol-dependent individuals receiving monthly motivation enhancement-based therapy in a double-blind, placebo-controlled, 3-month randomized controlled trial ($N = 157$). The initial dose of Naltrel® (150 mg) was delivered as a deep intramuscular injection into each buttock, and subsequent monthly doses were just 150 mg. Placebo injections were provided at the same frequency and constitution but lacked the active compound. Adverse events reported significantly more frequently in the Naltrel® group than in the placebo group included injection site reactions, chest pain, and upper abdominal pain. Placebo recipients were, however, more likely to report irritability than those who got Naltrel®. While 6 (3.8%) of the placebo recipients dropped out, 13 (8.2%) of those who got Naltrel® discontinued treatment. Naltrel® was superior to placebo at increasing the mean number of cumulative abstinent days (52.8 days, 95% CI 48.5–57.2 days, vs. 45.6 days, 95% CI 41.1–50.0 days, respectively; $p = 0.018$) and having a longer median time to first drink (5 days, 95% CI 3–9 days, vs. 3 days, 95% CI 2–4 days, respectively; $p = 0.003$). The effects of gender on treatment outcome were not examined.

Somewhat in contrast, a single-site, 6-week trial of 16 alcohol-dependent individuals who received one intramuscular dose of Naltrel® (300 mg) [89] suggested low tolerability, with 198 adverse events being reported. Of these, 17 were considered to be severe and included fatigue, gastrointestinal pain, irritability, nausea, somnolence (two reports), headache (four reports from three subjects), injection site pain, injection site mass, lethargy, depression, increased level of gamma-glutamyl transferase (an index of heavy drinking [53]), back pain, and flatulence. No serious adverse events were reported. Drinking outcomes showed an improving trend over the duration of the trial.

Nevertheless, further studies on the safety and efficacy of the Naltrel® formulation are warranted. Additional data are needed to determine whether, as with Vivitrol®, there is a differential response on drinking outcomes between men and women who get Naltrel®.

Depotrex®

Rather little public information is available on the Depotrex® depot formulation. Like the other depot formulations, Depotrex® appears to provide steady increases in plasma naltrexone levels [165] and is an effective mu-opioid receptor antagonist [7, 113]. Pharmacokinetic data from 12 heroin-dependent individuals who received low and high doses of Depotrex®—192 mg and 384 mg, respectively—showed that both doses maintained plasma naltrexone levels above 1 ng/ml for up to 4 weeks [52]. Average peak levels for the low and high doses of Depotrex® were 3.8 ng/ml and 8.9 ng/ml, respectively. Plasma beta-naltrexol, the major metabolite of naltrexone, was greater proportionately but could not be detected 5 weeks following Depotrex® administration. Both doses of Depotrex® antagonized the positive subjective effects of heroin. Reported adverse events were minimal and included mild discomfort at the injection site, with no irritation or erythema. The promising earlier study by Kranzler et al. [165] of Depotrex® (206 mg) in the treatment of alcohol dependence needs to be followed up.

In sum, depot formulations of naltrexone may offer some advantages such as increased compliance over the oral formulations. This advantage has, however, been difficult to demonstrate in randomized controlled trials but might become more apparent when these depot formulations are used in generic practices. Depot formulations do not appear to be more efficacious than the oral formulations, and with one of these—Vivitrol®—no therapeutic effect in women has been demonstrated. The adverse events profiles of depot formulations of naltrexone that have been reported in randomized controlled trials appear similar in frequency and intensity to those observed for the oral formulation. The different depot formulations do appear to be similar in characteristics and profile, and more clinical information about which one to select to treat a particular alcohol-dependent individual, if all are approved by the Food and Drug Administration, shall be needed.

Glutamate

Metabotropic Glutamate Receptor-5 Modulator and N-*Methyl*-D-*Aspartate Antagonist—Acamprosate*

Acamprosate's principal neurochemical effects have been attributed to antagonism of *N*-methyl-*D*-aspartate glutamate receptors [63, 320], which restores the balance between excitatory and inhibitory neurotransmission that is dysregulated following chronic alcohol consumption [64]. Recently, however, it also has been proposed that acamprosate modulates glutamate neurotransmission at metabotropic-5 glutamate receptors [111]. Evidence that acamprosate modulates a novel site of action at metabotropic-5 glutamate receptors comes from the finding that it inhibits the binding and neurotoxic effects of ±-1-aminocyclopentane-*trans*-1,3-dicarboxylic acid [111]. Acamprosate has been shown to decrease: (a) ethanol consumption in rodents [27, 57, 178], but this effect may not be specific in food-deprived C57BL/6 J mice as both ethanol and water were reduced in a schedule-induced polydipsia task [75]; (b) dopamine hyperexcitability in the nucleus accumbens during alcohol withdrawal [59, 259]; (c) general neuronal hyperexcitability [96, 282]; (d) glutamatergic neurotransmission in alcohol-dependent rats [28, 59]; (e) voltage-gated calcium channel activity, and (f) the expression of brain *c-fos*, an immediate early gene associated with alcohol withdrawal [185, 247]. Nevertheless, it is acamprosate's ability to suppress alcohol-induced glutamate receptor sensitivity [171], as well as conditioned cue responses to ethanol in previously dependent animals even after prolonged abstinence [273, 280, 281, 311], that has been linked with its therapeutic effect in humans—dampening negative affect and craving post-abstinence [130, 279] (Fig. 2).

Interestingly, there has been a paucity of human laboratory studies that have examined the potential effects of acamprosate on alcohol-related behaviors associated with its

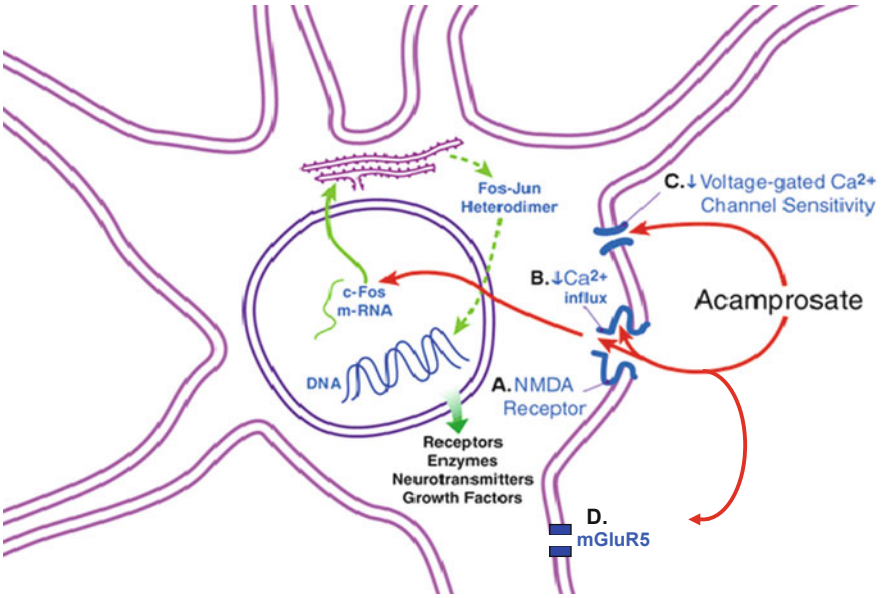

Fig. 2 Schematic representation of acamprosate's effects. Acamprosate has four principal effects: (**A**) reducing post-synaptic excitatory amino acid neurotransmission at *N*-methyl-*D*-aspartate (NMDA); (**B**) diminishing Ca^{2+} influx into the cell, which interferes with expression of the immediate early gene *c-fos*; (**C**) decreasing the sensitivity of voltage-gated calcium channels, and (**D**) modulating metabotropic-5 glutamate receptors (mGluR5). mGluR5 are post-synaptic and are coupled to their associated ion channels by a second messenger cascade system (not shown). Also shown in this representation is synthesis of *c-fos* and *c-jun* in the endoplasmic reticulum, which can bind with DNA to alter the transcription of late effector genes. Late effector genes regulate long-term changes in cellular activity such as the function of receptors, enzymes, growth factors, and the production of neurotransmitters. Embellished from Spanagel and Zieglgansberger [279]. Adapted from Johnson and Ait-Daoud [130], with kind permission from Springer Science+Business Media. Adapted version reprinted from Johnson [127], with permission from Elsevier

abuse liability. Evidence from a human magnetic resonance imaging study does, however, support acamprosate's ability to modulate glutamate neurotransmission as it decreases activity in brain regions rich in *N*-acetylaspartate and glutamate [28]. Human laboratory studies in both volunteers [199] and alcohol-dependent individuals [138] also have shown that acamprosate—i.e., calcium acetyl homotaurinate—is relatively safe, with the most important adverse events being diarrhea, nervousness, and fatigue, especially at a relatively high dose (3 g/day). Since acamprosate is excreted unchanged in the kidneys, there is no risk of hepatotoxicity, but it should be used with caution in those with renal impairment [138, 199]. Acamprosate has no significant clinical interaction with alcohol. Recently, it was shown that acamprosate can reduce heart rate response but not the increase in cortisol or subjective craving following the presentation of alcohol cues—a finding that suggests utility for acamprosate in managing autonomic dysregulation in abstinent alcoholics exposed to a high risk for relapse situations [237].

Most of the clinical evidence for the efficacy of acamprosate in the treatment of alcohol dependence comes from a series of European studies. In 2004, Mann et al. [194] wrote a meta-analysis of 17 published studies that included 4087 alcohol-dependent individuals. In that report, continuous abstinence rates at 6 months were greater than for those who got placebo (acamprosate, 36.1%; placebo, 23.4%; relative benefit, 1.47; 95% CI = 1.29–1.69; $p < 0.001$). The overall pooled difference in

success rates between acamprosate and placebo was 13.3% (95% CI = 7.8–18.7%), and the number needed to treat was 7.5. Similar results were obtained from another meta-analysis conducted at about the same time [30]. Generally, the effect size of acamprosate is small—0.14 for increasing the percentage of non-heavy drinking days [162] and 0.23 for reducing the relapse to heavy drinking [42]. Early studies also had some methodological problems, including non-standardization of diagnostic criteria and the psychosocial adjunct to the medication, which were resolved in later trials.

Despite approval by the Food and Drug Administration on July 29, 2004, for the use of acamprosate in the treatment of alcohol dependence, largely based on the data from European studies, the results of studies in the United States have been disappointing. In the United States multi-site trial by Lipha Pharmaceuticals, Inc., there was no overall clinical evidence that acamprosate was superior to placebo among a heterogeneous cohort of alcohol-dependent individuals; however, post-hoc analysis suggested that a subgroup of alcoholics with a treatment goal of abstinence might derive benefit [200]. Further, in 2006, the multi-site COMBINE study also failed to find any therapeutic benefit of acamprosate compared with placebo on any drinking outcome measures [10]. Obviously, the findings of these United States studies have reduced the enthusiasm for using it by addiction specialists in the United States. From a scientific perspective, these findings do beg the questions as to what type of alcohol-dependent individual benefits the most from acamprosate and why there is an important discrepancy between the results of United States and European studies.

From the European studies, acamprosate appears to benefit alcohol-dependent individuals with increased levels of anxiety, physiological dependence, negative family history, late age of onset, and female gender [297].

There are at least four possible explanations for the discrepancy between United States and European studies. First, the populations sampled differ, with European, compared with United States, studies having alcohol-dependent individuals with more prolonged drinking histories and alcohol-related neurological and psychosocial impairments. Thus, it is tempting to speculate that European studies might have included individuals with greater neuroplasticity and, therefore, higher response to the ameliorating effects of anti-glutamatergic agents such as acamprosate. Second, United States, compared with European, studies have tended to have higher levels of standardized psychosocial intervention as an adjunct to acamprosate, thereby masking the effect of the medication. Third, the therapeutic effect of acamprosate is small; hence, by chance, some trials can be expected to fail, especially those conducted in a multi-site rather than a single-site environment due to the greater heterogeneity and variability of the cohort and research settings. Fourth, it is possible that future research might uncover other important differences between United States and European cohorts to explain the discrepant findings such as potential differences in participants' subtype, stage of the alcoholism disease, or biomolecular constitution.

In sum, European studies have clearly demonstrated efficacy for acamprosate as a treatment for alcohol dependence. Acamprosate was Food and Drug Administration approved in the United States largely based on the results of the European studies. Acamprosate's therapeutic effect is small, but it is well tolerated, with the most prominent adverse events being diarrhea, nervousness, and fatigue, especially at a relatively high dose (3 g/day). In contrast, studies in the United States have, to date, been unable to find efficacy for acamprosate among a heterogeneous group of alcohol-dependent individuals. The reason for this discrepancy between the results of United States and European studies has not been established. Perhaps, however, this discrepant finding might be due to differences in participants' selection, subtype, stage of the alcoholism disease, or bio-molecular constitution that are yet to be determined. Intriguingly, preliminary results presented for the recently completed multi-site collaborative European Study—Project Predict—also did not

find an effect for acamprosate in the treatment of alcohol dependence [193]. Future studies are needed to delineate more clearly what type of alcohol-dependent individual can benefit from acamprosate treatment.

Other N-*Methyl*-D-*Aspartate Receptor Antagonists*

Other *N*-methyl-*D*-aspartate receptor antagonists such as memantine and neramexane are being studied for the treatment of alcohol dependence. Both compounds have been shown in animal models to suppress ethanol-induced *N*-methyl-*D*-aspartate receptor up-regulation, thereby reducing ethanol sensitization and the propensity for subsequent drug use (for a review, see Nagy [224] and Kotlinska et al. [160]). In a human laboratory study, memantine reduced alcohol craving prior to but not after the experimental administration of alcohol. This would suggest that memantine might have the effect of reducing post-cessation craving for alcohol [20]. This finding is supported by a later report that memantine might have comparable effects to diazepam at ameliorating alcohol withdrawal symptoms [170]. Nevertheless, despite the early preliminary findings, a recent pilot clinical trial comparing memantine with placebo for the treatment of alcohol dependence reported that the greater therapeutic effect at reducing the percentage of heavy drinking days and increasing the percentage of days abstinent [76] occurred among the placebo group. Although this pilot study did not provide support for memantine as an efficacious treatment for alcohol dependence, further studies are needed to make a final determination of memantine's therapeutic potential for this indication. Recently, it was reported that memantine was as effective as escitalopram (the S-enantiomer of citalopram, a selective serotonin reuptake inhibitor) for the treatment of alcohol dependence in individuals with comorbid major depressive disorder [217]. That study, however, lacked a placebo treatment arm; therefore, it has not been established that memantine is an efficacious treatment for alcohol dependence with comorbid major depression. No human study on the therapeutic effects of neramexane in treating alcohol dependence has been published.

Alpha-Amino-3-Hydroxy-5-Methylisoxazole-4-Propionic Acid and Kainate Glutamate Receptor Antagonist—Topiramate

Topiramate, a sulfamate-substituted fructopyranose derivative, has six important mechanisms of action. Additional to its ability to antagonize alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors and kainate glutamate receptors [99, 106, 274], topiramate also facilitates inhibitory gamma-aminobutyric acid-A-mediated currents at non-benzodiazepine sites on the gamma-aminobutyric acid-A receptor [305, 306], inhibits L-type calcium channels and limits calcium-dependent second messenger systems [317], reduces activity-dependent depolarization and excitability of voltage-dependent sodium channels [290], activates potassium conductance [118], and is a weak inhibitor of carbonic anhydrase isoenzymes, CA-II and CA-IV [65], which are found in both neuronal and peripheral tissues. In renal tubules, carbonic anhydrase isoenzyme inhibition reduces hydrogen ion secretion and increases secretion of Na^+, K^+, HCO_3^-, and water, thereby enhancing the likelihood of acidosis and renal stone formation [65, 268].

Johnson [124, 125] has proposed a neuropharmacological model by which topiramate can decrease alcohol reinforcement and the propensity to drink (Fig. 3). Nevertheless, few studies on the effects of topiramate on ethanol consumption in animals have been published. An initial animal study had shown complex effects of topiramate on ethanol drinking in C57BL/6 mice. In that study, high-dose (50 mg/kg) but not low-dose (1, 5, and 10 mg/kg) topiramate suppressed ethanol intake 2 h after it was injected into

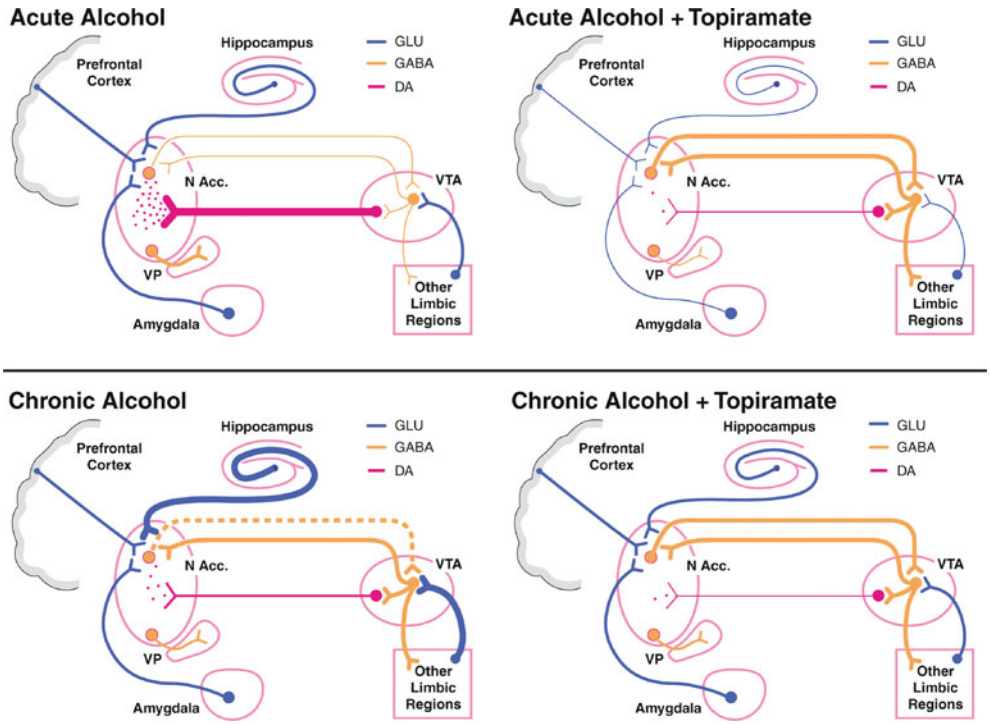

Fig. 3 Schematic illustration of the hypothesized effects of acute and chronic alcohol, both with and without topiramate, on the cortico-mesolimbic dopamine (DA) reward circuit [124]. (*Upper left*) Acute alcohol suppresses the firing rate of ventral tegmental area (VTA) gamma-aminobutyric acid (GABA) neurons, which leads to less suppression of VTA DA neuronal activity. This disinhibition leads to VTA DA neuronal firing and DA release in the nucleus accumbens (N Acc.) [124]. (*Lower left*) With chronic drinking, VTA GABA neurons are hyperexcitable, mainly because of increased glutamatergic input, less GABA tone from the N Acc., and rebound firing of GABA neurons because of their long-term suppression from repeated alcohol ingestion. This leads to VTA DA hypofunction and decreased release (compared with the acute condition) of DA in the N Acc. [124]. (*Upper right*) During acute drinking, the GABAergic influence of topiramate probably predominates, particularly in the N Acc. This leads to greater inhibition of N Acc. DA neurons, and greater GABA tone from the N Acc. to the VTA suppresses VTA DA cell firing. Topiramate concomitantly inhibits the excitatory effects of glutamatergic neurons on DA neurons in the VTA and N Acc. These combined actions of topiramate should lead to profound suppression of DA neuronal activity and DA release in the N Acc. Hence, topiramate reduces the DA-mediated reinforcing effects of acute alcohol [124]. (*Lower right*) During chronic drinking, the predominant neuronal activity resides with the hyperexcitable state of VTA GABA neurons. Because of GABA-mediated inhibition and glutamatergic blockade of these neurons, topiramate "normalizes" VTA GABA neuronal activity. Although this would, at first, suggest that DA release in the N Acc. would be enhanced, this does not occur, and DA release in the N Acc. is most likely reduced because these N Acc. terminals are contemporaneously inhibited by GABA inhibition and blockade of glutamate (GLU). In the chronic drinker, the anti-glutamatergic and L-type calcium channel effects of topiramate to block sensitization might predominate. Hence, topiramate would make it easier for a chronic alcoholic to withdraw from alcohol because rebound DA release would not occur (if drinking were ceased abruptly), and topiramate would aid in relapse prevention because alcohol's reinforcing effects would be decreased [124]. *Line weights* represent relative strengths of neuronal activity (heavy, medium, and light). The *broken line* represents decreased tone. VP, ventral pallidum. Reprinted from Johnson [124], courtesy of Blackwell Publishing, Inc.

the animal. Topiramate also decreased saccharin preference, but its ability to suppress ethanol preference was associated with some increase in water intake [88]. Notably, in an elegant, recent animal study, Nguyen et al. [232] demonstrated that topiramate can suppress ethanol drinking in C57BL/6 mice; additionally, in contrast with the effects of naltrexone and tiagabine in the

same animals, the mice treated with topiramate did not develop any tolerance to its anti-drinking effects. Furthermore, topiramate has been shown to suppress ethanol drinking persistently in alcohol-preferring (P) but not Wistar rats [35]. Additional to its ethanol-suppressing effects, there is evidence that topiramate can reduce alcohol withdrawal symptoms in a model of handling-induced convulsions [79]. Hence, the preponderance of the animal literature does support topiramate as a promising medication for the treatment of alcohol dependence. Nevertheless, the effect of topiramate on ethanol drinking in animals appears to be less striking than that on drinking outcomes in humans, which are presented below. This challenges the notion that animal models can predict directly treatment response in humans, especially when a variety of models have not been used or been available to characterize or "fingerprint" response [141]. The results of additional animal experiments examining topiramate's mechanistic effects on ethanol consumption or related behaviors in animals are, therefore, awaited eagerly.

Recently, Johnson et al. [137, 140] and Ma et al. [191] showed in a double-blind, randomized clinical trial that topiramate (up to 300 mg/day), compared with placebo, improved all drinking outcomes, decreased craving, and improved the quality of life of alcohol-dependent individuals who received 12 weeks of weekly brief behavioral compliance enhancement treatment [136]. The improvements in self-reported drinking outcomes were confirmed by plasma gamma-glutamyl transferase, an objective biochemical measure of alcohol consumption [53]. The therapeutic effect size for the primary efficacy variable—percentage of heavy drinking days—was 0.63.

In a 6-week experimental study of 76 heavy drinkers who were not seeking treatment, Miranda et al. [213] showed that low- and high-dose topiramate—200 mg/day and 300 mg/day, respectively—were significantly better than placebo at decreasing the percentage of heavy drinking days.

Further, in a subsequent 17-site ($N = 371$) United States trial, topiramate (up to 300 mg/day) was again superior to placebo at improving all self-reported drinking outcomes, gamma-glutamyl transferase level, and some measures of quality of life among alcohol-dependent individuals who received 14 weeks of weekly brief behavioral compliance enhancement treatment [144, 146]. Topiramate's therapeutic effect size for the reduction in percentage of heavy drinking days was 0.52, and the number needed to treat was 3.4 [143].

Taken together, these clinical studies provide strong evidence that topiramate is a promising medication for the treatment of alcohol dependence. Encouragingly, topiramate's therapeutic effect size is in the moderate range, and the clinical effects appear to increase with greater length of time on the medication.

Generally, topiramate has a favorable adverse event profile, with most reported symptoms being classified as mild to moderate [125]. The most common adverse events are paresthesia, anorexia, difficulty with memory or concentration, and taste perversion. Slow titration to the ceiling dose (up to 300 mg/day) for 8 weeks is critical to minimizing adverse events and improving tolerability (see Table 1); however, about 10% of individuals taking topiramate may experience some cognitive difficulty irrespective of the dose titration schedule [21]. Topiramate use has been linked with acute but rare visual adverse events. As of January 2005, there had been 371 spontaneous reports of myopia, angle-closure glaucoma, or increased intraocular pressure, for a rate of 12.7 reports per 100,000 patient-years exposure [127]. Usually, the syndrome of acute bilateral myopia associated with secondary angle-closure glaucoma presents as the acute onset of visual blurring, ocular pain, or both. Associated bilateral ophthalmologic findings can include myopia, shallowing of the anterior chamber, conjunctival hyperemia, and raised intraocular pressure. This syndrome resolves within a few days of discontinuing topiramate administration [125].

Table 1 Topiramate dose-escalation schedule

Week	AM dose	PM dose	Total daily dose (mg)
1	0 mg	1 25-mg tablet	25
2	0 mg	2 25-mg tablets	50
3	1 25-mg tablet	2 25-mg tablets	75
4	2 25-mg tablets	2 25-mg tablets	100
5	2 25-mg tablets	1 100-mg tablet	150
6	1 100-mg tablet	1 100-mg tablet	200
7	1 100-mg tablet	1 100-mg tablet and 2 25-mg tablets	250
8	1 100-mg tablet and 2 25-mg tablets	1 100-mg tablet and 2 25-mg tablets	300

Although topiramate has not shown efficacy in the treatment of bipolar disorder [296], there is an ongoing National Institutes of Health–funded study of its efficacy in the treatment of individuals with comorbid alcohol dependence and bipolar disorder. It is presumed that among individuals whose bipolar disorder is stabilized by concurrent medication prior to the trial, topiramate would have an added effect to improve drinking outcomes. Results of this study are awaited eagerly. Promisingly, another anticonvulsant, valproic acid, has been shown to decrease heavy drinking in alcohol-dependent individuals with bipolar disorder [261].

As a subgroup analysis of a 12-week double-blind, randomized, controlled trial, the effect of topiramate vs. placebo among alcohol-dependent smokers was evaluated [142]. Topiramate recipients were significantly more likely than placebo recipients to become abstinent from smoking (odds ratio = 4.46; 95% CI 1.08–18.39; $p = 0.04$). Using a serum cotinine level of $\leq$28 ng/ml to segregate non-smokers from smokers, the topiramate group had 4.97 times the odds of being non-smokers (95% CI 1.1–23.4; $p = 0.04$). The strength of these results showing topiramate's treatment efficacy is bolstered by the fact that smoking cessation was not a goal of the study, and no specific measures, advice or counseling, or therapeutic targets were provided to help the participants quit smoking; thus, the improvements in smoking rate represent a naturalistic change in behavior. Interestingly, cigarette consumption and serum cotinine levels lessened as individuals became more abstinent in the topiramate group. In contrast, increasing abstinence from alcohol was associated with greater consumption of cigarettes and higher serum cotinine levels for the placebo group. These findings provide initial support for the proposal that topiramate may be an efficacious medicine for the simultaneous treatment of alcohol dependence and smoking.

In sum, predicated upon a neuropharmacological conceptual model, there now is strong clinical support for topiramate as a promising medication for the treatment of alcohol dependence. Topiramate's therapeutic effects appear to be robust, with a medium effect size, thereby potentially ushering in a new era of a reliably efficacious medicine for the treatment of alcohol dependence with or without smoking. Intriguingly, although the animal data do provide support for topiramate's anti-drinking effects, more research is needed to characterize fully or "fingerprint" the pattern of response. Such preclinical studies should enable us to elucidate more clearly the basic mechanistic processes that underlie topiramate's efficacy as a treatment for alcohol dependence. Whilst it is not yet known whether topiramate will be useful in treating alcohol-dependent individuals with bipolar disorder, another anticonvulsant (i.e., valproic acid) has shown some promise.

Serotonin

For almost three decades, there has been intense interest in the effects of serotonergic agents in the treatment of alcohol dependence.

Encouraged by increased knowledge about the various serotonin receptor subtypes, researchers have examined the effects of various medications that bind to specific receptor sites. Here, we provide a synopsis of the preclinical and clinical studies that have been done on these serotonin function-altering medications in the treatment of alcohol dependence.

Serotonin Reuptake Inhibitors

For decades, it has been known that pharmacological manipulations that deplete the brain of serotonin decrease the preference for ethanol [221, 223]. Using preference paradigms, pharmacological agents that inhibit serotonin reuptake from the synapse reduce the voluntary consumption of ethanol solutions using the preference paradigm [60, 93, 101, 102, 206, 314]. Knockout mice at the serotonin transporter do, however, exhibit a general decrease in ethanol preference and consumption [31]. Thus, there is ample preclinical support for the notion that selective serotonin reuptake inhibitors suppress ethanol consumption in animals.

Although these preclinical studies have shown that selective serotonin reuptake inhibitors can reduce ethanol consumption, the selectivity of this effect on reinforcement as opposed to general consummatory behaviors has been questioned [25, 26, 204].

The inhibition of serotonin reuptake function has complicated the effects on food intake and fluid consumption [100]. Selective serotonin reuptake inhibitors do suppress food intake [104, 272] and fluid consumption [100] and decrease palatability [176]. Yet, motivational factors exert some control on the expression of these behaviors [285]. For instance, selective serotonin reuptake inhibitors enhance satiety [25] but selectively reduce preference for certain macronutrients (i.e., sweet items and carbohydrates) [180, 312, 313] cf. [114, 115] that increase the palatability and rewarding effects of food [78, 276, 310]. Hence, selective serotonin reuptake inhibitors might decrease ethanol consumption via the suppression of non-specific general consummatory behaviors and specific anti-reinforcing effects.

Studies conducted using operant techniques have also supported a role for selective serotonin reuptake inhibitors in the suppression of ethanol consumption. Haraguchi et al. [110] showed that same-day pretreatments with fluoxetine dose-dependently reduced ethanol responding. Nevertheless, whereas the chronic administration of selective serotonin reuptake inhibitors to C57BL/6 J male mice produced an initial suppression of lever pressing for ethanol, there was a later rebound to baseline levels of responding for ethanol and ethanol consumption [107]. These results are somewhat similar to those of Murphy et al. [218], who observed that fluoxetine administered to rats in a single daily infusion produced a significant reduction in ethanol-reinforced responding that started on the first day of treatment and increased on subsequent days of the 7-day treatment regimen. Responding for ethanol returned to pretreatment levels following cessation of fluoxetine treatment. Food intake, while somewhat suppressed initially, appeared to return to baseline levels on subsequent treatment days. Again, these results demonstrate that the suppression of ethanol intake by selective serotonin reuptake inhibitors follows a pattern of initial suppression of consummatory behavior followed by a reduction in reinforcement; thus, when the selective serotonin reuptake inhibitors are discontinued, there is an extinction-like pattern of a return to the baseline behavior.

Despite the promise of these preclinical results, there is, at present, little support for the proposal that selective serotonin reuptake inhibitors are an efficacious treatment for a heterogeneous group of alcohol-dependent individuals. Initial studies of small sample size reported that selective serotonin reuptake inhibitors can produce short-term (1–4 weeks) decreases in alcohol consumption among problem drinkers [225–229]. Nevertheless, these studies were limited by at least three factors. First, most of the studies were conducted in men, thereby limiting the generalizability of the results to the general population [225–227]. Second, the

adjunctive psychosocial treatment, which can decrease the apparent efficacy of the putative therapeutic medication because this too can have an important effect on drinking outcomes, was not standardized. Third, the treatment periods were short; thus, it was not possible to determine whether these initial effects, which could be due to non-specific factors, would be sustained. Indeed, the problem with studies of short duration that focus on a chronic relapsing disorder such as alcohol dependence was highlighted in a later study by Gorelick and Paredes [103], who found that there also was an effect for fluoxetine, compared with placebo, to decrease alcohol consumption by about 15% in the first 4 weeks of the trial but not over the entire length of the trial. Also, Naranjo et al. [231] did not demonstrate that citalopram (40 mg/day) was superior to placebo in a 12-week treatment trial. Further, neither Kabel and Petty [149] nor Kranzler et al. [163] in two separate 12-week studies found fluoxetine (60 mg/day) to be superior to placebo for the treatment of alcohol dependence.

There has been renewed understanding about how the administration of functionally different serotonergic agents can lead to different drinking outcomes among various subtypes of alcoholic (for a review, see Johnson [123]). Adapted from Cloninger's classification scheme [45], two methods for subtyping alcoholics have been used in these pharmacotherapy studies. Basically, a particular type of alcoholic (i.e., Type A-like or late onset) characterized by a later age of onset of problem drinking (typically over the age of 25 years), a preponderance of psychosocial morbidity, and low familial loading can experience improved drinking outcomes after selective serotonin reuptake inhibitor treatment.

Although early human laboratory studies showed that Type B-like or early-onset alcoholics, characterized by an early age of problem drinking onset (i.e., before the age of 25 years), high familial loading for alcohol dependence, and a range of impulsive or anti-social traits, might be centrally deficient in the major metabolite of serotonin, 5-hydroxyindoleacetic acid [38, 181, 182], the implications of this finding were, perhaps, oversimplified. At a cursory glance, it would appear that a selective serotonin reuptake inhibitor, by increasing serotonin turnover, would compensate for this dysfunction; thus, these Type B-like or early-onset alcoholics would then be expected to experience improved drinking outcomes following selective serotonin reuptake inhibitor treatment. Remarkably, the literature has demonstrated quite the opposite. For instance, Kranzler et al. [164] observed that fluoxetine treatment appeared to worsen the clinical benefit of the adjunctive cognitive behavioral treatment and there was no difference from placebo. Actually, Type A-like or late-onset alcoholics, with presumably more normative serotonin function, have been observed to experience improved drinking outcomes from sertraline both during active treatment [244] and at 6-month follow-up [70]. Also, Chick et al. [43] have shown that early-onset or Type B-like alcoholics were more likely to relapse than their late-onset or Type A-like counterparts following fluvoxamine treatment.

Obviously, the relationship between serotonergic dysfunction and Type B-like or early-onset alcoholism is not the simple result of a deficiency state. Indeed, Johnson [123] has hypothesized that an explanation for this effect might be allelic variation at the serotonin transporter, which leads to the differential expression of serotonin function. Of course, other bio-molecular explanations are possible, and further research is needed to elucidate this important area of research.

Fluoxetine has been reported to be beneficial for the treatment of alcohol-dependent individuals with suicidal tendencies and severe comorbid depression [54]. A recent study did not find that sertraline treatment was more beneficial than placebo in treating depressed men and women with alcohol dependence irrespective of the severity of the depression [168]. In another trial, sertraline was again found not to be beneficial in both men and women for the treatment of comorbid alcohol dependence and depression, although women did have a very slight but not clinically meaningful improvement in depressive symptoms [214]. Notably, it has not been shown that the reduction in dysphoria in depressed

alcoholics is associated with concomitant decreases in alcohol consumption [198, 208]. Hence, the only conclusion that can be drawn at present is that except for a subtype of depressed alcoholic with suicidal tendencies or, perhaps, in women, there is not much evidence to recommend selective serotonin reuptake inhibitors over placebo for the treatment of depressed alcoholics.

Sertraline might have some utility in the treatment of alcohol-dependent individuals whose comorbid post-traumatic stress disorder is associated with early trauma [34], thereby suggesting that different subtypes might vary in treatment response. Also, there is promise that paroxetine might prove useful in treating alcohol-dependent individuals with social phobia [249]. There is no specific treatment, apart from symptomatic management, for the treatment of alcohol-dependent individuals with comorbid generalized anxiety disorder [33].

In sum, despite strong animal data that would support the use of selective serotonin reuptake inhibitors as a promising treatment for alcohol dependence, there is no evidence that they are of therapeutic benefit to a heterogeneous group of alcohol-dependent individuals. Notably, however, there is growing confirmation that selective serotonin reuptake inhibitors can improve the drinking outcomes of Type A-like or late-onset alcoholics. Rather than being a cause for discouragement, this finding might (a) open up the possibility of identifying important bio-genetic or pharmacological mechanisms that underlie the alcoholism disease and (b) improve understanding about which type of alcohol-dependent individual can benefit the most from specific serotonergic treatment. Further, there is no current evidence that providing a selective serotonin reuptake inhibitor to a depressed alcoholic without severe depressive symptoms and suicidal tendencies is of therapeutic benefit. Hence, what is clear is that clinicians should be cautious in prescribing selective serotonin reuptake inhibitors to alcohol-dependent individuals for the treatment of minor depressive or affective symptoms. Not only is this strategy unlikely to be a therapeutic benefit over placebo, and perhaps appropriate psychosocial management, but drinking outcomes can actually be worsened, especially if the alcohol-dependent individual is Type A-like or of late onset. There is some evidence that selective serotonin reuptake inhibitors might be useful in treating a cohort of alcohol-dependent individuals whose post-traumatic stress disorder is associated with early trauma, and in treating alcoholics with social phobia.

Serotonin-1 Partial Receptor Agonist

Preclinical studies have suggested that the serotonin-1A partial agonist, buspirone, may be effective at reducing ethanol consumption. Buspirone decreased volitional alcohol consumption from 60 to 30% in macaque monkeys, but there was considerable inter-individual variation [47]. In Sprague-Dawley rats, buspirone significantly reduced ethanol intake in animals induced to drink by repeated brainstem injection of tetrahydropapaveroline. In a group of medium alcohol-preferring rats, buspirone (0.0025–0.63 mg/kg) reduced, while buspirone (>2.5 mg/kg) increased, alcohol consumption without affecting water consumption [211]. While buspirone is a partial serotonin-1A agonist, the net effect of its repeated administration is to enhance serotonin function via facilitation of the post-synaptic receptor, which is more sensitive than the autoreceptor, and down-regulation of autoreceptor function [22]. Nevertheless, this preclinical evidence would have been strengthened by operant studies examining the dose-response characteristics of buspirone as a function of ethanol concentration.

Buspirone has not been demonstrated to be an efficacious medication for the treatment of alcohol-dependent individuals without comorbidity. In a review of five published trials, buspirone was without a convincing effect in non-comorbid alcoholics; however, alcoholics with comorbid anxiety experienced some benefit [36, 192]. Hence, buspirone's anxiolytic effects

might translate to those who also are dependent on alcohol.

In sum, there is no current evidence that would suggest a role for buspirone in the treatment of alcohol dependence without comorbid anxiety disorder.

Serotonin-2 Receptor Antagonist

Preclinical studies have suggested that the serotonin-2 receptor antagonist, ritanserin, can reduce ethanol consumption in animals [212, 222] cf. [286]. Also, the serotonin-2 antagonists, amperozide [19, 219, 220, 241] and FG5974 [174, 253], significantly suppress ethanol intake without affecting water consumption. The exact mechanism by which serotonin-2 receptor antagonists might reduce ethanol consumption is unknown. It has, however, been suggested that they might exert their effects by acutely substituting for alcohol's pharmacobehavioral effects by facilitating burst firing in cortico-mesolimbic dopamine neurons [293], or by the suppression of dopamine neurotransmission following their chronic administration.

In the clinical setting, ritanserin is not an efficacious treatment for alcohol dependence. In a rigorously conducted, 12-week, multicenter clinical trial ($N = 423$) of ritanserin (2.5 or 5 mg/day) vs. placebo as an adjunct to weekly cognitive behavioral therapy, none of the ritanserin doses were superior to placebo [133]. In a later study using similar methodology, ritanserin (2.5, 5.0, or 10.0 mg/day) was not superior to placebo at improving drinking outcomes [307]. Although higher doses of ritanserin might be of therapeutic benefit, testing these doses is precluded by ritanserin's potential to cause dose-dependent prolongation of the QTc interval on the electrocardiogram, thereby increasing the potential for life-threatening cardiac arrhythmias.

In sum, there is no clinical evidence that would support the use of ritanserin as a treatment for alcohol dependence.

Serotonin-3 Receptor Antagonists

Preclinical studies provide strong support for the role of the serotonin-3 receptor in mediating alcohol's important neurochemical effects, and for serotonin-3 receptor antagonists to be promising treatment for alcohol dependence.

In neurophysiological experiments, ethanol potentiates serotonin-3 receptor-mediated ion currents in NCB-20 neuroblastoma cells [189, 319] and in human embryonic kidney 293 cells transfected with serotonin-3 receptor antagonist complementary DNA [190]. Serotonin-3 receptor antagonists block these effects [186]. Thus, the serotonin-3 receptor is a site of action for ethanol in the brain [187, 188].

Pharmacobehavioral studies show that many of alcohol's reinforcing effects are mediated by serotonin-3 and dopamine interactions in the cortico-mesolimbic system [12, 117, 131, 158, 309].

Serotonin-3 receptor antagonists have three principal effects that demonstrate their ability to modulate ethanol consumption and related behaviors. First, serotonin-3 receptor antagonists suppress hyperlocomotion in the rat induced by dopamine or ethanol injection into the nucleus accumbens [32]. Second, serotonin-3 receptor antagonists inhibit DiMe-C7 (a neurokinin)-induced hyperlocomotion, which also is reduced by the dopamine antagonist, fluphenazine [73, 109]. Third, serotonin-3 receptor antagonists reduce ethanol consumption in several animal models and across different species [12, 55, 71, 77, 121, 132, 205, 211, 256, 265, 291] cf. [15].

Human laboratory studies have generally supported a role for the serotonin-3 antagonist ondansetron in reducing preference and craving for alcohol. In two distinct experiments, Johnson and Cowen [131] and Johnson et al. [132] showed that ondansetron pretreatment attenuated low-dose alcohol-induced positive subjective effects (including the desire to drink). Swift et al. [289], using much higher alcohol and ondansetron doses, also discovered that ondansetron compared with placebo pretreatment reduced alcohol preference; however, a

mixture of both stimulant and sedative interactions between ondansetron and alcohol also was observed. Whereas Doty et al. [68] did not find an effect of ondansetron on alcohol-induced mood, their experimental model of using a group rather than individual experimental setting could have decreased the sensitivity of their assessments.

Three clinical studies have provided evidence that ondansetron is a promising treatment for alcohol-dependent individuals, particularly those with an early-onset or Type B-like subtype.

First, in a 6-week, double-blind, placebo-controlled study of 71 non-severely alcohol-dependent males, Sellers et al. [266] observed that the 0.5-mg dose but not the 4-mg dose of ondansetron was associated with a non-significant trend ($p = 0.06$) toward a reduction in alcohol consumption. Post-hoc analysis that eliminated 11 subjects who consumed less than 10 drinks/drinking day rendered the difference in drinking outcomes between the ondansetron 0.5 mg and placebo groups to be significant statistically ($p = 0.001$). Despite the limitations of this initial trial, which included a relatively short treatment period, the inclusion of just males, and the small number of subjects, the results of this study provided general support for ondansetron's promise in treating alcohol dependence. Also, these results showed that ondansetron may exhibit a non-linear dose-response effect in the treatment of alcohol dependence.

Second, in a large-scale ($N = 321$), 12-week, randomized, double-blind clinical trial in which alcohol-dependent individuals received weekly cognitive behavioral therapy, Johnson et al. [134] showed that ondansetron (1, 4, and 16 μg/kg b.i.d.) was superior to placebo at improving drinking outcomes of those of the early onset or Type B-like subtype but not the late onset or Type A-like subtype. The self-reported decreases in alcohol consumption were corroborated by the concomitant reduction in carbohydrate-deficient transferrin level—a biomarker of transient alcohol consumption.

Third, Kranzler et al. [166] provided replication of the results by Johnson et al. [134] by showing that early-onset (Type B-like) alcoholics had a significantly greater improvement in drinking outcomes compared with their late-onset (Type A-like) counterparts following 8 weeks of ondansetron (4 μg/kg b.i.d.) treatment.

Intriguingly, these results demonstrate a differential effect of ondansetron treatment by subtype of alcohol-dependent individual. Indeed, the contrast is striking when compared with the effects of selective serotonin reuptake inhibitors on different subtypes of alcohol-dependent individuals as described above. Basically, early-onset or Type B-like alcoholics with apparent serotonergic deficiency respond best to a medication that blocks the serotonin-3 receptor, whereas late-onset or Type A-like alcoholics with apparently normal serotonergic function derive the most benefit from a medication that can increase serotonin turnover and function. One potential disadvantage of subtyping by psychosocial variables is that they might not be stable across all populations (i.e., differences by ethnicity and regions could occur due to different exposure levels to alcohol), and the more complex algorithms for subtyping (e.g., into Type A or B) cannot be carried out prospectively or applied directly to a single individual. Arguably, more stable and generalizable dichotomization of different populations of alcoholics responsive to ondansetron might be achievable using pertinent and specific bio-molecular variables.

As mentioned earlier, Johnson [123] has proposed a bio-molecular explanation for these effects; however, other plausible possibilities might exist. A detailed elaboration of this concept is beyond the scope of this review. Nevertheless, the key feature is that polymorphic variation(s) at the serotonin transporter gene might result in a relative intrasynaptic hyposerotonergic state with consequent up-regulation of post-synaptic serotonin receptors. Alcohol-dependent individuals with these polymorphic types may be prone to a heavier and more chronic pattern of drinking [145, 267], perhaps through a counter-regulatory mechanism to increase serotonin turnover. Because this attempted counter-regulation through increased alcohol consumption can only be partially effective, as further drinking reduces the expression of the serotonin transporter gene further [145], a vicious cycle is set up. Johnson [128]

has proposed that ondansetron treatment may ameliorate heavy or severe drinking in such alcohol-dependent individuals, presumably by blockade of up-regulated post-synaptic serotonin receptors. Indeed, preliminary statistical analysis of a recent clinical trial does suggest that ondansetron may have an effect to decrease severe drinking among individuals with specific polymorphisms of the serotonin transporter gene. Publication of the details of these findings is expected soon. Obviously, a molecular genetic explanation for this effect, if proven, may enable a pharmacogenetic approach to treatment whereby the appropriate medication can be provided to the particular subtype of alcohol-dependent individual who would benefit the most from such treatment.

Intriguingly, ondansetron has shown efficacy in treating alcohol-dependent individuals with social phobia, presumably because of its anxiolytic effects [275]. The results of this study do, however, need to be validated by a larger clinical trial.

In sum, preclinical data support an important role for serotonin-3 receptors in mediating alcohol's important reinforcing effects associated with its abuse liability. Ondansetron is a promising medication for the treatment of early-onset or Type B-like alcohol dependence. Studies to determine whether alcohol-dependent individuals with allelic differences at the serotonin transporter gene respond differently to ondansetron shall be published soon. Ondansetron's potential to treat alcohol-dependent individuals with comorbid social phobia will need validation in larger clinical trials.

Acetylcholine: Cholinergic Receptor Antagonist—Varenicline

Varenicline is an agent that binds with high affinity to alpha-4/beta-2 nicotinic acetylcholine receptors to release dopamine in the cortico-mesolimbic dopamine system [46]. Hence, it might mimic the effect of alcohol to excite central nicotinic acetylcholine receptors and cause cortico-mesolimbic dopamine activation [23, 24, 74, 277]. Hence, varenicline might "substitute" for the stimulating effects of alcohol.

The Food and Drug Administration has approved varenicline as an aid to smoking cessation [126]. Interestingly, it was reported recently in a human laboratory study that varenicline attenuated alcohol-induced craving and positive subjective mood and decreased alcohol self-administration [209]. A randomized controlled clinical trial is needed to test varenicline's efficacy as a treatment for alcohol dependence in comorbid smokers.

Dopamine

Dopamine Receptor Antagonists

Cortico-mesolimbic dopamine neurons have been implicated as the principal pathway by which alcohol and most other abused drugs express their reinforcing effects associated with abuse liability [117, 158, 309]. Yet it has been difficult to show evidence that direct dopamine receptor antagonists have a role in the treatment of alcohol dependence. Presumably, direct opposition of dopamine pathways is associated with neuroadaptive changes that tend to reverse the initial effects of the blockade [125]. No traditional dopamine receptor blocker has been demonstrated to be an efficacious treatment for alcohol dependence. With the advent of atypical neuroleptics, there has been renewed interest in testing these medications as potential treatment for alcohol dependence. Indeed, medications such as aripiprazole and quetiapine are currently in clinical testing, and the results are awaited eagerly. Other medications that are selective for dopamine-3 receptor antagonism also are under development.

Dopamine Receptor Agonists

At low doses, dopamine-2/dopamine-3 agonists such as bromocriptine and 7-OH-DPAT can

reduce ethanol consumption in animals [201, 260, 304]. Although this might appear paradoxical to the dopamine theory of reinforcement for most abused drugs, it is possible that low-dose dopamine agonists preferentially augment autoreceptor function, thereby decreasing dopamine turnover.

Although an earlier report proposed that bromocriptine can decrease alcohol craving, subsequent studies have found no effect on alcohol drinking or related behaviors [66, 230, 246]. Nevertheless, perhaps due to the high addictive potential of dopamine agonists, this research approach has largely been abandoned in the clinical setting. Currently, dopamine receptor agonists do not hold promise as a treatment for alcohol dependence.

Gamma-Aminobutyric Acid-B Receptor Agonist—Baclofen

Animal studies have demonstrated that the gamma-aminobutyric acid-B receptor agonist, baclofen [beta-(4-chlorophenyl)-gamma-aminobutyric acid], causes decreases in voluntary ethanol intake [48], the ethanol-deprivation effect [49, 248], and morphine-induced stimulation of ethanol consumption [50].

Clinical trials have bolstered the findings of animal studies that suggest a role for baclofen in treating alcohol dependence. In an open-label, 4-week study, 9 alcohol-dependent men were given baclofen (up to 30 mg/day). Seven of the 9 subjects achieved abstinence, while the other 2 participants improved their self-reported drinking outcomes during the study period, according to self-reports corroborated by family members. Several objective biological markers of alcohol intake also showed significant reductions between the beginning and end of the study. Furthermore, craving, as measured by median Alcohol Craving Scale scores, decreased in the first study week and remained stable thereafter [1].

In a 4-week, randomized, placebo-controlled, double-blind clinical trial with 39 alcohol-dependent individuals, 14 of 20 (70%) participants treated with baclofen (up to 30 mg/day) achieved abstinence, compared with 4 of 19 (21.1%) in the placebo group ($p < 0.005$). Baclofen treatment improved significantly drinking outcomes, state anxiety scores, and craving measures. Baclofen generally was well tolerated and had no apparent abuse liability. Adverse events, none of which were serious, consisted of nausea, vertigo, transient sleepiness, and abdominal pain [2].

Recently, Addolorato and colleagues [3] reported in a randomized double-blind clinical trial that baclofen was more efficacious than placebo at promoting abstinence in alcohol-dependent individuals with liver cirrhosis. Because baclofen is primarily excreted unchanged in the urine and feces, it might be uniquely suitable for treating alcoholics with compromised hepatic function. Baclofen was well tolerated in this study, with few adverse events.

These findings indicate that baclofen is a promising medication for the treatment of alcohol dependence, particularly among those with compromised hepatic function. Additional studies of larger sample size and longer duration are awaited to establish the efficacy of baclofen for this indication.

Disulfiram

Disulfiram is a Food and Drug Administration–approved medication that has been used for treating alcoholism since the 1940s and is perhaps still the most widely used such medication in the United States today. Its principal mode of action is as an aversive agent. Disulfiram inhibits aldehyde dehydrogenase and prevents the metabolism of alcohol's primary metabolite, acetaldehyde. In turn, the accumulation of acetaldehyde in the blood causes unpleasant effects to occur if alcohol is ingested; these include sweating, headache, dyspnea, lowered

blood pressure, flushing, sympathetic overactivity, palpitations, nausea, and vomiting. The association of these symptoms with drinking discourages further consumption of alcohol [5]. Serious side effects also have been reported, including hepatitis, hepatotoxicity, depression, and psychotic reactions [238, 271]. Disulfiram also has been shown to reduce norepinephrine synthesis by inhibiting dopamine beta-hydroxylase [242], a mode of action that has been proposed to support early reports of its potential efficacy as a treatment for cocaine dependence. For further details on the pharmacological effects of disulfiram, see also Johnson [129]. While a review of disulfiram's potential effects on cocaine taking are outside the scope of this review, the reader is referred to recent studies by Petrakis et al. [242], Carroll et al. [41], and Baker et al. [11].

A 52-week, multi-site, randomized, controlled trial with 605 alcohol-dependent men found that disulfiram might help prevent relapse in compliant individuals yet be ineffective at promoting continuous abstinence or a delay in the resumption of drinking [87].

Disulfiram has no significant effect on craving for alcohol. Hence, individuals must be highly motivated to maintain disulfiram treatment, whereas those who wish to drink can simply stop taking the medication. The efficacy of disulfiram generally is limited to those who are highly compliant or who receive their medication under supervision—i.e., the type of alcohol-dependent individuals who might be likely to abstain on their own, without adjunctive pharmacotherapy. Including a supportive spouse or partner in a disulfiram treatment plan helps to improve outcome [5, 9].

Disulfiram has been combined with naltrexone as a potential treatment for alcohol dependence with comorbid depression [243]. Although the combination appeared to be well tolerated, there was no significant advantage of the combination over either of the medications alone or placebo. These results do not support the use of the combination of disulfiram and naltrexone as a treatment for comorbid alcohol dependence and depression.

Potential Treatments on the Horizon

Cannabinoid-1 Receptor Antagonists

Endocannabinoid receptors are found ubiquitously in the central nervous system, particularly in the cortex, hippocampus, basal ganglia, and cerebellum. Endogenous cannabinoids include anandamide and 2-arachidonylglycerol, which are metabolized by fatty acid amide hydrolase [112].

In C57BL/6 J mice, cannabinoid-1 receptor blockade reduced ethanol consumption to the amounts ingested by cannabinoid-1 receptor null mutant mice [303]. Endocannabinoids may be involved in the neurochemical expression of susceptibility to the effects of ethanol. For instance, ethanol exposure can increase levels of brain 2-arachidonylglycerol and anandamide and down-regulate cannabinoid-1 receptors [13, 39]. In pharmacobehavioral studies, cannabinoid-1 receptor antagonists suppress ethanol intake in rats with a chronic history of alcohol administration [173, 257], reduce ethanol drinking in alcohol-preferring sP rats [51, 95], and decrease operant responding and cue-induced reinstatement of ethanol consumption [44, 72]. It is plausible, however, that an important method by which cannabinoid-1 receptors influence ethanol taking is via their extensive connections to modulate other neuronal systems including monoamine pathways and their metabolism [216, 284, 292]. Figure 4 shows the interactions between cannabinoid-1 and other neuronal systems [126].

In Europe, initial human studies of the effects of cannabinoid receptor blockade on the drinking outcomes of alcohol-dependent individuals have been completed, and the results are awaited eagerly. Nevertheless, the recent finding that the cannabinoid-1 receptor antagonist (rimonabant) can increase mood disturbance and suicidality in smokers, which precluded the Food and Drug Administration from granting approval for that indication, might also impact the development of similar compounds for the treatment of alcohol dependence.

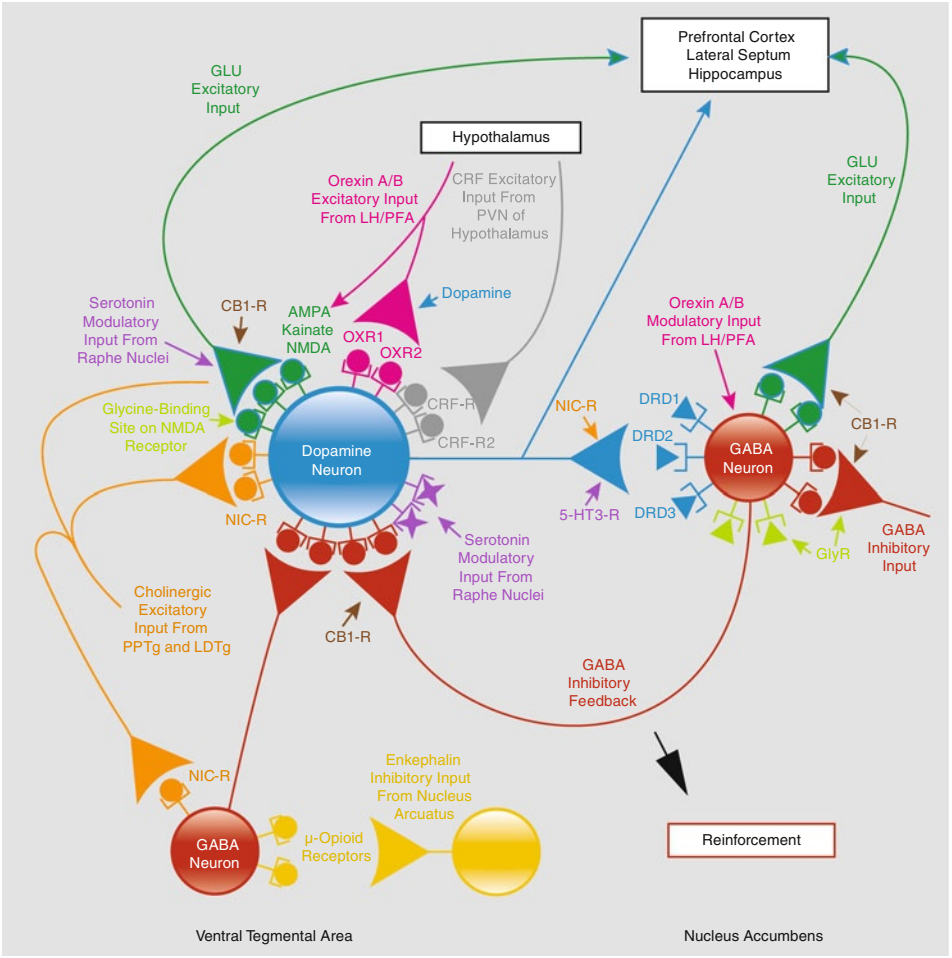

Fig. 4 Neuronal pathways involved with the reinforcing effects of alcohol, nicotine, and other abused drugs. Cholinergic inputs that arise from the caudal part of the pedunculopontine tegmental nucleus (PPTg) and laterodorsal tegmental nucleus (LDTg) can stimulate ventral tegmental area (VTA) dopamine (DA) neurons. The VTA DA neuron projection to the nucleus accumbens (nACC) and cortex, the critical substrate for the reinforcing effects of abused drugs (including alcohol), is modulated by a variety of inhibitory [gamma-aminobutyric acid (GABA) and opioid] and excitatory [nicotinic (NIC-R), glutamate (GLU), and cannabinoid-1 receptor (CB1-R)] inputs. The GLU pathways include those that express alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainate, and *N*-methyl-*D*-aspartate (NMDA) receptors. Serotonin-3 receptors (5-HT3-R) also modulate DA release in the nACC. The glycine system, orexins, and corticotrophin-releasing factor also are shown. LH/PFA: perifornical region of the lateral hypothalamus; PVN: paraventricular nucleus; GlyR: glycine receptor; CRF-R1 and CRF-R2: corticotrophin-releasing factor receptors 1 and 2, respectively; OXR1 and OXR2: orexin receptor types 1 and 2, respectively; DRD1, DRD2, and DRD3: DA receptors D1, D2, and D3, respectively. Adapted and embellished from Johnson [126] (copyright ©2006, American Medical Association; all rights reserved) and reprinted with permission from Johnson [*The American Journal of Psychiatry* (2010) 167:630–639] (copyright ©2010 American Psychiatric Association)

Other Neurochemicals and Small Molecules

Presently, there are a host of other neurochemicals with potential benefit in treating alcohol dependence. At this stage, testing remains within the animal literature and other preclinical models, and it would, therefore, be beyond the scope of this review to discuss them in detail. These compounds include antagonists at metabotropic-5 glutamate receptors, metabotropic-2/3

glutamate receptor agonists, stress-related neuropeptides such as corticotrophin-releasing factor antagonists and modulators of neuropeptide Y, and nociceptin (for a review, see Heilig and Egli [112]). Recently, data from a combination of preclinical and human laboratory experiments were unveiled, showing that the neurokinin-1 antagonist LY686017 might be a promising medication for the treatment of alcohol dependence [94]. These early results are being followed up by phase II clinical efficacy trials. Interestingly, there has been renewed interest in gamma-hydroxybutyrate as a treatment for alcohol dependence; however, its successful use would require the development of a formulation that has very low addictive potential. For recent reviews, see Caputo and colleagues [40] and Addolorato and co-workers [4].

Combination Treatments

Combination treatments offer the promise of augmenting the effects of single medications by engaging multiple neuronal networks associated with the expression of alcohol's reinforcing effects associated with its abuse liability. While this idea is alluring, medication combinations do create the potential for reduced compliance (due to the need to take additional tablets), heightened or new treatment emergent adverse events, or even inefficacy if the medications counteract one another.

Perhaps the best studied medication combination so far has been that of naltrexone and acamprosate. This combination has been proposed to be of potential added therapeutic benefit for three reasons. First, naltrexone, by its action on endogenous opioids, modulates cortico-mesolimbic dopamine activity, thereby reducing the reinforcing effects of alcohol [116, 158]. Acamprosate modulates alcohol withdrawal-induced increases in extracellular glutamate in the cortico-mesolimbic system [58, 59]. Thus, the combined effect of both naltrexone and acamprosate may be to modulate both the neurochemical effects responsible for triggering drinking and those associated with conditioned responses to drink even after a prolonged period of abstinence. Second, while naltrexone decreases positive craving for alcohol [300], acamprosate attenuates negative or conditioned craving post-drinking cessation [279]. It is, therefore, tempting to speculate that the combination of naltrexone and acamprosate would make it easier both to abstain and to prevent a "slip" from turning into a relapse. Third, acamprosate can increase blood levels of naltrexone, thereby augmenting its neurochemical effects [138, 199].

In a European study, Kiefer et al. [154] showed that the combination of naltrexone and acamprosate was clinically additive at improving the drinking outcomes of alcohol-dependent individuals, but only the effect of the combination vs. acamprosate achieved statistical significance. Nevertheless, the recently completed COMBINE study in the United States did not find any therapeutic advantage to combining the two medications [10]. Hence, at present, it is not possible to advise practitioners to combine naltrexone and acamprosate. Further research may, however, provide a definitive answer as to the utility of the combination.

Mechanistically, there are many other medication combinations that are possible, some of which are being pursued. For instance, the combination of naltrexone and sertraline was tested recently in a pharmacotherapy trial for the treatment of alcohol dependence. Unfortunately, there was no evidence that the combination was any better than naltrexone alone, and, therefore, it cannot be recommended as a treatment strategy [80]. Notably, however, preliminary clinical evidence suggests that the combination of ondansetron and naltrexone may result in added or synergistic therapeutic effects on alcohol drinking [6, 135]. The results of definitive confirmatory trials are awaited.

In sum, medication combinations may afford the opportunity to augment the treatment effects of single medications for the treatment of alcohol dependence. Such studies should, however, be conducted where there is a compelling pharmacological rationale for combining the medicines.

This is because there also is the potential for reduced compliance, heightened or new treatment emergent adverse events, and inefficacy. Further, there are important issues that must be determined for all medication combinations, such as optimal dosing, sequencing of the medications, duration of treatment, and the increased complexity of managing such protocols.

Conclusions

Recently, there has been renewed interest in developing efficacious medicines for the treatment of alcohol dependence. Naltrexone and its depot formulations have demonstrated utility, but their therapeutic effect size is small. Despite Food and Drug Administration approval of acamprosate based upon the positive results of European studies, there has, as yet, not been a clear demonstration of its efficacy in United States studies. Even in the European studies, the therapeutic effect size of acamprosate is small. These discrepant findings might be the result of different populations of alcohol-dependent individuals, selection criteria, chronicity of the alcoholism disease, bio-molecular differences, different methodologies between United States and European studies, or sampling error due to the small effect size. For both naltrexone and acamprosate, research is ongoing to determine what type of alcohol-dependent individual benefits from using either medication. There also is the possibility that a pharmacogenetic approach may make it possible to improve the therapeutic outcome for those who receive naltrexone. At present, the combination of naltrexone and acamprosate cannot be recommended to be of therapeutic benefit, but this conclusion might change with future research. Topiramate is a promising medication for the treatment of alcohol dependence with or without comorbid smoking. Based on two studies, its therapeutic effect size appears to be in the medium range. Future research is needed to extend these results to other subpopulations of alcohol-dependent individuals. Serotonergic medications need to be administered with care to ensure that they are provided to the subtype of alcohol-dependent individual who will benefit the most from such treatment. While selective serotonin reuptake inhibitors benefit late-onset or Type A-like alcohol-dependent individuals, the serotonin-3 receptor antagonist ondansetron has efficacy in treating early-onset or Type B-like alcohol-dependent individuals. Molecular genetic studies are ongoing to understand the underpinnings of this differential response among various subtypes of alcoholic to different serotonergic agents. Selective serotonin reuptake inhibitors might have utility in treating alcohol-dependent individuals with comorbid post-traumatic stress disorder associated with early trauma and, probably, alcohol-dependent individuals with major depression associated with suicidality. Both selective serotonin reuptake inhibitors and ondansetron appear effective in treating alcohol-dependent individuals with comorbid social phobia. Baclofen is a promising medication for the treatment of alcohol-dependent individuals with compromised hepatic function, but further studies are needed for this to be established. Although disulfiram is also Food and Drug Administration approved for the treatment of alcohol dependence, it is perhaps best utilized under supervised conditions. New medications in development for the treatment of alcohol dependence with or without comorbid psychiatric disorder or smoking include varenicline, cannabinoid-1 receptor antagonists, and the neurokinin-1 receptor antagonist LY686017. Neuroscientific effort to uncover medication combinations with additive or synergistic therapeutic effects is ongoing.

Acknowledgments We are grateful to Elsevier for permission to reproduce some text from a recent review article [127]. We also thank the National Institute on Alcohol Abuse and Alcoholism for its support through grants 5 R01 AA010522–14, 5 R01 AA012964–06, 5 R01 AA014628–04, and 5 R01 AA013964–05; the National Institutes of Health for its support through University of Virginia General Clinical Research Center Grant M01 RR00847, and Robert H. Cormier, Jr., Ann Richards, and Dr. Chamindi Seneviratne for their assistance with manuscript preparation.

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Alcohol Withdrawal: Treatment and Application

Nassima Ait-Daoud and Robert Malcolm

Contents

Introduction

Alcohol was used in Egypt since the time of the pharaohs, when wine played an important part in ceremonial life [11]. Egyptian texts over 8,000 years old made reference to alcohol abuse and its consequences. The ancient Greeks were also experienced with alcohol abuse and alcoholism. They first drank as part of a religious ritual to please their gods and forget their worries [21, 36] but soon realized that it caused seizures. Around 400 B.C., Hippocrates described seizures related to alcohol abuse and withdrawal, and the Romans used the term "morbius convivialis" to describe alcohol-related seizures [13]. European physicians in the late eighteenth and early nineteenth centuries gave detailed clinical descriptions of delirium tremens and noted a 50% mortality rate. Although delirium tremens was described as early as 1787, its relationship to acute alcohol withdrawal was not firmly established until the twenty first century [15, 37].

Victor and Adams [44] described a series of alcohol-dependent patients admitted to a specialist unit in the United States. They identified the now well-recognized spectrum of symptoms, including tremor, nausea, anxiety, tinnitus, muscle cramps, diaphoresis, seizures, hallucinations, and delirium tremens, that constitute the alcohol withdrawal syndrome. Severe alcohol withdrawal has a mortality rate of up to 35% if untreated; if treated early, death rates range from 5 to 15% [8].

Alcohol withdrawal is defined as a maladaptive behavioral change, with accompanying physiological and cognitive symptoms, that occurs in an individual whose blood- or tissue-alcohol concentrations decline following prolonged heavy use of alcohol [1]. Withdrawal symptoms can occur when an individual who has consumed excessive alcohol daily stops drinking suddenly or reduces the quantity of alcohol. The likelihood of withdrawal symptoms increases with both the chronicity and quantity of drinking, the number of previous withdrawals, and the presence of complicating comorbid conditions [3]. Symptoms associated with the withdrawal

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_48,

syndrome include anxiety, psychomotor agitation, sweating, nausea, vomiting, insomnia, tremor, and rapid heart rate. In severe cases, delirium tremens, hallucinations, grand mal seizures, and disturbances in consciousness can occur [1].

The goals of treatment for alcohol withdrawal include treating the immediate symptoms, preventing complications, and initiating long-term preventative therapy. The current agents of choice for the treatment of mild-to-moderate alcohol withdrawal in the outpatient setting are benzodiazepines [29]. While the use of benzodiazepines is supported by an extensive literature, their use is limited by their potential for abuse, psychomotor sedation, cognitive impairment, and the possibility of a pharmacological interaction with alcohol. Additionally, benzodiazepines might increase the risk of relapse to abuse of other substances in individuals with genetic predisposition to alcoholism or comorbid anxiety or personality disorder [22, 26].

In light of the limitations associated with benzodiazepine use, there has been a growing interest in alternative treatment options for the alcohol withdrawal syndrome. A number of recent studies suggest that anticonvulsants might provide safe and effective alternatives to benzodiazepines, especially among those with moderate to severe alcohol withdrawal symptoms. These agents have demonstrated mood-stabilizing or anxiolytic effects, or both, in addition to their anticonvulsant activity, and are widely used in psychiatric practice.

Although their mechanism of action is not understood completely, the efficacy of anticonvulsants in the alcohol withdrawal syndrome is thought to be related to their ability to reduce "kindling" and facilitate gamma-aminobutyric acid inhibitory neurotransmission [22]. The kindling hypothesis proposes that long-term alcohol dependence combined with repeated withdrawal episodes induces long-lasting neuronal and neurochemical changes in the brain. As a result of these neurobiological changes, the individual's response to alcohol is affected, resulting in increasingly severe episodes of withdrawal. An agent that ameliorates the kindling response might, therefore, prevent the summative effects of repeated drinking and withdrawal [30].

Recently, Polycarpou et al. [34] published a *Cochrane Database* review of 48 studies with 3610 participants on the utility of anticonvulsants for treating alcohol withdrawal. Compared with placebo, there was a trend for anticonvulsants to improve the participants' global assessment of efficacy, and there was added protection against the development of seizures. Protection from seizures occurred whether anticonvulsants were given alone or in combination with other medications. Also, anticonvulsants appeared to be superior to non-anticonvulsants at reducing the frequency of hallucinations, sweating, gastrointestinal symptoms, and sleep disorders. Furthermore, data from a subset of 12 of these studies ($N = 960$) that used anticonvulsants as anti-withdrawal agents—and in which mortality was reported as an outcome—showed that no participants died. Individuals who received anticonvulsants during detoxification from alcoholism, compared with those who received either placebo or benzodiazepines, were less likely to discontinue treatment due to adverse effects. The data from which the researchers could draw any conclusions to compare the efficacy of various anticonvulsants, especially the newer agents, against one another were too limited. Nevertheless, the authors of the *Cochrane Database* review exercised caution with the interpretation of their results because most studies were of small sample size, outcome measures were generally heterogeneous (a recommendation was made for the revised Clinical Institute Withdrawal Assessment for Alcohol scale [43] to be used as the standard), and there was little consistency between studies on the methods and parameters for randomizing participants to treatment groups.

Anticonvulsants were found to be relatively safe and efficacious medications for treating alcohol withdrawal. Carbamazepine, the most studied medication compared with benzodiazepines, appears to confer added advantages such as fewer adverse events, no demonstrated abuse potential, and the lack of potentiation of

alcohol's psychomotor and cognitive effects. Other anticonvulsants appear to share these properties, as well as being useful for reducing the frequency of a range of other withdrawal symptoms including hallucinations, sweating, gastrointestinal disturbance, and sleep disorders. While the *Cochrane Database* review did not provide any specific recommendations based upon the statistical analysis, clinical experience suggests that anticonvulsants should be considered the medication of choice among those with the potential to experience moderate to severe alcohol withdrawal symptoms and who can tolerate an oral route of administration. Adding benzodiazepines to an anticonvulsant regimen might confer some benefit among those with delirium tremens or severe agitation.

Anticonvulsants in the Treatment of Alcohol Withdrawal

New insights into the pathophysiology of alcoholism have paved the way for studies of novel pharmacological tools for treating the behavioral, cognitive, and physiological symptoms associated with dependence. Among anticonvulsant agents evaluated for efficacy in alcohol dependence, some studies have found that carbamazepine treatment might reduce drinks per drinking day and time to first drink after withdrawal [26, 30]. Small studies of valproate in alcohol-dependent individuals suggest that it might reduce relapse to heavy drinking and promote abstinence [7, 22]. Interestingly, in a recent placebo-controlled trial among alcoholics with comorbid bipolar disorder, valproate treatment was associated with improved drinking outcomes [40].

Sodium Valproate

Sodium valproate is an antiepileptic compound with an unknown mechanism of action although it is suggested that its antiepileptic action may be attributed to increased gamma-aminobutyric acid levels in the brain.

Sodium valproate has been used for over 30 years for the treatment and prevention of alcohol withdrawal. A number of anecdotal and open-label studies indicate that the efficacy and safety of the anticonvulsant valproate (divalproex sodium) are similar to the effects of the anticonvulsant phenobarbital and the benzodiazepine lorazepam in reducing symptoms of alcohol withdrawal [24]. For example, Reoux et al. [35], in a study of individuals with moderate alcohol withdrawal characterized as a score of $\geq$10 on the revised Clinical Institute Withdrawal Assessment for Alcohol scale [43], showed that sodium valproate treatment was well tolerated, reduced the need for benzodiazepine treatment, and led to a decreased likelihood of progression in severity of withdrawal symptoms compared with placebo.

A recent unblinded pilot study by Longo et al. [22] used stringent inclusion and exclusion criteria to compare the safety and efficacy of valproate with those of standard benzodiazepines for detoxification in a small ($N = 16$) inpatient population of individuals with mildly to moderately severe alcohol dependence and moderate alcohol withdrawal. Subjects received standard benzodiazepine detoxification (with lorazepam or chlordiazepoxide), 5-day detoxification with valproate, or detoxification with valproate plus 6-week maintenance. Valproate was administered using a loading-dose strategy (20 mg/kg/day in two doses 6–8 h apart on day 1, then twice daily for 4 days or 6 weeks). Although the differences were not significant, perhaps due to small sample size, alcohol withdrawal symptom reduction tended to be more rapid in the valproate treatment group than in the benzodiazepine control group at 12- and 24-h intervals. Four out of five subjects (80%) in the valproate maintenance group were completely abstinent at the 6-week follow-up, compared with 5 out of 11 (45%) in the combined detoxification-only groups. Furthermore, the participants receiving valproate showed lower liver transaminase levels than at baseline and no other hematological

abnormalities at the 6-week follow-up [22]. This study demonstrated the importance of using a loading dose to achieve rapid therapeutic anticonvulsant blood levels. Despite the small sample size of this pilot study, the finding of higher abstinence rates at the 6-week follow-up in the valproate group supports further investigation of anticonvulsants as post-detoxification relapse prevention agents.

Notably, most trials have been open-label; seizure rates were reported by only a few authors, and standardized multidimensional alcohol rating scales were seldom included. A notable limitation to the use of valproate for the prevention and treatment of alcohol withdrawal symptoms was its disadvantageous adverse events profile. Fatalities due to hepatic failure, life-threatening pancreatitis, and thrombocytopenia have all been reported among individuals who had received valproic acid or its derivatives. Because non-specific gastrointestinal symptoms also have been reported following the ingestion of valproic acid, its clinical utility as an anti-withdrawal agent has been limited.

Carbamazepine

Recent studies support the use of the potent anticonvulsant, carbamazepine, as a pharmacological agent for the treatment of acute alcohol withdrawal. Several double-blind studies have demonstrated that carbamazepine has efficacy at reducing alcohol withdrawal symptoms equal or superior to that of lorazepam, oxazepam, clomethiazole, tiapride, and placebo [24, 26]. It also has been reported that carbamazepine can reduce effectively some measures of alcohol consumption (drinks per drinking day, number of heavy drinking days, and time to the first drinking day) during the post-withdrawal phase [26, 30].

Malcolm et al. [26] examined the efficacy of carbamazepine vs. lorazepam for the treatment of alcohol withdrawal symptoms as well as drinking behavior in the 7 days immediately following the treatment period. They hypothesized that while both carbamazepine and lorazepam would suppress alcohol withdrawal, carbamazepine would show the greater efficacy at ameliorating symptoms and reducing post-treatment drinking among those with a history of multiple episodes of previously treated alcohol withdrawal. In that double-blind trial ($N = 136$), carbamazepine 600–800 mg on day 1—tapered to 200 mg on day 5—was compared with lorazepam 6–8 mg on day 1—reduced to 2 mg on day 5—in a group of individuals experiencing moderate alcohol withdrawal. Participants were randomized to receive the carbamazepine or lorazepam fixed-dose taper across two levels of detoxification histories (0–1 or $\geq$2 prior medicated detoxifications). Also, participants were administered the 10-item revised Clinical Institute Withdrawal Assessment for Alcohol scale [43], an aggregate measure of the severity of alcohol withdrawal that assessed individual symptoms such as nausea, tremor, sweating, anxiety, and agitation [26], prior to medication treatment, daily for 5 days during the treatment phase, and on days 7 and 12 of the post-treatment period. The authors reported that carbamazepine and lorazepam were equally effective at decreasing the acute symptoms of alcohol withdrawal. There were no significant differences by treatment group in revised Clinical Institute Withdrawal Assessment for Alcohol scale scores when all 12 study days were considered. There was, however, a significant treatment-group effect on post-treatment drinking. Participants who had zero or one previous detoxification episode showed no differences in post-treatment drinks per day based on treatment group. Among participants with multiple detoxifications, those who received carbamazepine drank an average of <1 drink/day compared with about 5 drinks/day among the lorazepam group ($p = 0.004$). Furthermore, the relative risk of having a first drink during the post-treatment period was 3 times higher for the lorazepam-treated group than for the carbamazepine group [26]. Potential limitations of the study were the reliance on subjects' reports of previous medically treated withdrawal episodes, the fairly homogeneous demographic profile, and the low level of concomitant substance abuse

by the participants. Nonetheless, the results of the study showed that carbamazepine was as efficacious as lorazepam at treating acute alcohol withdrawal, and had greater efficacy than lorazepam in preventing post-treatment relapse to drinking.

Psychosocial domains such as anxiety, depression, sleep quality, and the ability to return to work might be equally important in mediating outcomes of outpatient treatment, but are often given only limited attention in the outpatient setting. Malcolm et al. [25], therefore, extended their findings by comparing the effects of previous withdrawal history and treatment with carbamazepine or lorazepam on psychosocial outcome measures. In that study, designed as a 2 × 2 factorial (carbamazepine vs. lorazepam, 0–1 vs. ≥2 prior detoxifications), subjects completed a variety of self-rated measures of psychosocial function during the study period. The authors reported a statistically significant effect for scores to be lower for carbamazepine compared with lorazepam on the Zung anxiety scale (34.8 vs. 38.9, respectively; $p = 0.01$) but to be higher on the visual analog scale of sleep quality (i.e., 62.1 vs. 51.2, respectively; $p = 0.02$). Neither the treatment group nor the number of previous withdrawals significantly affected the depression scores. Both the carbamazepine and lorazepam treatment groups did not produce a statistically significant effect on the ability to return to work [25].

The finding that carbamazepine was more efficacious than lorazepam at reducing anxiety and improving sleep is clinically important because the treatment of these psychiatric symptoms during acute detoxification could result in less distress and improved sleep during withdrawal—both of which could reduce the likelihood of relapse. Furthermore, these results have important implications for the subtle withdrawal symptoms, known as "protracted withdrawal syndrome", which can persist for weeks to months following the 5- to 7-day acute detoxification [25]. The symptoms that occur during the protracted withdrawal syndrome include anxiety, sleep disturbances, and mood instability. During the protracted withdrawal period, there is an increased risk of relapse to drinking. Thus, the effective treatment of the symptoms of protracted withdrawal with carbamazepine during the acute detoxification period might improve long-term drinking outcomes.

In sum, carbamazepine and valproate appear to be as effective as benzodiazepines in reducing the symptoms of mild-to-moderate alcohol withdrawal in relatively healthy individuals. The doses given in these studies were generally lower than those that are used when the goal is to achieve anticonvulsant effects. Also, carbamazepine appears to have efficacy that is superior or at least equal to that of other agents such as clomethiazole and tiapride in reducing withdrawal symptoms [24]. Despite the potential advantages of carbamazepine over benzodiazepines, its use can be associated with hepatotoxicity. Therefore, the use of carbamazepine is contraindicated for the treatment of alcohol withdrawal among those with clinically significant hepatic disease. Because carbamazepine can cause blood dyscrasias, it should not be prescribed to individuals with either a propensity toward or a pre-existing hematological disorder.

Gabapentin

Gabapentin has a structural relationship similar to gamma-aminobutyric acid [28], and its mechanisms of action, though understood imperfectly, include the blockade of L-type calcium channels as well as facilitation of gamma-aminobutyric acid synthesis [28, 33]. Preclinical studies show that gabapentin decreases ethanol withdrawal-induced hyperexcitability in isolated slices of hippocampus [2] as well as convulsions and anxiety in alcohol-withdrawn mice [46]. Additional to these pharmacological properties, gabapentin's suitability as a promising candidate medication for treating alcohol withdrawal symptoms is aided by the fact that it does not induce hepatic enzymes and it is excreted unmetabolized in the urine. Hence, gabapentin will not exacerbate alcohol's hepatotoxic effects.

Preliminary evidence supporting the potential of gabapentin to reduce alcohol withdrawal symptoms came from a case report [9] and a few case series that investigated the open-label use of the medication [4, 6, 18, 31, 45]. In a double-blind trial (N = 101), gabapentin was more efficacious than lorazepam at reducing insomnia during alcohol withdrawal [27]. Additionally, it has been proposed, from a case series, that gabapentin could be useful for a particular facet of a severe alcohol withdrawal syndrome—the reduction of tonic-clonic seizures [39].

Nevertheless, in a controlled study by Bonnet et al. [5] of gabapentin (400 mg four times daily) vs. placebo for treating alcohol withdrawal symptoms, there was no significant difference between the two groups in the frequency and severity of their withdrawal symptoms or in the frequency with which the "rescue medication", clomethiazole, was used in the first 24 h. Thus, despite earlier evidence for a potential role of gabapentin in treating the alcohol withdrawal syndrome, such an effect remains to be substantiated by controlled trials. Additionally, large-scale controlled studies are needed to determine whether gabapentin can be useful in treating tonic-clonic seizures that occur during severe alcohol withdrawal.

Although other modulators of gamma-aminobutyric acid function such as tiagabin and vigabatrin—anticonvulsants that inhibit gamma-aminobutyric acid transport and metabolism [41], respectively—have been proposed as potential treatment agents for alcohol withdrawal symptoms [23], there is at present no empirical support for their utility.

Topiramate

Topiramate, a sulfamate-substituted derivative of fructopyranose, was identified originally as a potential anti-diabetic agent [42]. Due to its structural similarity to known anticonvulsants, it was tested and found to have activity in several animal-seizure models. The compound was subsequently developed as an anticonvulsant based on its potency, duration of action, and neuroprotective effect [42]. The anticonvulsant effects of topiramate have been validated in the traditional rodent maximal-electroshock seizure test, as well as in several animal models of epilepsy. In the rat and mouse maximal-electroshock seizure test, topiramate showed potency similar to that of phenytoin and carbamazepine and greater than that of valproate [42].

Recent studies of topiramate suggest that its pharmacokinetic properties provide several advantages over other antiepileptic agents. These advantages include its rapid and complete absorption, minimal metabolism, and minimal interaction with other medications, such as oral contraceptives. Similar to most marketed anticonvulsant agents, topiramate exerts its anticonvulsant effects through blockade of voltage-dependent Na^+ and L-type high voltage-gated Ca^{++} channels and facilitation of gamma-aminobutyric acid-ergic neurotransmission via gamma-aminobutyric acid-A. Additionally, topiramate inhibits the activity of the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate subtypes of glutamate receptors, rather than the more traditional action at the N-methyl-D-aspartate subtype, and selectively inhibits carbonic anhydrase-II and carbonic anhydrase-IV [42]. Topiramate also has been reported to activate potassium conductance due to its ability to inhibit carbonic anhydrase [14].

Titrating topiramate (over a range of 200–800 mg/day) produces a dose-proportional increase in its plasma concentration; both the maximal plasma concentration (C_{max}) and the area under the plasma concentration-time curve are linear and increase in proportion to the dose of topiramate at doses from 200 to 800 mg/day [12, 32]. Due to its low binding to plasma proteins (9–17%), topiramate is unlikely to be displaced by highly protein-bound medications, thus limiting the likelihood for its interaction with other agents [12]. Furthermore, because topiramate is eliminated predominantly in the urine, with an elimination half-life of approximately 21 h [12, 32, 42], and is not metabolized extensively in humans (~20%) [12], topiramate

will not exacerbate the hepatic-enzyme-inducing effects of alcohol.

The pharmacokinetic properties of topiramate might be altered in some special populations. While no specific age-related changes in topiramate clearance or elimination half-life have been reported, a decline in renal function might occur with normal aging. Thus, renal function should be evaluated in all elderly individuals receiving topiramate, since decreased renal function can alter the pharmacokinetics of medications eliminated by the kidneys, and adjustments of topiramate dose might be necessary in individuals with impaired renal function as well as in those undergoing hemodialysis [12, 32].

Topiramate's activity profile would appear to make it an ideal treatment for alcohol withdrawal. Topiramate might reduce the overactivity of the sympathetic nervous system and neuronal hyperexcitability commonly seen in the early phase of alcohol withdrawal, through suppression of glutaminergic input, facilitation of gamma-aminobutyric acid-A-mediated inhibitory impulse, blockade of sodium and calcium channels, and facilitation of potassium conductance.

Indeed, a recent inpatient study by Choi et al. [10] found that topiramate 50 mg/day ($N = 25$) was as efficacious as lorazepam up to 4 mg/day ($N = 27$) at treating alcohol withdrawal, while allowing the individual to transition into outpatient care on the same regimen without the potential for abuse or the increased risk of relapse commonly seen in alcoholics treated with benzodiazepines. Previously, Rustembegovic et al. [38], in a pilot open-label study ($N = 12$), found topiramate (50 mg twice daily) to be efficacious in the treatment of tonic-clonic seizures associated with alcohol withdrawal, with no side effects. Furthermore, Krupitsky and colleagues [20], in a placebo-controlled, randomized single-blind study comparing the safety and efficacy of three antiglutamatergic agents including topiramate (25 mg four times daily), memantine (10 mg thrice daily), and lamotrigine (25 mg four times daily) versus diazepam (10 mg thrice daily) for the treatment of alcohol withdrawal and detoxification in moderately severe alcoholic male patients ($N = 127$), found that all active medications significantly reduced observer-rated and self-rated withdrawal severity, dysphoric mood, and supplementary use of diazepam compared with placebo. All medications were well tolerated. This study also provided suggestive evidence of subtle advantages of lamotrigine over memantine and topiramate in reducing observer-rated (revised Clinical Institute Withdrawal Assessment for Alcohol scale [43]) and self-reported withdrawal severity. However, this study compared only single doses of each drug; the dose used for topiramate is not the one shown to be efficacious in outpatient trials, thereby rendering it difficult to extrapolate such conclusions from this study.

Because topiramate can be initiated while an alcohol-dependent individual is still drinking, and has been shown to improve drinking outcomes in such individuals [16, 17], it is reasonable to hypothesize that topiramate treatment might be a strategy that can be used to decrease alcohol withdrawal as well as initiate and maintain abstinence from alcohol. Individuals who receive topiramate treatment do, however, need to be monitored closely during dose escalation to avoid adverse events such as sedation, paresthesia, anorexia, and cognitive impairment, and at all times for the rarer adverse events of glaucoma, transient blindness, depression, and suicidal ideation.

Neurosteroids—Another Promising Non-Benzodiazepine Approach to Decreasing the Anxiety Response in Alcohol Withdrawal

Another approach has been to determine the potential utility of neurosteroids. Of these, one compound that appears to be promising is alphaxalone (5alpha-pregnan-3alpha-ol-11,20-dione). Alphaxalone might modulate the sympathetic and other neuronal systems by inhibiting nicotinic acetylcholine receptors, and has been used clinically as an anesthetic.

Alphaxalone has been shown to modulate ethanol-induced, withdrawal anxiety-like behavior in rats ($F = 10.58$; $p < 0.001$) without affecting locomotor activity [19]. While studies in other animal models, as well as future human studies, would be required to evaluate this compound further, this effort will be limited by the withdrawal of alphaxalone from the market by its manufacturer because of its ability to cause anaphylactic reactions.

Summary and Conclusions

The use of anticonvulsant medications in treating alcohol-dependent individuals proffers the novel approach of an anti-withdrawal agent, an anti-drinking medication, or both. Anticonvulsants appear to be more effective against a larger range of withdrawal symptoms than benzodiazepines, especially among alcohol-dependent individuals with moderate to severe withdrawal symptoms. Additionally, anticonvulsants such as sodium valproate and topiramate might have a further advantage to benzodiazepines in that they appear useful both for treating the acute withdrawal symptoms and, once abstinence has been achieved, for preventing relapse by modulating post-cessation craving and affective disturbance. Obviously, this is an attractive pharmacological prospect as the use of a single medication that is efficacious at the various stages of treatment reduces the need for polypharmacy, facilitates the buildup of dosing levels early in treatment, and minimizes the potential for unexpected adverse events and alcohol/medication interactions. Research specifically designed to determine the utility and feasibility of such an approach is needed.

Because of the potential utility of certain anticonvulsants (e.g., valproate) in treating other psychiatric disorders such as bipolar disorder, it is possible that their utility might also be extended to treating alcohol-use disorders with a comorbid psychiatric condition.

Notably, the adverse events profile of anticonvulsants has limited their use for treating the alcohol withdrawal syndrome. These limitations have highlighted the need for newer pharmacological agents that suppress withdrawal rapidly and have fewer adverse events, limited interaction with alcohol and other medications, and low potential for abuse. These agents should also be well tolerated in alcohol-dependent individuals with comorbid psychiatric conditions. With the ongoing explosion of neurobiological knowledge associated with the treatment of alcohol-related disorders, other classes of medications such as neurosteroids might find a therapeutic role.

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Nicotine

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Contents

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Tobacco Use: A Global Health Epidemic

One in five Americans are current smokers [36]. Between 1997 and 2004, national prevalence rates of tobacco use showed a significant decline (24.7–20.9%); however, recent trends indicate that this decline has stalled [36]. Other developed regions in the world, such as countries of Western Europe (Great Britain, France), have also witnessed a plateauing of smoking prevalence rates [268]. Compounding these disappointing recent trends is the dramatic increase in tobacco use in low-income countries such as China and India [243]. Estimates from 2002 suggest that one-third of adults in China and India are current smokers [148], and, with intensive marketing strategies being employed by the tobacco companies in these regions, these rates are expected to increase.

Each year, cigarette smoking causes more than 400,000 premature deaths in the United States and 4.2 million premature deaths around the world from cancer, cardiovascular and respiratory diseases, and perinatal conditions [37]. Tobacco use accounts for at least 30% of all cancer deaths in the United States and smoking has been causally linked to lung, head and neck, esophageal, pancreatic, bladder, kidney, cervical, endometrial, and gastric cancer, and acute myeloid leukemia [255]. By the year 2030, more than 80% of world's deaths attributable to tobacco use are expected to be among smokers in developing countries [148, 243].

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_49,

Given this global health epidemic, there is a need to gain a greater understanding of the determinants of tobacco use and dependence as well as effective treatment approaches. We begin this chapter with a brief overview of the neurobiology of nicotine's effects. Next, we summarize research on the environmental and genetic etiology of nicotine dependence, followed by a discussion of conditioned factors that contribute to smoking persistence, in parallel with nicotine's pharmacologic effects. This background information is followed by a brief review of methods for assessing nicotine dependence, available treatments for nicotine dependence and individual differences in treatment response, and the cost-effectiveness of these treatments in the context of public policy.

Neurobiology of Nicotine Dependence

Nicotine is the addictive component of tobacco that has been consistently shown to perpetuate cigarette smoking behavior, even if the user intends to quit [10, 206]. Inhaled nicotine is rapidly absorbed into the lungs and then passes to the brain within 10 S of absorption [12]. Once in the brain, nicotine binds to nicotinic acetylcholine receptors located on dopaminergic neurons in the ventral tegmental area, as well as other neuronal cell bodies [51, 158]. To date, at least 17 nicotinic acetylcholine receptor subunits have been identified (α1–α10, β1–β4, γ, δ, and ε) [159]. The α4β2 subunit-containing nicotinic acetylcholine receptors predominate in the ventral tegmental area and have higher affinity for nicotine, as compared with homomeric α7 nicotinic acetylcholine receptors that are less abundant in this region [40, 265].

A single cigarette provides sufficient nicotine to occupy approximately 90% of α4β2–containing nicotinic acetylcholine receptors for several hours [30]. Stimulation of these nicotinic acetylcholine receptors by nicotine increases burst firing of dopamine neurons, increasing dopamine levels in the nucleus accumbens and rewarding effects [200]. Over time, however, the proportion of unbound nicotinic acetylcholine receptors increases, producing a corresponding increase in smoking urges [235]. Further, during nicotine withdrawal, neurotransmitter release (including dopamine) is reduced and smokers report symptoms that include negative mood, fatigue, and mild cognitive deficits [139, 163]. This anhedonic state can be reversed by smoking a cigarette [2, 121].

Many additional neurotransmitters play a role in nicotine's effects, including norepinephrine, acetylcholine, glutamate, serotonin, beta-endorphin and γ-aminobutyric acid (GABA) [14]. α4β2 nicotinic acetylcholine receptors are also located on GABAergic interneurons, although these nicotinic acetylcholine receptors desensitize quickly, while α7 nicotinic acetylcholine receptors on glutamate neurons desensitize more slowly [53]. The endogenous opioid system also contributes to these influences, via release of beta-endorphin, which binds to mu-opioid receptors on GABAergic interneurons in the ventral tegmental area [141, 238].

Etiology of Nicotine Dependence

Abundant evidence from twin studies indicates that nicotine dependence arises from both genetic and environmental influence [141, 237]. Indeed, approximately 60–70% of the variability in nicotine dependence and smoking persistence is due to genetic factors [31, 115, 122, 141, 156]. Adoption studies, likewise, indicate that nicotine dependence has heritable components [179]. However, as a complex trait, nicotine dependence is most likely the result of genes, environment, and their interactions.

Smoking initiation is partly determined by peer influences, parental exposure, and tobacco advertising [56, 65, 253]. In fact, it is estimated that the odds of a teenager initiating a smoking habit are increased 1.5- to 2-fold if he or she has a parent or close childhood friends who smoke [29]. Experimentation with cigarettes

among adolescents is also strongly influenced by tobacco marketing [188, 189]. Another important environmental determinant in the process of initiation and development of a regular smoking habit is access to cigarettes. Data from the Youth Risk Behavior Surveillance System report that approximately one-quarter of teenagers buy their own cigarettes (23.5%) while 30% had someone else purchase them [109]. State-level tobacco control policies to limit teen access to cigarettes significantly deter smoking behavior among teens [120, 226].

Evidence from twin studies for genetic influences on smoking has prompted intense investigation of the role of specific genes and polymorphisms associated with nicotine dependence and related phenotypes. A likely candidate for association is the gene that codes for the enzyme CYP2A6, which metabolizes nicotine [149]. Associations of CYP2A6 have been replicated in independent studies [125, 150, 164]. Specifically, persons carrying low-activity alleles (slow metabolizers) smoke fewer cigarettes per day and report lower levels of nicotine dependence [125, 150].

Given the important role of neuronal nicotinic acetylcholine receptors in nicotine reinforcement [152, 187, 212] (see Fig. 4 in Chapter "Pharmacotherapy for Alcoholism and Some Related Psychiatric and Addictive Disorders: Scientific Basis and Clinical Findings"), genetic variation in these receptors has also been recently examined. Variants in the gene coding for the α4 nicotinic acetylcholine receptor subunit, *CHRNA4*, have been related to nicotine dependence [61, 102, 142], as have variants in *CHRNA3* and *CHRNA5* [15, 209, 244]. In contrast, associations of nicotine dependence with polymorphisms in *CHRNB2* have not been identified, but most studies did not have sufficient coverage of single nucleotide polymorphisms in this gene [146, 231]. A haplotype in *CHRNB1* has also been associated with nicotine dependence among African Americans and Caucasians [145].

Congruent with the central role of dopamine signaling in the rewarding effects of nicotine [83, 121, 173], genes in this pathway have been a particular research focus. Association studies have reported a higher prevalence of the Taq1A A1 allele in the ANKK1 gene (about 10 kb upstream of the *DRD2* gene) among smokers compared with nonsmokers [46, 234], while other findings have been negative [18]. A variable number tandem repeat polymorphism in the 3′ end of the dopamine transporter (*SLC6A3*) gene has also been associated with smoking behavior [130, 208]; however, this has not been replicated in other studies [259]. Finally, two independent studies have provided evidence for interacting effects of the *ANKK1* Taq1A and *SLC6A3* variants on the likelihood of cessation [132, 242]. A separate study found associations of *SLC6A3* genotypes with cessation following treatment with either nicotine replacement therapy or bupropion [178]. The high-activity (Val) allele of the $Val^{158}Met$ polymorphism in the catechol-*O*-methyltransferase gene has also been associated with nicotine dependence and relapse in smoking cessation treatment [17, 45, 108, 169, 245]. Lastly, the reduced activity 7-repeat allele of the *DRD4* gene variable number tandem repeat has been related to cue-elicited smoking behavior [101] and smoking persistence [221], and a synonymous single nucleotide polymorphism of unknown function in the dopamine beta-hydroxylase gene has been related to smoking behavior [107, 157].

Consistent with neurobiological evidence described above, the mu-opioid receptor (OPRM1) Asn40Asp functional variant (Asp40 allele) has been associated with smoking persistence [135], as well as reduced nicotine reward among women [198]. A recent study comparing smokers with high versus low levels of nicotine dependence did not find associations with this *OPRM1* variant; however, haplotype analysis suggests that other variants, which may be in linkage disequilibrium with the Asn40Asp polymorphism, are related to this smoking phenotype [270]. Finally, despite effects of nicotine on serotonin neurotransmission, there is no strong evidence linking smoking cessation with genes in the serotonin pathway [55, 129, 166] although associations with nicotine dependence have been reported [165].

In general, it has proven difficult to identify candidate genes with robust, replicable associations with nicotine dependence and smoking persistence. Consequently, the candidate gene approach is being supplemented by genome-wide association studies that have identified novel genes associated with smoking behaviors [19]. For example, a recent genome-wide association study of smoking cessation identified several novel genes involved in signaling as well as cell adhesion molecules [257].

Conditioned Rewarding Factors and Smoking Persistence

In addition to the highly addictive nature of nicotine, a growing body of literature has also documented how the sensory aspects of smoke inhalation become reinforcing through a behavioral conditioning process. Indeed, denicotinized cigarettes produce significant increases in levels of smoking satisfaction and reward and reductions in craving [205, 263]. Consistent with these data are results showing that when the sensory aspect of inhalation is blocked, smokers' subjective ratings of smoking a denicotinized cigarette are attenuated [204].

Environmental cues associated with nicotine delivery also can reinstate self-administration, supporting the extension of the conditioning process to learned environmental associations [143]. Human laboratory studies have shown that smoking cues, such as a lit cigarette and the smell of smoking a cigarette, reliably induce subjective and physiological responses in smokers [35, 57, 160]. This physiological reactivity is associated with a decreased likelihood of sustained abstinence among treatment-seeking smokers [174]. Overnight abstinent smokers "work" harder to earn cigarette puffs in a computer game of the reinforcing value of nicotine when exposed to cigarette cues than in the absence of such cues [183]. Neuroimaging studies also provide evidence for increased activation in the brain's visuospatial and reward pathway during passive viewing of smoking-related versus neutral cues [155, 233]. Moreover, this brain response is accentuated among smokers with higher levels of nicotine dependence [233]. Importantly, these effects may occur only when smokers have an expectation to smoke immediately after the scan [153].

The data described in this section suggest that smoking persistence is maintained, not only by pharmacologic factors, but also by conditioned rewarding factors, suggesting the importance of addressing both the biological and behavioral influences in smoking behavior within treatment programs. In the following sections, we turn to clinical issues in nicotine dependence, such as methods of assessment and treatment efficacy.

Assessment of Nicotine Dependence

Two formal diagnostic systems for nicotine dependence have been developed by the American Psychiatric Association and the World Health Organization. The American Psychiatric Association diagnostic system is the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition [5], and the World Health Organization system is the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [267]. The latest *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, criteria require that a smoker meet at least 3 of the following criteria in the same 12-month period: (1) tolerance (i.e., a need for increased amounts of nicotine to achieve the desired effect or a decreased effect from using the same amount of nicotine); (2) withdrawal (see below); (3) nicotine is often taken in larger amounts or over a longer time period than was intended; (4) repeated unsuccessful attempts to quit smoking; (5) a great deal of time is spent in activities necessary to obtain or use the substance (i.e., chain smoking) or to recover from its effects; (6) giving up recreational or occupational activities for smoking, and (7) continued use despite health risks.

The International Statistical Classification of Diseases and Related Health Problems, 10th Revision system includes the criteria of tolerance, withdrawal, unsuccessful attempts to stop, use in larger or longer amounts and giving up activities to use as well as compulsion to use tobacco. Unlike the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition conceptualizes nicotine withdrawal as a separate disorder [7]. Occurring within 24 h of abstinence, nicotine withdrawal is present if four or more of the following criteria are experienced: (1) dysphoria or depressed mood; (2) insomnia; (3) irritability; (4) frustration or anger; (5) anxiety; (6) difficulty concentrating; (7) restlessness; (8) decreased heart rate; and (9) increased appetite. In addition to experiencing 4 or more of these criteria within 24 h of abstinence, the symptoms should also produce clinically significant levels of distress that interfere with the individual's capacity to function [8].

In the clinical research setting, assessment of nicotine dependence is more typically carried out using the Fagerstrom Test for Nicotine Dependence [60]. This 6-item self-report measure of nicotine dependence has received criticism for having low internal consistency (Cronbach's alpha=0.64) [194] and for defining nicotine dependence as a unidimensional, physiological construct [82], despite evidence to the contrary [28, 89, 192]. Further, data show poor concordance between the *Diagnostic and Statistical Manual of Mental Disorders*/International Statistical Classification of Diseases and Related Health Problems criteria with the Fagerstrom Test for Nicotine Dependence [94, 161]. In terms of criterion validity, some studies have shown that higher levels of dependence (as measured by the Fagerstrom Test for Nicotine Dependence and/or single Fagerstrom Test for Nicotine Dependence items) are inversely related to quitting success [26, 104, 171] whereas other studies have shown the Fagerstrom Test for Nicotine Dependence to have limited ability to reliably predict abstinence [20, 92, 116], especially for more dependent smokers [124]. Despite these concerns, the Fagerstrom Test for Nicotine Dependence remains a widely used and reported test of nicotine dependence [236].

Food and Drug Administration-Approved Treatments for Nicotine Dependence

Nicotine Replacement Therapies

Currently, five nicotine replacement therapies are approved by the United States Food and Drug Administration for the treatment of nicotine dependence: the gum, the transdermal patch, the nasal spray, the inhaler, and the lozenge (see Table 1). Nicotine replacement treats nicotine dependence by: (1) relieving withdrawal symptoms (e.g., irritability, restlessness, depressed mood, increased appetite) that characterize initial physical and psychological reactions to cessation; (2) reducing the experience of nicotine craving, and (3) providing a safer way to experience the neurobiological and psychophysiological effects of nicotine. Meta-analyses have demonstrated that nicotine replacement therapies double cessation rates, versus placebo (pooled odds ratio = 1.58, 95% CI: 1.50–1.66) [236]. Yet, only one-quarter to one-third of smokers who use nicotine replacement therapies to aid their smoking cessation attempt can expect to have quit by 6 months after treatment [201, 214, 215, 223, 248].

Nicotine Gum

In 1996, the nicotine gum became the first over-the-counter treatment for smoking cessation [203, 227]. Despite some adverse side-effects such as oral and gastric symptoms, jaw ache and under-dosing, nicotine gum has been found to produce significantly higher quit rates,

Table 1 Food and drug administration-approved medications for tobacco dependence

Medication	Recommended duration and dose[a]	Estimated quit rate[b] (95% CI) number of studies [reference]	Advantages	Disadvantages	Cost
Nicotine Gum	Up to 12 weeks; 2 mg (for those who smoke < 25 cigarettes/day); 4 mg (for those who smoke ≥ 25 cigarettes/day)	17.4% (17–18%) 52 Trials [230]	Treat oral behavioral ritual and cue-elicited craving; prevent weight gain	Adverse side effects and poor compliance	$4.00-$5.00/day
Nicotine Patch	Up to 10 weeks; Dose duration varies by cigarettes/day	13.7% (13–15%) 37 Trials [230]	Better compliance and nicotine replacement; few side effects	Does not treat cue-elicited craving	$2.50/day
Nicotine Spray	Up to 6 months; 8–40 sprays/day	24% (20–28%) 4 Trials [230]	Nicotine is rapidly absorbed; treat cue-elicited craving	Unpleasant side effects and poor compliance	$5.00-$15.00/day
Nicotine Inhaler	Up to 6 months; 6–16 cartridges/day	17% (14–21%) 4 Trials [230]	Treat oral behavioral ritual and cue-elicited craving	Unpleasant side effects and poor compliance	$7.00-$18.50/day
Nicotine Lozenge	Up to 12 weeks; 2 mg (for those who smoke their first cigarette more than 30 min after waking) and 4 mg (for those who smoke their first cigarette within 30 min of waking)	17% (15–20%) 4 Trials [230]	Good nicotine replacement; treats oral behavioral ritual and treats cue-elicited craving; few side effects	Compliance is unknown	$3.00-$4.00/day
Bupropion	Up to 12 weeks; 300 mg/day; 150 mg per day for 3 days then 300 mg/day from day 4 to end of treatment	30.5% (23–38%) 2 Trials [64] 31 Trials [95]	Good side effect profile; low abuse liability; prevent weight gain	Relatively more costly	$4.00-$5.00 (300 mg)
Varenicline	Up to 12 weeks; 2 mg/day; 0.5 mg for days 1–3, 0.5 mg twice daily for 4 days, and 1 mg twice daily from day 8 to end of treatment	35% (33.5–36.7%) 3 Trials [75, 112, 266]	Well-tolerated by the majority of users; reduces withdrawal and reinforcing effects of nicotine	A Food and Drug Administration warning regarding some side effects (depressive symptoms) may deter users	Unknown

[a]Recommendations are taken from the manufacturer of the agent and/or from Fiore [64]
[b]6-month or greater point-prevalence quit rates, biochemically verified

compared with placebo [39, 229]. In one of the first randomized, double-blind, controlled trials, participants who received nicotine gum (2 mg) were significantly more likely to be abstinent at the 1- and 6-month follow-up assessments than placebo controls [90]. In a review of 108 randomized clinical trials that incorporated at least a 6-month follow-up assessment, participants using the gum were over one-and-a-half times more likely (odds ratio=1.66) to remain abstinent at 1-year post-quit date, compared with placebo [229]. The 4-mg gum capsule produces higher quit rates than the 2-mg dose, particularly among highly-dependent smokers [68, 210, 246], while the addition of smoking cessation counseling bolsters the effectiveness of nicotine gum further [39].

A novel formulation of the standard nicotine gum in the form of a rapid release gum has recently become available. This may provide greater relief of craving compared with the standard nicotine gum. A study with 319 smokers exposed subjects to a smoking cue (i.e., lighting a cigarette, but not smoking it) and then randomly assigned them to standard or the rapid-release nicotine gum, and repeatedly assessed nicotine craving. Compared with standard nicotine gum, the rapid-release gum significantly reduced cravings [176]. The nicotine gum is easily available, has low abuse potential, and is effective for many smokers [224, 236].

Transdermal Nicotine Patch

The nicotine patch is one of the most widely used forms of nicotine replacement therapy, presumably because of the relatively few side effects and the ease with which it can be administered [62, 262]. In a meta-analysis of 17 studies and over 5,000 participants, quit rates among patch users were found to be more than double those for placebo at the end of treatment (27% vs. 13%, respectively) and at 6-month follow-up (22% vs. 9%) [62]. Other randomized controlled trials have yielded similar results (e.g., [52, 98, 140, 247]).

An important question is whether higher patch doses (e.g., 42 mg) or using the nicotine patch for a longer duration increases quit rates. Studies comparing the efficacy of a 42-mg patch with the standard 21-mg dose have had mixed results. One study found the 42-mg dose to produce non-significantly higher quit rates than the 21-mg dose at a 4-month follow-up (39% vs. 24%); another study reported that, while the two doses produced similar quit rates, the 42-mg dose significantly increased rates of side effects (nausea, vomiting, erythema) vs. the 21-mg dose [110]. In contrast, another study reported a significant effect of patch dosage on abstinence rates at 8 weeks post-quit date; however, at 1-year follow-up, differences in abstinence rates by patch dosage were no longer significant (67% vs. 35%) [50]. Thus, although the higher patch dose (i.e., 42 mg) may produce higher quit rates than the standard 21-mg dose, in the short term, evidence for enhanced efficacy in the long-term is lacking.

Currently, there are few data available to evaluate the efficacy of extended treatment with transdermal nicotine [62, 228]. A meta-analysis compared the odds ratios for transdermal nicotine trials with $\leq$8 weeks of treatment with the odds ratios from trials with >8 weeks of treatment found no effect for treatment duration [230]. In this comparison, only 3 trials were used to represent studies that provided >8 weeks of patch treatment. The review concluded that there was no difference in the odds ratios for cessation. However, this comparison included studies that varied in terms of sample size, treatment duration, patch dose, presence of adjunctive behavioral counseling, and outcome measures utilized. A close look at these studies underscores the lack of complete data to assess the relative benefits of maintenance therapy with transdermal nicotine. Two studies used fewer than 100 participants [22, 72], and the third study only assessed continuous abstinence, a far more conservative measure of cessation no longer recommended [249]. The recent Agency for Healthcare and Research Quality clinical guidelines state that extended treatment with nicotine patch or gum is an effective treatment strategy and

advocate extended treatment for nicotine dependence as being preferable to returning to smoking [258]. Thus, an important area of future research is the systematic evaluation of maintenance therapy with transdermal nicotine for nicotine dependence.

Nicotine Spray

Nicotine nasal spray more closely mimics the rate of nicotine delivery that is achieved by cigarettes [213]. While transdermal nicotine patch has been shown to reach a flat peak of plasma concentration within 5–10 h and the gum within 30 min, nicotine nasal spray reaches this peak within 10 min [85]. However, this more rapid nicotine delivery produces side effects such as burning sensation and watery eyes that have been reported to deter adherence, particularly in the first week of a quit attempt [97]. These effects typically dissipate after one week of treatment, as smokers develop tolerance to the spray's effects. Nevertheless, nicotine nasal spray has been reported in numerous randomized, controlled clinical trials to produce significantly higher abstinence rates than placebo spray [20, 86, 215, 240]. At 6- and 12-month follow-up, abstinence rates of 29–32% and 18–27% have been reported, while placebo quit rates at the same time points have ranged from 10–18% to 8–17% [20, 86, 215, 240].

Nicotine Inhaler

The nicotine inhaler is "puffed" by the user to obtain vaporized nicotine and, as such, is thought to mimic the behavior of smoking more closely than other forms of nicotine replacement therapy [93]. Three randomized clinical trials have shown the active inhaler to be more effective than placebo [87, 216, 248]. For example, 6-month quit rates of 17–35% vs. 8–9% have been reported for the inhaler versus placebo [87, 216, 248]. More recent studies comparing preference for different forms of nicotine replacement therapy and patterns of use have shown the nicotine inhaler (in addition to nasal spray) to be the preferred mode of nicotine replacement therapy among heavier smokers [262]. Additionally, highly dependent smokers using the nicotine inhaler were reported to have lower relapse rates than those using other nicotine replacement therapy products (e.g., patch, spray, gum). However, compliance rates for the nicotine inhaler may be lower than for other forms of nicotine replacement therapy [77].

Nicotine Lozenge

Fewer studies have evaluated the efficacy of the nicotine lozenge. The pharmacokinetic properties of the lozenge are comparable to those of nicotine gum, where the nicotine is rapidly absorbed via the buccal mucosa, providing a "peak" level of nicotine that declines with time [41]. Levels of nicotine absorption from the nicotine lozenge are reported to be 25–27% higher than nicotine gum at both the 2 and 4-mg doses [41]. This difference has been attributed to the fact that nicotine gum retains some nicotine in the gum base whereas the lozenge does not [41]. With regard to efficacy, both the 4-mg and 2-mg lozenges have been shown to produce significantly higher quit rates than placebo (e.g., 4 mg vs. placebo: 49% vs. 21%; 2 mg vs. placebo: 46% vs. 30% at 6 weeks follow-up) [223]. The lozenge may also reduce self-reported withdrawal symptoms such as anxiety, craving, difficulty concentrating, impatience, and restlessness [170]. Additionally, one study has shown the lozenge to be particularly effective for smokers who were unable to quit using other forms of pharmacotherapy [225]. Taken together, these studies suggest that the lozenge is a potentially effective form of treatment that warrants further study.

Comparing and Combining Nicotine Replacement Therapies

Studies that have compared the efficacy of the different forms of nicotine replacement both

directly [77, 134] and indirectly [230] suggest that no one form of nicotine replacement therapy outperforms the other. For example, in a randomized clinical trial that compared the short-term efficacy of nicotine gum vs. patch vs. nasal spray vs. inhaler, there were no significant differences in sustained abstinence rates at a 3-month follow-up (gum 19.7%; patch 21.0%; spray 23.8%; inhaler 24.4%) [77].

Meta-analytic assessments of combined nicotine replacement therapy vs. a single therapy indicate that combination therapy is more effective [63, 230]. Specific studies have shown that patch plus gum is more efficacious than gum alone [123, 196], while another study showed that patch plus spray outperformed patch alone [21]. In contrast, Tonnesen and Mikkelson [250] reported that quit rates were equivalent among smokers treated with patch plus inhaler versus either nicotine replacement therapy alone, and Croghan et al. [49] showed no differences in quit rates among smokers treated with the patch plus the nasal spray, compared with either nicotine replacement therapy alone. Despite the over-the-counter availability of some forms of nicotine replacement therapy (gum, patch, lozenge), less than one quarter of treatment-seeking smokers reported using over-the-counter nicotine replacement therapy in their most recent quit attempt [190]. Identification and implementation of efficacious strategies to improve the uptake of these pharmacotherapies is an important area of work that warrants greater attention.

Non-Nicotinic Treatments for Nicotine Dependence

Bupropion Sustained Release

Many studies have demonstrated the efficacy of sustained release bupropion as a treatment for tobacco addiction and relapse prevention [63, 154]. The 300-mg dose of bupropion outperformed placebo and transdermal nicotine patch both at end of treatment and at one-year follow-up [99, 111]. Specifically, one-year quit rates of 30% were achieved by bupropion recipients, compared with 16% of those who received patch and 16% for those who received placebo [111]. Bupropion has also demonstrated efficacy for African-American smokers, producing a quit rate of 36% at the end of treatment for participants taking bupropion compared with 19% for placebo [4]. Finally, bupropion has been shown to reduce relapse rate, especially among older smokers and those who gained little or no weight when quitting [100].

Bupropion's precise mode of action has yet to be determined, although evidence suggests that it inhibits post-synaptic uptake of dopamine and norepinephrine [9, 47, 211]. Consistent with this, bupropion reduces negative affective states associated with abstinence [219]. There is also evidence that bupropion is a nicotinic receptor antagonist, leading to the hypotheses that treatment may reduce the reinforcing effects of smoking [232]. This putative mechanism has received some support in a recent study that compared the effects of an acute dose of bupropion versus placebo in a sample of non-treatment-seeking smokers [48]. Smokers treated with a single dose of bupropion had significantly lower ratings of cigarette intensity than those treated with placebo, and there was a trend for a reduction in ratings of smoking satisfaction; however, they also smoked significantly more cigarettes during an ad-lib smoking phase, leading to speculation that they were compensating for reduced rewarding effects of nicotine [48]. While bupropion's mode of action remains to be identified, its role as an efficacious smoking cessation treatment has been well established.

Varenicline

In May 2006, varenicline was approval by the United States Food and Drug Administration as a treatment for nicotine dependence. Varenicline is a selective $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor partial agonist (up to 60%)

[106]. By activating α4β2 nicotinic acetylcholine receptors, which are expressed widely on dopamine and γ-aminobutyric acid neurons in the ventral tegmental area, varenicline attenuates nicotine's effect on dopamine release, while maintaining dopaminergic tone [44, 106]. Varenicline's agonist function is thought to minimize craving and withdrawal, while its antagonist properties are expected to attenuate the reinforcing effects of nicotine, thereby reducing satisfaction from a "slip" cigarette and the likelihood of relapse [66].

Data from three large scale randomized clinical trials have demonstrated varenicline's efficacy as a treatment for nicotine dependence. The first two trials randomized 2,052 smokers to placebo, 300-mg bupropion, or 2-mg varenicline for 12 weeks and assessed quit rates up to 1 year following the start of treatment [75, 112]. Assessment of continuous quit rates for the last 4 weeks of treatment (weeks 9–12) across the two trials at the end of treatment showed an advantage for varenicline (44%), versus bupropion (30%) and placebo (18%). The continuous quit rate for varenicline at the 1-year follow-up diminished (22%), but it remained significantly better than for bupropion (16%) or placebo (10%). In a third study [251], smokers received open-label varenicline (1 mg twice daily) for 12 weeks; subjects who remained abstinent at the end of 12 weeks were randomized to 12 additional weeks of 1 mg twice daily of varenicline or placebo. Quit rates were assessed 28 weeks from the end of the second 12-week treatment phase. The quit rate at the end of the first 12-week treatment phase was 63%. The continuous abstinence rate at the end of the 28-week follow-up period was significantly greater for the varenicline-treated participants, versus placebo (71% vs. 50%). Across all three trials, adverse events and rates of discontinuation were similar across the placebo and varenicline arms, indicating that the agent was well tolerated as well as efficacious. Subsequent studies found varenicline to be significantly more effective than placebo among male Asian and Japanese smokers [172, 252]. Finally, one study that reported on the safety and efficacy of 52 weeks of varenicline versus placebo found that although adverse events were reported by 96% of the subjects receiving varenicline and 83% of those receiving placebo, at the end of treatment (52 weeks), varenicline produced significantly higher quit rates (37% vs. 8%) [266]. In 2008, the Food and Drug Administration issued a warning regarding side effects such as suicidal ideation and severe changes in mood and behavior that were noted by smokers taking varenicline [256]. To date, this "black box" warning remains in effect.

Other Potential Medications for Nicotine Dependence

Despite the availability of Food and Drug Administration-approved treatments for smoking cessation (nicotine replacement therapy, bupropion, and varenicline), only 1 in 4 smokers can expect to remain abstinent using these therapies [217]. The identification and testing of potential new medications for the treatment of nicotine dependence remain a research priority [138, 217]. To date, several early-stage trials (Phase II or III) have evaluated: monoamine oxidase inhibitors such as lazabemide, selegiline, and moclobemide; selective serotonin reuptake inhibitors such as paroxetine, fluoxetine, and sertraline; mu-opioid receptor antagonists such as naltrexone; GABAergic agents that include baclofen and gabapentin; nicotinic agents such as mecamylamine and the nicotine vaccine; and the cannabinoid receptor-1 antagonist, rimonabant. A comprehensive review of these potential treatments can be found in a review article by Schnoll and Lerman [217]. Additionally, the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate glutamate receptor antagonist, topiramate, has shown potential as a safe and promising medication for the treatment of cigarette smoking in alcohol-dependent individuals [105] and as an aid to smoking cessation among men [6].

Individual Differences in Treatment Response

Investigation into individual differences in response to various treatments for nicotine dependence has been an extensive area of study. A primary goal of this line of work is to identify subgroups of smokers for whom different treatments might be more effective. In this way, specific criteria for prescribing treatments can be identified, and targeted treatments for smoking cessation can become more of a reality. Studies to date have evaluated individual differences in response to treatment based on gender, race, depression, and genetic variation.

Gender

Recent population data indicate that, although fewer women than men are current smokers (18% vs. 24%, respectively), the quit ratio (former smokers to current smokers) is lower for women than for men (42% vs. 48%, respectively) [36, 38]. Consistent with these data are results from clinical trials of nicotine replacement therapy (gum, transdermal nicotine) showing that women tend to respond less favorably than men [117, 264]. In contrast, data from two meta-analyses showed that nicotine replacement therapies have comparable efficacy for men and women [118, 163]. These meta-analyses included trials that provided only partial outcome data, omitted some relevant trials, and may have possessed limited statistical power to examine gender differences in light of low absolute abstinence rates [218].

Several hypotheses have emerged to account for the gender differential response to cessation treatments. These include: concern about post-cessation weight gain [184, 193], reduced response by women to physical smoking cues (i.e., onset of withdrawal, craving) compared with "behavioral" smoking cues (i.e., smell of tobacco, coffee, situational prompts) [182, 185]; reduced effect of nicotine replacement therapy treatments (i.e., patch, spray, gum, etc.) [184]; and elevated rates of depression (both clinical and sub-syndromal) [1, 23, 24, 71]. Menstruation has also been shown to influence quitting success. Preliminary data suggest that women whose quit dates occur in the follicular phase of their menstrual cycle as compared with their luteal phase had better treatment outcomes [67]. Lastly, women have significantly higher rates of nicotine metabolism than men, particularly when using oral contraceptives [96], indicating that women may require higher nicotine replacement therapy doses.

Gender differences in treatment response to non-nicotine based treatments such as bupropion and varenicline have been more equivocal. One the one hand, Killen et al. reported that women showed lower quit rates following bupropion compared with men [119]. On the other hand, another study that tested the efficacy of bupropion reported 52-week quit rates for men and women at 37.8% and 36.4%, respectively [74]. More recent studies that have examined gender differences in response to varenicline showed that biochemically confirmed continuous abstinence rates at weeks 9 through 12 were roughly equivalent for men and women (43% vs. 46%, respectively) [44]. Moreover, a pooled analysis of data from three trials showed no gender differences in 12-month quit rates in varenicline-treated participants [199]. Thus, bupropion may reduce the reported gender disparity in smoking cessation outcomes.

Race

Data suggest that there are important differences in smoking behavior across United States ethnic/racial groups. African Americans smoke approximately 35% fewer cigarettes than Caucasian smokers and tend to prefer mentholated, high-nicotine cigarettes [3, 43]. African-American smokers also tend to have slower nicotine metabolism [13, 34, 181, 261], and show a different smoking topography, compared with Caucasians [3, 13]. Despite smoking fewer

cigarettes, African Americans bear a disproportionately higher prevalence of the negative health-related illnesses associated with smoking as well as having higher rates of smoking-related morbidity and mortality compared with any other ethnic group [81].

Data suggest that African-American smokers are motivated to quit smoking and are more likely than Caucasians to have quit for at least one day in the last year; yet, African Americans are less likely to achieve sustained tobacco abstinence than their Caucasian counterparts [254]. Some suggest that this is attributable to African Americans' reduced utilization of available treatments for nicotine dependence [191]; these treatments may lack cultural relevance [207, 260]. However, a recent study showed that while smoking cessation materials that were targeted to African-American treatment seekers were used significantly more than the generic materials, there was no difference in 6-month smoking cessation rates (targeted materials: 18%; generic materials: 14.4%) [177].

Biological factors may contribute to differences in sustained abstinence rates in African-American compared with Caucasian smokers. For example, African Americans report higher levels of nicotine dependence, even when number of cigarettes smoked per day is controlled [181, 261]. African Americans are more likely to smoke higher nicotine/tar cigarettes, inhale more deeply, and puff more frequently [3, 13]. This more efficient smoking topography is believed to result in increased exposure to tobacco smoke toxins and greater susceptibility to disease and illness [13].

Racial differences in the genetic basis of nicotine dependence have also been reported. A recent study evaluated the role of the genes β-arrestin 1 and 2 (*ARRB1* and *ARRB2*) in nicotine dependence in a sample of African-American and European-American smokers [239]. Results from this study showed that the *ARRB1* and *ARRB2* variants contributed significantly to determining the time to first cigarette of the day among European-American but not African-American smokers. More recent data have shown racial differences in taste receptor genes (*TAS2Rs*) such that decreased oral sensitivity was positively associated with nicotine dependence among African-American but not European-American smokers [151].

Depression

Smokers are more likely to report a history of, or current, major depressive disorder or sub-syndromal forms of depression than non-smokers [27, 114]. The process of smoking initiation and progression to a regular habit typically occurs in adolescent and young adult populations. While tobacco use and depression commonly co-occur in these groups [197], the temporal relationship between these variables is less clear. Specifically, while there is evidence that adolescents with higher levels of depression symptoms are more likely to initiate smoking behavior than those who report lower levels of depression symptoms [58], still other studies have shown the opposite, namely that regular smoking behavior is a precursor to the development of depression symptoms [42, 76]. In a recent study that used data from the National Longitudinal Study of Adolescent Health to examine the relationship between smoking initiation, progression and depression symptoms, the authors reported that among adolescents who reported never smoking at the baseline assessment, level of depressed mood at baseline predicted smoking uptake, but not the progression of a regular smoking habit [168]. Further, among those adolescents who reported never smoking at the baseline assessment, starting to smoke was associated with higher levels of depression symptoms at the 1-year follow-up assessment, independent of the baseline depression symptoms, and this effect was even more pronounced for females [168]. Together, these data suggest that there is a degree of reciprocity between smoking initiation, progression, and depression symptoms that future research can elucidate.

With regard to smoking cessation, depression has been identified as a barrier to sustained

abstinence [70]. From the outset, smokers are more likely to report having depression symptoms than their non-smoking peers [69, 70, 202], and smokers reporting major depression have a greater likelihood of relapse. There are several hypotheses as to why major depressive disorder is more prevalent among smokers and why smokers with this history are less likely to be able to quit. First, depressed smokers may use nicotine to moderate negative affect and depression symptoms [33, 128, 175]. Depressed smokers, compared with non-depressed smokers, are more likely to report smoking as a means to reduce negative affect and increase stimulation [128]. Treatment-seeking smokers with a history of major depressive disorder have also been reported to experience increased levels of depression and anger while quitting than those without a history of depression (e.g., [69]). Heightened feelings of depression and negative affect following cessation have been found to prompt relapse [222]. Finally, smokers with higher levels of depression have been found to be more likely to have higher levels of nicotine dependence [128]. In turn, a higher level of nicotine dependence at baseline is predictive of continued smoking (e.g., [25]).

Smoking cessation interventions targeted to smokers with a history of depression have typically included strategies for management of depressive symptoms and negative affect (e.g., [32, 78, 79, 139]). Hall and colleagues (1998) found that 10 sessions of cognitive-behavioral therapy that included mood management techniques produced higher quit rates among participants with a history of major depressive disorder than those without such a history [79]. Similarly, another study that compared the efficacy of a cognitive-behavioral treatment with a depression component with a standard smoking cessation intervention found that the cognitive-behavioral treatment was more efficacious for participants with recurrent major depressive disorder [32]. These studies indicate the need for more intensive, tailored interventions for individuals who have a history or recurrent major depression.

Genetic Influences on Treatment Response

The emerging field of pharmacogenetics has the potential to advance the science and practice of smoking cessation treatment by facilitating our understanding of how inherited differences in drug metabolism and drug targets have important effects on treatment toxicity and efficacy [59, 195].

One such area of research has been the role of variation in the nicotine-metabolizing enzyme *CYP2A6* in response to nicotine replacement therapy. Data from an open-label trial of nicotine patch versus nicotine nasal spray showed that *CYP2A6* slow metabolizers had significantly higher levels of plasma nicotine after 1 week of nicotine patch treatment, compared with those homozygous for the wild-type alleles [150]. Data from this trial also showed that the 3-hydroxycotinine/cotinine ratio, a phenotypic marker of *CYP2A6* activity, predicted both plasma nicotine levels after 1 week of patch therapy, as well as abstinence, in this treatment group [137]. A recent study, which evaluated whether nicotine metabolism measured by this phenotype affected response to bupropion treatment, showed that, among fast metabolizers, bupropion significantly improved end-of-treatment quit rates, compared with placebo (34% vs. 10%), whereas the difference in quit rates among slow metabolizers who had received bupropion versus placebo was equivocal (32% for both groups) [180].

Response to bupropion treatment is also influenced by the *CYP2B6* gene that has been implicated in bupropion kinetics and brain metabolism of nicotine [126, 131]. Data show that smokers with the slower metabolism *CYP2B6* variant report greater increases in cravings for cigarettes following the target quit date and have significantly higher relapse rates than those with the faster metabolism variant [131]. Further, among females, greater bupropion efficacy was observed for those with the decreased activity variant. There is also evidence that genetic polymorphisms in CYP2B6, such as CYP2B6*6 (versus CYP2B6*1), can also affect

response to bupropion treatment. Specifically, among smokers with the CYP2B6*6 variant, bupropion produced significantly higher abstinence rates than placebo, whereas, in the CYP2B6*1 group, bupropion was no more effective than placebo [127].

Additional investigations have examined the role of genetic variation in the dopamine pathway and response to nicotine replacement therapy. For example, one trial reported that carriers of the *DRD2* A1 allele had significantly higher quit rates from using the nicotine patch, compared with placebo, whereas there was no difference in treatment response for carriers of the more common A2 allele [107]. A longer-term follow-up of this analysis supported the association of the *DRD2* variant with abstinence at 6- and 12-month follow-up; however, the effect was observed only among women [269]. Other data have shown that smokers carrying the low-activity DRD2 allele (Del C) reported significantly higher quit rates on nicotine replacement therapy compared with high-activity allele carriers (Ins C) [136]. Another dopamine variant that has been shown to modify response to nicotine replacement therapy is the catechol-O-methyltransferase enzyme that has been shown to inactivate dopamine [73, 113, 220]. Smokers carrying the high-activity catechol-O-methyltransferase allele (Val) have been shown to experience stronger dependence on nicotine's dopamine stimulating effects [144], and demonstrate a significantly lower likelihood of smoking cessation as shown in both case control and prospective clinical trials [45, 108, 169].

With regard to genetic variation in the dopamine pathway in the context of response to bupropion therapy, there is preliminary support for enhanced efficacy of bupropion among smokers who carry increased-activity alleles for *DRD2* [54, 136, 241]. This effect appears to be modified by the *CYP2B6* genotype [54]. Similarly, smokers with the increased-activity alleles for *DRD2* 141 Insertion (141 Ins C allele) were shown to have a more favorable response to bupropion as compared with the low-activity allele carriers (Del C allele) [136]. Finally, there is recent evidence for an association between bupropion treatment outcome and genetic variation in the catechol-O-methyltransferase enzyme that inactivates dopamine [16].

The mu-opioid receptor (OPRM1) gene has been a focus of pharmacogenetic investigations of treatment response. In an open-label trial that randomized participants to transdermal nicotine versus nicotine nasal spray, a differential treatment response was reported whereby smokers receiving transdermal nicotine, carriers of the Asp40 variant (G, reduced activity) were significantly more likely to be abstinent than carriers of the Asn40 variant, whereas there was a non-significant difference among smokers receiving nicotine nasal spray [135]. A more recent study reported that carriers of the Asn40 variant had a more favorable response to nicotine replacement therapy than those with the Asp40 variant [167]. Data from this study also showed an interaction between the *OPRM1* genotype and sex whereby female carriers of the Asp40 variant were significantly more likely to have quit by the end of treatment as compared with females with the Asn40 variant, while the reverse was true for males [167]. A potential mechanism for this interaction between sex and *OPRM1* genotype in response to nicotine replacement therapy was implicated by data published by Ray and colleagues showing an association of the *OPRM1* A118G variant with the relative reinforcing value of nicotine among females [198]. Specifically, among females, the Asp40, low-activity G allele was associated with a reduced reinforcing value of nicotine; among male smokers, there was no association with genotype. Further work is needed to reconcile these findings.

Public Policy: Cost-Effectiveness of Smoking Cessation Treatments

Given the constraints in the health care system, it is critical to consider the cost-effectiveness of treatment for nicotine dependence. Overall,

smoking cessation treatments and programs are cost-effective when considering the medical care costs associated with treating health-related consequences from smoking. Indeed, smoking cessation has been identified as one of the three most important preventative medicine approaches [147].

Evaluation of the cost-effectiveness for a smoking cessation program typically requires consideration of the cost of treatment in relation to the benefits of cessation such as life years saved and health care costs savings [11, 80]. With the outcome variable of 12-month employer cost-savings per non-smoking employee, treatment with varenicline was a more cost-saving treatment method than bupropion ($540.60 vs. $269.80 for bupropion generic and $150.80 for bupropion brand) in a general population of smokers [103]. Consistent with these data, a recent study conducted in Europe reported that varenicline was a more cost-effective treatment than either bupropion or nicotine replacement therapy [88].

An important clinical question addressed by the cost-effectiveness literature is whether targeting smoking cessation treatments is a more cost-effective approach than applying a "one-size-fits-all" treatment model that traditionally recommends pharmacotherapy on the basis of patients' prior experiences and preferences [91]. This question is particularly salient in the area of pharmacogenetics, where treatments for nicotine dependence can potentially be recommended on the basis of genetic make-up [131, 133, 136]. In a recent report, Heitjen and colleagues [84] evaluated simulation models of the costs and effectiveness of five alternative strategies for managing cigarette smokers who were attempting to quit: (1) no treatment plan, (2) treatment of all individuals with transdermal nicotine, (3) treatment of all individuals with bupropion, (4) a genetically tailored plan that chooses between transdermal nicotine and bupropion based on the result of a genetic test that predicts therapy outcome [136], and (5) treatment of all individuals with varenicline. When the primary outcome of cost-effectiveness based on discounted life-years and lifetime tobacco cessation treatment costs was compared across the five treatment strategies, the results showed that either the non-tailored varenicline or bupropion treatment approaches were the most cost-effective approaches. Although tailoring treatment using pharmacogenetic data produced negligible survival benefits over the non-tailored approaches, when the simulations imposed several favorable assumptions including a large treatment-by-genotype interaction, the results showed that the pharmacogenetic approach simultaneously improved abstinence rates and reduced the number of quit attempts needed to achieve long-term abstinence [84]. These data suggest that, under some circumstances, pharmacogenetically tailored treatment can be advantageous. The continual evaluation of smoking cessation treatment cost-effectiveness is a priority, especially with the advent of novel approaches designed to enhance treatment efficacy.

Conclusions

The growing prevalence of worldwide smoking in combination with the high percentage of treatment-seeking smokers who fail to quit using currently Food and Drug Administration-approved medications warrants the identification and appropriate dissemination of new treatments for nicotine dependence as well as finding alternative methods for using existing treatments to boost treatment response. With regard to the identification of novel treatments for nicotine dependence, work is ongoing to develop clinically valid animal and human laboratory models that support the translation of knowledge from laboratory studies to clinical research [138, 186]. For example, recent work suggests that utilizing treatment-seeking smokers, as opposed to unmotivated quitters, in short-term, screening laboratory studies that are used to test novel medications, may provide a more valid indication of how these therapies will perform in later-stage clinical trials [186]. Improving the medication development continuum can only shorten the process of finding new and effective nicotine dependence treatments [138].

As reviewed in this chapter, there are several other lines of research in the field of nicotine and tobacco research that provide some optimism. First is the Food and Drug Administration approval of varenicline, the most recent addition to the list of treatments approved for nicotine addiction treatment. Second, research concerning smoker characteristics related to responsiveness to nicotine replacement therapies and the potential development of fast-acting nicotine replacement therapies may help clinicians to tailor the use of nicotine replacement therapy type, dose, and duration to the smoker's characteristics, thereby enhancing nicotine replacement therapy effectiveness. Third, methods to offset the costs of nicotine replacement therapy and innovative marketing approaches to increase the appeal of, and access to, nicotine replacement therapies may significantly increase utilization of nicotine replacement therapy products, in turn, broadening the impact of over-the-counter therapies on the population smoking rate. Finally, results from pharmacogenetic studies of treatments for nicotine addiction, although preliminary at this stage, offer future potential for individualizing patient care. There is much reason to speculate that combined these efforts can help improve outcomes for treatment-seeking smokers.

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Pharmacotherapy of Cocaine Addiction

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Strategies for Selecting Candidate Medications for Testing

Bottom–Up Approach: Modulation of Appetitive Drives

Preclinical animal models of cocaine addiction, self-administration, reinstatement, and cue reactivity are commonly used to screen compounds for their potential as medications for treating cocaine dependence. These models, though helpful in selecting compounds, have very limited predictive validity. This issue is a critical one and will not be resolved fully until an effective medication is found that can be tested in animals for model validation. Until then, these limitations need to be factored in any go-no-go decision for advancing compounds for further development.

Preclinical Data

The role of corticotropin-releasing factor in drug addiction is very important, especially for relapse (which has been reviewed extensively [41, 56, 65]). Corticotropin-releasing factor appears to be a mediator of stress-induced reinstatement in rodent models. This effect was found not to be unique only to cocaine in the rat models of stress-induced relapse [23, 59] but also has been shown in heroin [59, 60] and alcohol [43]. These data support the well-known notion that stress is a major

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_50,

precipitator of relapse in abstaining individuals. Modulating the stress circuitry will be beneficial not only for cocaine but also for other substances. Multiple corticotropin-releasing factor-1 antagonists are currently in development for the treatment of depression and anxiety. One that is being developed in collaboration between the National Institute on Drug Abuse and the National Institute of Mental Health will be tested for addiction as well.

Dopamine D3 receptors, cloned in 1990 [1], are located mainly in the accumbens. This dopamine receptor subtype was found to be up-regulated in post-mortem brains of individuals with cocaine addiction who died of cocaine overdose [63]. D3 agonists exhibit cocaine-like effects in rodents and primates [1, 63]. D3 partial agonists have been shown to block cue-induced cocaine reinstatement [20, 52], cocaine-primed cocaine seeking [20, 27], and footshock-induced reinstatement of cocaine self-administration in rats [69], suggesting overall a potential role for D3 antagonists in preventing the three triggers of relapse.

The cannabinoid-1 receptor antagonists have been shown in different animal models to have potential to treat multiple addictions [4, 44]. Cannabinoid-1 antagonists act either by blocking the subjective/rewarding effects of drugs such as tetrahydrocannabinol or by blocking the ability of conditioned cues to promote reinstatement of drug-seeking behavior in animals, presumably through the endocannabinoid system. Taken together, results suggest a role for the cannabinoid system for polysubstance addiction.

Vigabatrin is a gamma-aminobutyric acid transaminase inhibitor, which leads to marked elevation of gamma-aminobutyric acid levels in the brain. It has been shown to be very effective in animal models to block cocaine self-administration, and to block dopamine release in a primate positron emission tomography imaging study [19]. Early open-label pilot data in cocaine- and methamphetamine-addicted individuals showed promising results in facilitating abstinence [8]. Vigabatrin has been reported to cause visual field defects following prolonged use, which may be an issue in its development for addiction treatment. Safety and proof-of-concept trials are planned to clarify this issue further.

Other compounds with interesting preclinical data include metabotropic glutamate receptor 5 [12], alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonists [2, 16], orexin-A receptor antagonists [6, 30], opioid receptor-like 1 agonists [13, 14], muscarinic M5 receptor ligands [3, 25], and N-acetylated-alpha-linked-acidic dipeptidase inhibitors [62].

Bottom–Up Approach: Pharmacotherapy of Reversal Learning

Another pharmacotherapy target that has been discovered by basic neuroscience researchers is cocaine-induced deficits in reversal learning. Reversal learning, a test of cognitive flexibility, involves an organism's ability to determine that reward contingencies have changed and act accordingly. Cocaine has been shown to produce reversal learning deficits in an odor-discriminating task in rats trained to self-administer cocaine [9]. Lesions of the orbitofrontal cortex in rats also have been shown to cause reversal learning deficits in the odor discrimination model [57] and a serial discrimination reversal learning model [5]. Cocaine, administered for 14 days, can cause a failure to signal adverse outcomes in rats that also fail to reverse their cue selectivity, suggesting a failure of plasticity mechanisms in this brain region caused by the drug [64]. Cocaine administered to Vervet monkeys for 14 days produced a reversal learning deficit of learned object discrimination [33]. Chronic cocaine users, but not amphetamine users, demonstrated reversal learning deficits in a probabilistic reversal learning task [24].

Pharmacological modulation of reversal learning is in the early stages of testing. The serotonin-6 receptor antagonist Ro 04-6790

improved reversal learning in isolation-reared rats in the Morris water maze spatial discrimination task [45]. Several serotonin-6 receptor antagonists are in clinical testing [31], suggesting that medications with this mechanism could be tested in chronic cocaine users in the probabilistic reversal learning task. The noradrenergic medications atomoxetine, desipramine, and methylphenidate improved reversal learning in a four-position discrimination task in rats and a three-choice visual discrimination task in Vervet monkeys [58] while the dopamine transporter inhibitor GBR-12909 did not alter reversal learning. The authors noted that methylphenidate impaired retention in both rats and monkeys. Since it has been demonstrated that cocaine can produce reversal learning deficits, the obvious next studies that should be performed would be to test serotonin-6 receptor antagonists and norepinephrine transporter inhibitors in cocaine-affected animals. Positive results would provide a rationale for testing these medications in human subjects in the probabilistic reversal learning task mentioned above.

Top–Down Approach

Marketed medications have been evaluated in different paradigms for efficacy in treating cocaine addiction. These medications were chosen based on different scientific rationales related to a known mechanism of action as a cocaine agonist or antagonist, and through modulating dopamine functions and the reward system. Some of these medications are direct dopamine agonists or antagonists, serotonin modulators, gamma-aminobutyric acid agonists (both A and B), and glutamate modulators.

Our understanding of the addictive processes and neurobiology has greatly improved in the last two decades, thereby impacting and helping us to fine-tune our approach to pharmacological treatment.

Data are emerging from preclinical and clinical studies that would suggest a selective role for specific medications in the addictive process. This would suggest that certain medications could be targeted at a specific phase of treatment or at a specific function involved in the addictive process—for example: (1) withdrawal phase (e.g., propranolol, amantadine); (2) active use phase (e.g., modafinil, vigabatrin); (3) abstinence maintenance and relapse prevention (e.g., topiramate, other gamma-aminobutyric acid agonists), stress modulators (e.g., corticotropin-releasing factor antagonists, lofexidine), cue-induced relapse (e.g., D3 antagonists, D-cycloserine), and priming (e.g., cannabinoid-1 antagonists); (4) improvement of cognition (e.g., nootropic agents, D1 agonists); (5) modulation of frontal inhibitory mechanisms, such as strategic thinking and impulse control (e.g., modafinil), and (6) modulation of reversal learning deficits (e.g., serotonin-6 antagonists, atomoxetine).

Clinical Trials in Cocaine Addiction

Table 1 summarizes most of the double-blind controlled trials conducted in the last decade for cocaine addiction.

Disulfiram, topiramate, modafinil, and ondansetron are leading the marketed medications as far as effect sizes and/or consistent findings in multiple trials. They currently are being pursued in larger phase III confirmatory studies. Disulfiram efficacy is thought to be related to its ability to inhibit the enzyme dopamine beta-hydroxylase, which is responsible for the conversion of dopamine to norepinephrine, in turn making more dopamine available. This may help in restoring the depleted dopamine store and the hypodopaminergic state following chronic cocaine use. The ongoing work with disulfiram is exploring the different dopamine beta-hydroxylase phenotypes and their link to the response to disulfiram. However, disulfiram also inhibits the plasma esterase that metabolizes cocaine to benzoylecgonine and leads to an increase in cocaine blood levels when co-administered with cocaine [48]. This results in an increase in heart rate and blood pressure

Table 1 Summary of data on published medication trials for cocaine dependence

Authors	Study	Outcome	Results
Dackis et al. [17]	*A double-blind, placebo-controlled trial of modafinil for cocaine dependence.* 62 randomized received a single morning dose of modafinil (400 mg) or matched placebo.	The primary efficacy measure was cocaine abstinence based on urine benzoylecgonine levels. Secondary measures were craving, cocaine withdrawal, retention, and adverse events.	Subjects treated with modafinil provided significantly more cocaine-negative urine samples when compared with the placebo group.
Kampman et al. [40]	*Effectiveness of propranolol for cocaine dependence treatment may depend on cocaine withdrawal symptom severity.* 108 randomized received 100 mg propranolol or matched placebo.	Quantitative urinary benzoylecgonine level was the primary outcome measure. Secondary included treatment retention, Addiction Severity Index results, cocaine craving, mood and anxiety symptoms, cocaine withdrawal symptoms, and adverse events.	No comparison overall between the 2 groups with the exception of cocaine withdrawal symptoms in the propranolol subjects. However, propranolol-treated subjects with more severe cocaine withdrawal symptoms responded better than their placebo counterparts.
Kampman et al. [38]	*A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms.* 199 randomized received 300 mg/day of amantadine, 100 mg/day of propranolol, a combination of 300 mg/day, or matching placebo.	Cocaine abstinence was the primary outcome measure.	The odds of cocaine abstinence improved significantly over time in propranolol-treated subjects that were highly adherent to study medication but not in placebo-treated subjects.
Brodie et al. [7]	*Treating cocaine addiction: from preclinical to clinical trial experience with gamma-vinyl GABA.* 20 randomized with a titration dose (1, 1.5, 2 g) of vigabatrin.	Measuring 28 consecutive days clean (negative for cocaine).	Eight subjects successfully completed the program and were drug-free for periods ranging from 46 to 58 days.
Brodie et al. [8]	*Safety and efficacy of gamma-vinyl GABA (GVG, vigabatrin) for the treatment of methamphetamine and/or cocaine addiction.* 30 randomized.	Designed to include extensive visual field monitoring as well as outcome measures of therapeutic efficacy.	Sixteen subjects of 18 who completed the trial tested negative for methamphetamine and cocaine during the last 6 weeks of the trial. Vigabatrin did not produce any visual field defects or alterations in visual acuity.

Table 1 (continued)

Authors	Study	Outcome	Results
Kampman et al. [39]	*A pilot trial of topiramate for the treatment of cocaine dependence.* 40 randomized titrating up to 200 mg daily of topiramate.	Cocaine abstinence was the primary outcome measure verified by twice weekly urine benzoylecgonine.	The topiramate-treated subjects were more likely to be abstinent from cocaine compared with placebo-treated subjects.
Gonzalez et al. [28]	*Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: results of a randomized pilot study.* 45 randomized to 12 or 24 mg of tiagabine or matched placebo.	Reduction of use as measured by cocaine-free urines.	In weeks 9 and 10, cocaine-free urines increased from baseline by 33% in subjects taking 24 mg/day, increased by 14% (12 mg/day), and decreased by 10% with placebo-treated subjects.
Carroll et al. [11]	*Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram.* 122 randomized with 250–500 mg of disulfiram vs. psychotherapy control (1 of 5 treatments).	Duration of continuous abstinence from cocaine or alcohol; frequency and quantity of cocaine and alcohol use by week, verified by urine toxicology and Breathalyzer® screens.	Disulfiram treatment was associated with better retention in treatment as well as longer duration of abstinence from alcohol and cocaine use. The 2 active psychotherapies (cognitive behavioral therapy and 12-step facilitation) reduced cocaine use over time compared with the supportive treatment (contingency management).
George et al. [26]	*Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial.* 20 randomized to 250 mg of disulfiram vs. matched placebo.	Duration of abstinence from cocaine verified by urine test.	The total number of weeks abstinent from cocaine was higher in the disulfiram group versus placebo-treated subjects.
Petrakis et al. [51]	*Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts.* 67 randomized to 250 mg disulfiram vs. matched placebo.	Weekly assessments of the frequency and quantity of drug and alcohol use, weekly urine toxicology screens, and Breathalyzer® readings.	Cocaine use was significantly decreased in quantity and frequency in subjects treated with disulfiram as compared with placebo-treated subjects.
Carroll et al. [10]	*Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial.* 121 randomized to 250 mg/day of disulfiram or matched placebo.	Random regression analyses of self-reported frequency of cocaine use and results of urine toxicology screens.	Disulfiram-treated subjects reduced their cocaine use more than placebo-treated subjects.

Table 1 (continued)

Authors	Study	Outcome	Results
Martell et al. [46]	*Vaccine pharmacotherapy for the treatment of cocaine dependence.* 18 total randomized (10 received TA-DC 400 μg and 8 received 2,000 μg, vs. matched placebo).	Cocaine abstinence as verified by urine test.	The likelihood of using cocaine decreased in subjects who received the more intense vaccination schedule.
Kosten et al. [42]	*Desipramine and contingency management for cocaine and opiate dependence in buprenorphine-maintained patients.* 160 randomized to 150 mg/day or matched placebo (with and without contingency management).	Cocaine abstinence as verified by urine test.	Cocaine-free and combined opiate- and cocaine-free urines increased over time in those treated with either desipramine or contingency management, and those receiving both had more drug-free urines (50%).
Poling et al. [53]	*Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population.* 106 randomized to 300 mg/day of bupropion or matched placebo (with and without voucher control and contingency management).	Reduction of cocaine use as tested by thrice-weekly urine toxicologic test results for cocaine and heroin.	Overall, voucher-based control and buprenorphine groups had fewer cocaine-positive urine drug screens than the other groups.
Ciraulo et al. [15]	*Nefazodone treatment of cocaine dependence with comorbid depressive symptoms.* 69 randomized to 200 mg (b.i.d.) of nefazodone or matching placebo.	Cocaine use measured by urine benzoylecgonine and self-report.	Median weekly benzoylecgonine declined in the nefazodone group, and scores for strength of cocaine craving decreased compared with placebo.
Winhusen et al. [68]	*A double-blind, placebo-controlled trial of reserpine for the treatment of cocaine dependence.* 119 randomized to 0.5 mg/day of reserpine or matching placebo.	Cocaine use as determined by self-report confirmed with urine benzoylecgonine, cocaine craving, Addiction Severity Index, and Clinical Global Impression scores.	No significant differences between reserpine and placebo.
Winhusen et al. [67]	*A double-blind, placebo-controlled trial of tiagabine for the treatment of cocaine dependence.* 140 randomized to 20 mg/day of tiagabine or matching placebo.	Cocaine use as determined by self-report confirmed with urine benzoylecgonine, qualitative and quantitative urine toxicology measures.	Qualitative urine toxicology results suggest a possible weak signal for tiagabine in reducing cocaine use.

Table 1 (continued)

Authors	Study	Outcome	Results
Kahn et al. [37]	*Multi-center trial of baclofen for abstinence initiation for severe cocaine dependence.* 160 randomized to 60 mg of baclofen (maximum dose).	Cocaine use as determined by self-report confirmed by urine benzoylecgonine.	No significant effect between baclofen over placebo-treated subjects.
Shoptaw et al. [61] (in preparation)	*Randomized, placebo-controlled trial of cabergoline for the treatment of cocaine dependence.* 70 randomized to 0.5 mg/wk of cabergoline or matched placebo.	Retention, self-report, cocaine use verified by urine drug screen, Hamilton Rating Scale for Depression, cocaine craving, and Clinical Global Impression rating.	Cabergoline reduced craving ratings over placebo-treated subjects.
Elkashef et al. [22]	*Double-blind, placebo-controlled trial of selegiline transdermal system (STS) for the treatment of cocaine dependence.* 300 subjects randomized to 20 mg of selegiline.	Self-reported cocaine use substantiated by urine benzoylecgonine.	There was no effect of selegiline over placebo-treated subjects.
Moeller et al. [49]	*Citalopram combined with behavioral therapy reduces cocaine use: a double-blind, placebo-controlled trial.* 76 randomized to 20 mg/day of citalopram or matched placebo (with cognitive management and cognitive behavioral therapy).	Reduction in cocaine-positive urines.	Cocaine-treated subjects showed a significant reduction in positive urines during treatment as compared with placebo-treated subjects.
Johnson et al. [36]	*A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence.*	Cocaine use by urine benzoylecgonine.	The 8-mg/day group had the lowest dropout rate and a greater rate of negative urine benzoylecgonine ($p = 0.02$) compared with placebo. Ondansetron was well tolerated, with no serious adverse events.

and makes disulfiram an undesirable medication to pursue for cocaine treatment.

A recently completed multisite trial of modafinil for cocaine showed an effect only in the non-alcoholic, cocaine-addicted individuals and no effect in the dually dependent, cocaine-addicted, alcoholic individuals; this finding is very similar to the earlier pilot data conducted by Dackis et al. [17]. Two more trials for modafinil are under way, and data from these trials will help to shed more light on the role of modafinil in cocaine addiction.

Ondansetron is approved for nausea and is mostly prescribed for cancer patients receiving chemotherapy. It is thought to decrease dopamine release through the serotonin-3

receptor system in the accumbens. It has been shown to be efficacious in alcohol studies. The proof-of-concept study showed that the 8-mg dose was superior to other lower doses and placebo in helping individuals achieve abstinence from cocaine. It is currently being investigated in larger trials to study its effects on combined cocaine and alcohol addiction.

Topiramate, a gamma-aminobutyric acid agonist and AMPA antagonist anti-seizure medication, showed positive effects in treating alcohol and nicotine addiction. It also is known to cause weight loss. The dual mechanism of action makes it unique among other gamma-aminobutyric acid agonists in that it may not only reduce dopamine release through its gamma-aminobutyric acid effect but also help reduce craving and cue-induced relapse, which has been shown with other AMPA antagonists [66]. The proof-of-concept trial conducted in cocaine-dependent individuals [39] showed that topiramate's therapeutic effect was in the subgroup of participants who were able to stop using cocaine for a few days prior to randomization, making it a potential medication for low-to-moderate users with mild withdrawal symptoms and possibly for cue-induced relapse prevention. Topiramate's therapeutic effect in alcohol-dependent individuals would also make it a candidate for dually dependent individuals or for polysubstance addiction. These hypotheses are being elucidated in the ongoing larger confirmatory trials.

Cocaine Withdrawal

Amantadine and propranolol have shown efficacy in helping individuals with severe withdrawal symptoms, as assessed by the Cocaine Symptom Severity Assessment scale devised by Kampman et al. [40]. In a follow-up placebo-controlled study of either medication alone and their combination, only propranolol showed efficacy in the medication-adherent group analysis and not the intent-to-treat analysis. The combination did not prove to be superior to either medication alone [38].

Comorbid Populations

Comorbid mental illness is more common than not in the addicted population. Prevalence rates range from 20% for attention deficit disorders to 60% for bipolar disorders [54]. This adds another complexity to the treatment approach and to participant selection criteria in clinical trials. This population has been ignored either intentionally or passively by mental health and addiction medication studies. Considering how common these conditions are, it is more sensible to face this issue head on and be more inclusive of this population with a priori hypotheses to test for variations in response or in biology, based on the underlying condition, or to stratify and balance the groups in clinical trials based on a common existing mental illness—e.g., depression scores in trials where an antidepressant or a mood stabilizer is being tested for its effect on drug use. A recent meta-analysis [50] showed that treating the underlying depression or anxiety was associated with some reduction in drug use; however, complete abstinence was hard to achieve.

Participant Heterogeneity

Participant demographics and clinical characteristics including patterns of use seem to be an important factor in predicting outcome. Baseline use always has been deemed one of the strongest predictors of outcome; this was very obvious in the data from the study of topiramate for cocaine dependence and the study of bupropion for methamphetamine dependence, where bupropion was found to be efficacious only in the group with low-to-moderate use at baseline. More recently, data from alcohol and nicotine studies highlight the role of pharmacogenomics as a very promising tool in predicting outcome [18, 55].

Genetic and clinical biomarkers predicting outcome could only improve our results and are being incorporated in many ongoing addiction trials to help elucidate subgroup response.

Polysubstance Abuse

Although most drug addicts would cite a drug of choice, most use more than one drug. This could be good or bad news. Having a polysubstance dependence could lead to treatment resistance, as in the case of the recently completed modafinil study for cocaine addiction, where the alcohol/cocaine dually dependent group showed no response to modafinil.

On the other hand, the good news is that medications that address common mechanisms in addiction could help polysubstance-addicted individuals; for example, topiramate seems to be promising for alcohol, stimulants, nicotine, and food addiction. Naltrexone has shown efficacy in alcohol, opiate, and stimulant addiction. New molecular entities cited above—e.g., corticotropin-releasing factor, cannabinoid-1, and D3 antagonists—are all promising for polysubstance addiction as well. Further studies will tell.

Pharmacotherapy and Behavioral Therapy Combinations

Recent data from cocaine studies suggest that the effect of the medication could be synergized when combined with contingency management. Two separate studies, one using bupropion and one using desipramine, in opiate-dependent, cocaine-abusing populations showed an enhanced effect of the combination of medication plus contingency management compared with each treatment arm alone [42, 53].

Immunotherapy

A non-pharmacological approach of recent interest is the development of a vaccine to treat drug dependencies, in this case a vaccine for cocaine dependence. The cocaine vaccine is a new tool in early development that works by conjugating the non-antigenic cocaine molecule to a hapten that evokes an antibody response. When cocaine was used alone, the antibodies generated were able to recognize and tag the cocaine molecule, thereby preventing it from reaching the brain or other organs. Specifically, the vaccine is made by producing an immunogenic carrier through covalently linking succinylnorcocaine to recombinant cholera toxin B-subunit protein, adsorbed onto aluminum hydroxide adjuvant [32, 34, 35]. The pilot safety study showed a good dose response where the antibody titer was correlated to the vaccine dose, with a reported subjective attenuation of the cocaine high by most subjects in the follow-up, and with no reported serious adverse events [46]. In a recent human laboratory study of 10 non-treatment-seeking, cocaine-dependent men, the cocaine vaccine blunted some of the subjective effects of cocaine among individuals with the highest, but not with low, antibody titer [29]. Similarly, in a randomized controlled trial in 115 methadone-maintained, cocaine-dependent individuals, only 21 of the vaccinated subjects (38%) who achieved serum immunoglobulin G anti-cocaine antibody levels of 43 μg/mL or higher (i.e., a high immunoglobulin G level) had significantly more cocaine-free urine samples than those with levels less than 43 μg/mL (i.e., a low immunoglobulin G level) and the placebo-receiving subjects during weeks 9–16 (45% vs. 35% cocaine-free urine samples, respectively). Even among those who achieved high immunoglobulin G anti-cocaine levels, the blockade lasted only 2 months [47]. Furthermore, the present vaccination regimen (i.e., 5 vaccinations over a 12-week period) is only likely to be practical to treat cocaine-dependent individuals with quite high levels of motivation or compliance. Hence, despite the early promise of this approach, much improved vaccines requiring less frequency of injection will be needed for cocaine vaccines to be a practical and efficacious treatment for cocaine dependence. Similar vaccine-based approaches in nicotine addiction are showing very positive results in phase II studies [21].

Summary

Progress in cocaine pharmacotherapy has made some strides over the last two decades. Promising medications are being explored further in confirmatory trials. A vaccine-based approach continues to be developed. Many other new molecules are in early development. Pharmacogenomics and biomarkers will greatly improve the yield of our trials and help us better understand how to use medications for our client population.

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Opioids: Heroin and Prescription Drugs

Jason M. White

Contents

Introduction

This chapter will focus on the pharmacotherapies used in the treatment of opioid dependence, including maintenance pharmacotherapies such as methadone and buprenorphine, the use of antagonists such as naltrexone and medications used in the management of withdrawal. The interest in this aspect of addiction treatment has generated a range of pharmacotherapies broader than is found in other areas of addiction treatment. In addition to the inherent interest in this area, opioids offer a window to the future development of pharmacotherapies for other types of drug dependence.

Opioid Dependence

The term "opioids" refer to drugs acting through μ-, κ-, or δ-opioid receptors, but the principal receptor of interest is the μ-opioid receptor. Opioid drugs acting through this receptor produce a variety of effects, including those regarded by users as desirable such as analgesia, relief of emotional distress and euphoria, as well as adverse effects, such as respiratory depression, sedation, nausea and vomiting. There are a variety of sources of drugs that produce these effects.

The original use was in the form of opium, with morphine as the principal active component. Opium smoking is still practiced in some parts of the world, particularly the opium growing areas such as Northern Burma, Thailand and Laos and Afghanistan. More commonly, the morphine extracted from the opium poppies is converted into diacetyl morphine, or heroin. Illicit heroin has been the primary drug leading to opioid dependence for many decades.

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_51,

Recently, there has been increasing recognition of the large number of people who become dependent on prescription opioids [6, 70]. Undoubtedly, this has occurred as long as opioids have been used medically, but with the increased rate of prescribing of these analgesics, it can be expected that the number of people who become dependent on prescription opioids, either through treatment for pain relief or through illicit markets, is likely to increase.

Amongst the opioids used illicitly there is a clear preference for short-acting drugs. Morphine from the opium poppy as well as its derivative, heroin, and the preferred prescription opioids, oxycodone, hydromorphone and morphine, are all short-acting agents. The favored routes of administration are by intravenous injection and inhalation of vapor. Both routes result in very rapid onset of action with maximum effect achieved within minutes of administration. The use of short-acting opioids by these routes results in a pattern of administration in dependent users characterized by rapid onset of intoxication followed by milder and decreasing effects over a few hours before the onset of withdrawal symptoms. These symptoms can include nausea, vomiting, pain, cramps, diarrhoea, fever, lacrimation and rhinorrhoea. Re-administration of the opioid results in intoxication and elimination of these withdrawal symptoms. Thus, in the dependent user who administers heroin or another short-acting opioid multiple times per day, there is a cycling of intoxication through the day, potentially including withdrawal if administration does not occur with sufficient frequency. Both the intoxication and the withdrawal result in significant impairment in physiological, psychological and social functioning.

Maintenance Agonist Treatment

One approach to treatment of opioid dependence is immediate cessation of drug use, but this results in a withdrawal syndrome that includes both acute and protracted phases. The alternative is to stabilize the individual with an opioid that prevents the withdrawal occurring and allows relatively normal functioning. In contrast to the rapid cycling of intoxication and withdrawal that is characteristic of illicit use of short-acting opioids, the aim is to produce a slow onset and a gradual offset of action with minimal intoxication and minimal withdrawal. This includes a change in route of administration to oral or sublingual, so that onset of effect is very gradual with minimal or no euphoric effects. A long duration of action will maximize the chances of complete withdrawal suppression and allow dosing on a daily basis or less often.

In recognition of the chronic nature of opioid dependence, maintenance agonist treatment is typically of long duration, with many recommending a minimum treatment duration of one year, but for a number of individuals this may extend over many years. Longer durations of treatment are associated with higher rates of abstinence from illicit opioids. Maintenance agonist treatment aims to normalize the physiological, psychological and social functioning of the individual, and this can be achieved by a dose of agonist drug that suppresses withdrawal with minimal direct effects. However, it should also be recognized that a second role of maintenance agonist treatment is to reduce the effect of any additional opioid administered. This can occur both through receptor occupancy and through the tolerance that develops with repeated daily doses, particularly when relatively high maintenance doses are used.

While there are now a range of opioids that could be used for treatment of opioid dependence, much of the history of opioid maintenance treatment has been the use of methadone as the maintenance agent. More recently, buprenorphine has become available and there have been trials of other medications that may also play a future role.

Methadone Maintenance

Methadone has been and remains the most widely used drug in maintenance treatment of

opioid dependence. Its use is generally attributed to Dole and Nyswander working in New York in the 1960s.

Pharmacology of Methadone

Methadone binds primarily to the mu-opioid receptor, but does have some affinity for the kappa and delta receptors. In addition to its opioid action, it has some non-opioid effects, including action as a non-competitive antagonist at the *N*-methyl-*D*-aspartate receptor and an inhibitor of the re-uptake of noradrenalin and serotonin. The clinical significance of these actions is unknown, but both are of potential interest. Non-competitive antagonists at the *N*-methyl-*D*-aspartate receptor may have a role in treatment of neuropathic pain and hyperalgesia and may retard the development of opioid tolerance, but can also produce adverse effects. Inhibition of the re-uptake of noradrenalin and serotonin can result in an antidepressant effect.

Methadone is most commonly administered as a 50/50 ratio of the R and S enantiomers. The only exception is in Germany where it is also available as the pure R enantiomer. The opioid activity of methadone lies principally in the R enantiomer that has a 20-fold higher affinity for the mu-receptor. R-methadone is approximately 50 times more potent than S-methadone in producing analgesia and is effective in preventing opioid withdrawal, whereas S-methadone is ineffective. S-methadone does have non-opioid effects, such as *N*-methyl-*D*-aspartate receptor action, and could contribute to the adverse effects of racemic methadone [19, 58].

For maintenance treatment, methadone is generally administered as a solution, whereas it is normally administered in tablet form for pain relief. It is readily absorbed from the gastrointestinal tract and the bioavailability averages between 80–90 per cent, although there is significant variability between individuals. Peak plasma concentration is reached approximately 2.5–3 h after oral administration.

Methadone is extensively metabolized by the hepatic cytochromes P450 enzyme family. The primary pathway is to the inactive 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, with CYP3A4 the major enzyme. A number of other P450 enzymes may be important, including CYP2B6, 3A5 and 2D6 [10]. CYP2B6 exhibits stereoselective metabolism so that there can be significant differences in the plasma concentrations of R and S methadone even though it is administered as a 50/50 ratio.

Clinically significant changes in methadone concentration, with consequences such as increased sedation or increased withdrawal, can arise from the co-administration of inhibitors or inducers of CYP450 enzymes. Inhibitors such as fluconazole, ketoconazole, fluvoxamine and others have been shown to increase plasma methadone concentrations, while inducers such as rifampicin, barbituates, nevirapine, efavirenz, amprenavir, nelfinavir and ritonavir decrease plasma methadone concentrations.

There is considerable variability in the pharmacokinetics of methadone between individuals [18]. This can arise through variations in absorption and metabolism and lead to different profiles of concentration change over the dosing interval. While the ideal is a low peak to trough ratio, so that effects and withdrawal symptoms are minimal, some individuals exhibit much more pronounced concentration changes, as illustrated in Fig. 1. These individuals may be at greater risk for adverse effects at the time of peak concentration, but a rapid decrease in concentration following the peak has also been associated with greater withdrawal severity [17].

Clinical Use of Methadone

Assessing Suitability for Methadone Maintenance Treatment

Most individuals who participate in methadone maintenance treatment satisfy criteria for opioid dependence and have significant physical dependence. Evidence for satisfying these criteria can be obtained through participant interview,

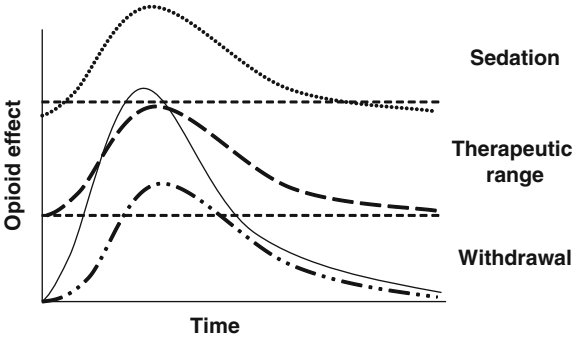

Fig. 1 Methadone effects increase over the first 3 h after administration before gradually declining. Ideally, these effects fall into the desired therapeutic range so that the individual experiences neither sedation nor withdrawal (------). High doses result in excessive sedation (· · · · · ·) and low doses excessive withdrawal (– . . – . .). In some individuals, the change in concentration is more pronounced and they may experience some sedation at time of peak concentration, but withdrawal at time of trough concentration (———). For this last group, divided doses or changing to a different medication (e.g., buprenorphine, slow-release morphine) is likely to be the best therapeutic strategy

physical examination to determine evidence of withdrawal and evidence of injecting drug use, and urinalysis. Individuals presenting for such treatment, even those who present seeking only methadone treatment, should be offered alternatives such as the use of other maintenance medications and abstinence based therapies. In addition to this group, there are some people who may not fulfill all these criteria, but who may be deemed suitable for treatment. These people are normally using at lower levels that would not necessarily be associated with strong withdrawal on cessation or a full dependence syndrome. They include users at high risk of overdose, pregnant women, prisoners with a history of opioid use (for treatment while in prison and on release) and people who may be at high risk of contracting or infecting others with HIV or other infectious diseases.

Commencement of Maintenance Treatment

As is the case with all opioid agonists, administration of methadone carries the risk of death through respiratory depression. In methadone maintenance, the maximal period of risk is during the first 1–2 weeks of treatment. While methadone maintenance is associated with an overall four-fold reduction in mortality, the risk of death rises during this induction period [81]. There are several reasons for this. First, in the absence of objective indicators of tolerance, selecting an appropriate first dose and rate of dose increase is based principally on clinical experience. Second, the long half-life of methadone means that it can take 5 days or more to reach a steady-state after each dose change. Clinicians rarely have the opportunity to wait this long before seeing the full effects of a dose change during induction. Third, when individuals experience significant withdrawal, they may self-medicate with opioids, benzodiazepines, or other drugs to relieve these symptoms. The resultant interactions may lead to mortality. The initial dose, most commonly between 20–30 mg, and the dose increments must be determined based on the balance between achieving adequate withdrawal suppression as rapidly as possible, without placing the individual at risk from methadone-induced respiratory depression. In most clinical situations, individuals are observed on a daily basis during this induction period and observations made of withdrawal signs and symptoms as well as evidence of intoxication. Dose adjustments are based on this evidence plus participant self-report. Ideally, during the induction period individuals would be observed at time of peak as well as at time of trough

concentration, but for practical reasons this is done in relatively few clinics.

Maintenance Dose of Methadone

The end of the induction phase should see the participant reach a relatively stable daily dose of methadone. In practice, over the following months dose changes are likely to occur and indeed may reoccur on an occasional basis though a history of years of treatment.

Early evidence concerning methadone dose failed to reveal marked differences in outcomes between lower doses (typically less than <50 mg/day) and high doses (frequently greater than 80 mg/day). More recent evidence from double-blind trials has suggested that higher doses are generally more effective than lower doses. The major difference lies not in treatment retention as this often similar across different doses, but in rates of illicit opioid use, which tend to be lower in those administered high doses. The result of this change of research outcomes has also been a change in clinical practice in the United States toward higher doses [11].

It is important to recognize that in these clinical trials, doses are often fixed or fixed within a range. In practice, the dose that is effective for an individual may vary over a considerable range. As the dose is increased, the proportion of individuals who are abstinent from illicit opioids increases, but even at low doses, some participants are retained in treatment and not using illicit opioids [73].

Unsupervised Dosing

Methadone for treatment of opioid dependence is normally administered as a once a day medication. Regulations in most countries require that all or a significant proportion of these doses are dispensed under supervision of a pharmacist. The major exception has been the United Kingdom, where individuals have been able to take away a week's supply or more. Where they are allowed unsupervised doses, rules are usually based on national or local guidelines or regulations. Typically, as a person is shown to be successful in maintenance treatment, the number of unsupervised or take home doses increases. The risk of take-home doses is three-fold. First, the client may administer the dose by injection with the associated risks of respiratory depression and the effects of injection of other substances in the methadone solution. Second, the drug may be sold into the illicit market. Third, there is a risk of infant ingestion of methadone doses stored in clients' homes. Against these risks is the difficulty of sustaining a normal lifestyle, particularly employment, when 7-days-per-week attendance at a clinic or pharmacy is required. It is clear that unsupervised doses allow more normality in the clients' lifestyles and are perceived as a benefit of stability while on a methadone maintenance program.

Cessation of Methadone Treatment

The timing at which an individual ceases methadone treatment is a matter of clinical judgment. Some clients may never cease treatment if they are not experiencing adverse effects and there is significant risk of relapse. In general, withdrawal from methadone is best achieved by very gradual dose reduction [69]. Even with such a gradual dose reduction, clients are often extremely sensitive to small dose changes and may require periodic stabilization of dose for some weeks before further dose reductions.

Managing Adverse Effects

Methadone, in common with other opioids, has a rang of short-term and long-term adverse effects. The long-term effects are discussed in more detail below. A number of studies have shown that adverse effects of methadone can influence client satisfaction with treatment and severe adverse effects may lead to treatment drop-out. Commonly reported effects include

excessive sedation, mood swings, sweating, constipation and decreased libido. It is important to minimize these adverse effects whilst maintaining doses of methadone that are effective in suppressing illicit opioid use. Most of these symptoms are attributable to excessive opioid effect or to breakthrough withdrawal [16]. Those attributable to excessive opioid effect, such as sedation at time of peak concentration, can be reduced by decreasing the dose, but this needs to be balanced against the potential for increasing the risk of illicit opioid use. Similarly, breakthrough withdrawal can be alleviated by dose increases, but these may result in elevated risk of opioid adverse effects at the time of peak concentration. Those individuals described in Fig. 1 who show a pronounced difference between peak and trough concentration may be particularly difficult to manage as they can potentially show significant adverse effects at time of peak concentration and breakthrough withdrawal at time of trough concentration. These individuals are much better suited by multiple daily administration. While this may be most appropriate for as many as one third of individuals on methadone maintenance [16], many clinics are reluctant to allow such split dosing because of the risk of dose diversion.

Evidence for the Effectiveness of Methadone Maintenance

There have been only two randomised placebo-controlled trials involving the effectiveness of methadone treatment. The first [62] was conducted in Hong Kong. All participants were stabilized on 60 mg of methadone in an inpatient unit. On discharge half continued on methadone maintenance with the option of dose changes, while the other group commenced a reduced dosing regime followed by placebo treatment. The results clearly showed much higher retention and lower heroin use in the methadone maintenance group.

The second, [72], compared treatment with 0, 20, and 50 mg/day of methadone. When the 50 and 0 mg groups were compared, retention was significantly higher in the 50 mg group and rates of positive urines were lower.

In addition to these two studies, there have been other randomised studies that did not include a placebo control [15, 29], that also showed positive outcomes for participants in methadone treatment groups. In addition, surveys carried out of drug treatment effectiveness have confirmed the effectiveness of methadone maintenance treatment. Together, these results show that treatment with methadone reduces illicit opioid use and retains individuals in treatment.

Other Outcomes

In addition to the effects on illicit opioid use, a number of positive outcomes have been demonstrated from the use of methadone maintenance. Illicit opioid use is associated with high rates of criminal involvement and of infectious diseases such as HIV and hepatitis C. The relationship between illicit opioid use and criminality is a complex one. Illicit opioid users may have a history of criminal involvement prior to their commencement of opioid use or they may have commenced criminal activity only as a consequence of their drug use. In addition, some aspects of the criminal involvement may be linked solely to obtaining funds to support their drug use, while other aspects of their criminal behavior are unrelated. Nevertheless, there is significant evidence that methadone maintenance treatment has an effect on rates of criminality [71].

Two prospective cohort studies in the US have shown a protective effect of methadone maintenance on HIV infection. One [56] found a much lower increase in HIV seropositivity amongst those in methadone-maintenance treatment group compared to those out of treatment. In addition, the seropositivity in the methadone treatment was due entirely to people who had dropped out of treatment. The second [59] found that clients who had spent less than a year in methadone maintenance were nearly three times more likely to be HIV positive than those who had spent more than a year in treatment.

Cost-Effectiveness

Increasingly, health care interventions need to show not only that they are effective, but also that they are cost-effective. This issue has been addressed in a number of studies for methadone maintenance. It has been shown that every year of life saved by methadone treatment incurs a cost of just under $6,000 [4]. Even with variation in the assumptions, this cost was less than $10,000 per life year. By comparison, a standard of $50,000 per life year is often judged as demonstrating sufficient cost-effectiveness to justify a medical treatment. When compared with detoxification, the costs of methadone maintenance were higher, but methadone recipients incurred lower costs for substance abuse and mental health care outside of the study [50]. Methadone maintenance also had advantages with regard to years of life saved. When a lifetime benefit model is used the benefit-cost ratio approaches 38:1 [82].

Predictors of Success in Methadone Treatment

The evidence presented above shows that methadone maintenance is a highly effective and cost-effective intervention. Nevertheless, there is room for improvement. In particular, a significant proportion of individuals never reach the 1 year duration of treatment widely regarded as a minimum for increasing the chances of long-term abstinence from illicit opioids. By examining the predictors of treatment success, it may be possible to design programs that have the best possible outcomes. There are two major sources of variability leading to differential outcomes: program-related factors and individual factors. Unfortunately, the information available on these factors provides relatively little direction. In the case of program characteristics, these have rarely been assessed quantitatively. It is generally regarded that clear program policies and protocols, well-trained staff that have empathy with the clients, and good counseling support, all contribute to good outcomes. There is also research supporting the provision of counseling and other services in addition to the basic provision of methadone (see below). The most influential of all the program factors is the dose provided. Those programs that provide only low doses of methadone have worse outcomes than those that have a dose range that includes a significant proportion of relatively high methadone doses.

Research on client characteristics that predict outcomes have yielded a range of significant findings, but little that can be used in a practical manner. For example, the most consistent client characteristic predictive of outcome is age, with older people tending to do better than younger ones. Other factors such as psychiatric comorbidity, criminal involvement and social stability have also been shown to have some influence in at least some studies.

One client characteristic that has some predictive value and that can be influenced, is the concentration of methadone achieved by the individual. The inter-individual differences in methadone pharmacokinetics, noted above, mean that dose is not closely linked to concentration. A wide range of trough plasma methadone concentrations (from 100 to 600 mg/ml racemic methadone) have been proposed as representing a suitable minimum concentration [18]. In the only prospective study that measured trough plasma methadone concentrations of subjects from commencement of methadone maintenance treatment [34] the authors identified a threshold of 220 ng/ml racemic methadone above which almost all individuals did well.

Resolution of the value of measuring a plasma concentration requires additional research on a therapeutic drug monitoring approach. It may be that concentrations will prove to be valuable predictors of outcome. At present, however, measurement of plasma concentrations is not routine in most clinics. It is often confined to determining plasma concentration changes in those individuals who seem to have an abnormal pattern of opioid effect and/or opioid withdrawal.

Problems Associated with Methadone Maintenance Treatment

While there are considerable benefits of methadone maintenance treatment, there is increasing recognition of the adverse effects of chronic opioid administration. Some problems of chronic administration have been recognized for a considerable period of time, while others such as risk of osteoporosis have emerged only in recent years. As a result, there is often inadequate information on which to base clinical decisions regarding long-term treatment. However, as further research evidence accumulates, the relative costs and benefits of extended, particularly lifetime, opioid administration in methadone maintenance will become more apparent.

Chronic opioid administration, including methadone maintenance, is associated with hypogonadism that may be more pronounced in men than in women [30, 31]. In men this may be associated with erectile dysfunction [32].

Increasing evidence associates long-term opioid administration with low bone mineral density. One survey found that more than three-quarters of a sample of participants in methadone maintenance treatment had low bone mineral density [41]. This may be attributable to several effects of opioids, including hypogonadism, described above, and inhibition of osteoblast function. Comorbid conditions such as tobacco dependence and HIV infection may also play a role. With increasing age of many individuals on methadone maintenance, there is concern over the risks of osteoporosis and its sequelae in long-term clients.

There has been increasing evidence that methadone may prolong the QT_c interval in a minority of individuals. Such prolongation of QT_c interval is more frequent when higher doses of methadone are used, in individuals also administered drugs that inhibit CYP3A4 activity (thereby increasing methadone concentration), in those administered other QT_c-prolonging drugs, and in those with medical conditions that may predispose to such prolongation [21].

Increasing evidence is suggesting that long-term opioid administration is associated with hyperalgesia, a hypersensitivity to at least some kinds of painful stimuli [2]. Thus, for some types of pain, long-term opioid administration may actually increase the response to a painful stimulus rather than decrease it. Hyperalgesia may predispose individuals to chronic pain problems and make it difficult to achieve acute analgesia when it is required for medical treatment. Individuals being treated for opioid dependence are experienced opioid users and thus methadone treatment is not a cause of hyperalgesia, but may maintain a hyperalgesic state in someone chronically exposed to opioids.

Cognitive impairment has long been a concern for prescribers and for individuals maintained on opioids for treatment of pain and opioid dependence. Early studies suggested that there was little reason for caution unless participants had experienced a recent dose increase or were new to methadone treatment. However, recent studies have suggested that individuals maintained on methadone are significantly impaired. Impairments have been reported on a wide range of cognitive functions, such as attention, visual orientation, psychomotor speed, memory and decision making after controlling for gender, age, intelligence and pre-existing neurologic or psychiatric conditions. Reports comparing methadone recipients with people who were previously illicit opioid users also show significant impairment [13, 74]. While it is difficult to design studies of cognitive impairment that do not have at least some methodological shortcomings, this recent evidence raises concern regarding the functioning of individuals in activities such as motor vehicle operation, various types of employment and normal social and family functioning.

In summary, more recent evidence has implicated chronic opioid administration, and in particular methadone administration, in a range of adverse health impacts. For many of these impacts research findings are still accumulating and it is difficult to make definite conclusions. Nevertheless, the benefits of very long-term

opioid administration need to be balanced against these health risks.

Buprenorphine Maintenance

For approximately 30 years methadone was almost the sole opioid used in maintenance treatment. Then in 1995 the partial agonist buprenorphine began to be used in France for the same purpose. Buprenorphine had an extensive history of use as an analgesic, but there was also an increasing body of research suggesting that it would be valuable in the treatment of opioid dependence. Since that time buprenorphine has been approved for opioid maintenance treatment in a number of countries. It is available alone and in combination with naloxone in a dose ratio of 4:1.

Pharmacology of Buprenorphine and Naloxone

Buprenorphine is a partial agonist at the μ-opioid receptor where it has high affinity but low intrinsic activity. It is also a partial agonist at κ-opioid receptors and an antagonist at the δ-opioid receptor.

As a partial agonist at the μ-opioid receptor, buprenorphine would be expected to have opioid agonist effects similar to those of methadone, but a lower maximum effect. There is evidence that this is true for at least some effects of buprenorphine. For example, buprenorphine-induced respiratory depression shows a lower peak effect than the full agonist methadone [76]. Subjective responses show a similar relation. However, this may not be true for all effects of buprenorphine. Recent evidence suggests that the dose response curve for analgesic effects of buprenorphine shows a pattern similar to that of a full agonist [12].

Buprenorphine is metabolized to an active metabolite, norbuprenorphine, through the action of CYP3A4. There is evidence that norbuprenorphine acts as a full agonist at the μ-opioid receptor and that buprenorphine, with its relatively higher affinity and lower efficacy, may block the actions of norbuprenorphine [54].

Buprenorphine has very low oral bioavailability due to extensive first-pass metabolism. Bioavailability is higher by the usual sublingual route of administration. Peak plasma concentrations are reached approximately 1.5 h after administration, but this is highly variable. Buprenorphine is widely distributed in the body and readily crosses the blood-brain barrier, but there is evidence that it does not readily cross the placental barrier [60].

Following sublingual administration the terminal half-life of buprenorphine is long (approximately 26 h), but highly variable (range 9–69 h) [52]. The extended duration of action of buprenorphine is likely to be due to a combination of this long elimination half-life as well as the tight binding of buprenorphine to the μ-opioid receptor.

In subjects maintained on sublingual buprenorphine, peak plasma concentrations of buprenorphine are approximately ten-fold higher than trough concentrations, but opioid effects show relatively little change over the dosing interval [48]. Thus, compared to methadone, over the dosing interval there is greater change in plasma concentration, but less change in effect.

To date, there has been little research on drug interactions with buprenorphine. As it is primarily metabolized by CYP3A4, many of the drugs that exhibit pharmacokinetic interactions with methadone will also influence buprenorphine concentrations. There is some evidence that HIV protease inhibitors such as ritonavir and antifungals such as ketoconazole inhibit buprenorphine metabolism. The clinical impact of such interactions is yet to be determined.

Naloxone is a μ-opioid receptor antagonist. The bioavailability of naloxone via the sublingual route is very low (approximately 10%). The low bioavailability combined with the short elimination half-life of naloxone (1–2 h), means that when administered sublingually, the amount of naloxone absorbed is extremely small. In contrast, when administered via the

intravenous route, naloxone will be present in concentrations sufficient to produce an antagonist effect. For example, a person who administers 16 mg buprenorphine + naloxone via intravenous administration is receiving a 4 mg dose of naloxone with 100% bioavailability. Such a dose of naloxone is sufficient to reduce the peak effects of buprenorphine and to precipitate withdrawal in someone who is opioid dependent [55].

Clinical Use of Buprenorphine

While the criteria for buprenorphine maintenance treatment are much the same as those for methadone maintenance treatment, and there are many similarities in the way buprenorphine and methadone are used, there are also some important differences. In some countries, such as the United States, the setting may be different with buprenorphine + naloxone used largely in office based treatment while methadone treatment is centered in specialist clinics. In other countries, the settings are similar with both methadone and buprenorphine used in clinics and office-based treatment.

Commencement of methadone treatment carries significant risk of respiratory depression and therefore needs to be approached cautiously. In contrast, the relative safety of buprenorphine allows rapid escalation of dose. Even though buprenorphine has a long half-life and hence the full effects of a dose increase may take a number of days, it appears to be safe to reach a maintenance dose (such as 12 mg) on the third day of administration.

In contrast to methadone, however, buprenorphine carries the risk of precipitated withdrawal. As an agonist with high affinity but low intrinsic activity, it will displace most opioid agonists from the μ-opioid receptor, but produce insufficient activity to maintain physical dependence. Thus, buprenorphine dosing is normally commenced only when the individual exhibits mild signs of opioid withdrawal.

Buprenorphine is a more potent drug than methadone and doses tend to be considerably lower. For most clients, maintenance doses are in the range 8–16 mg/day. In contrast to methadone, there is no clear evidence of better outcomes at higher doses, at least when the dose is 8 mg/day or higher. Thus, current clinical recommendations are to titrate the dose in order to achieve effective withdrawal suppression and blockade of heroin use. In contrast to methadone, buprenorphine can be administered every second day or even every third day [49]. Clinical practice varies, with some strongly encouraging clients toward every-second-day dosing and others finding that most clients prefer daily dosing.

Regulations regarding unsupervised doses of methadone vary considerably. When implemented in France in the 1990s, buprenorphine was dispensed as a single drug and clients were not required to have doses supervised. More recently, the buprenorphine + naloxone combination has been approved in the United States without the dosing supervision associated with methadone. In other countries, the degree of dosing supervision is similar to that for methadone, even when buprenorphine is used in combination with naloxone.

Cessation of buprenorphine treatment is somewhat easier than cessation of methadone treatment. While abrupt termination of buprenorphine dosing is associated with a withdrawal syndrome and clients who gradually reduce the dose also experience some withdrawal, the intensity appears to be less than for methadone. Where a decision has been made to cease maintenance treatment with buprenorphine, gradual dose reductions may be implemented over a number of weeks.

Evidence for the Effectiveness of Buprenorphine Maintenance

There have been four studies comparing buprenorphine maintenance with placebo or active placebo. Two studies of buprenorphine compared to placebo were conducted in the United States [25, 37] and a third in Sweden [39]. In a fourth trial, conducted in the United States, buprenorphine doses of 4, 8 and 16 mg

were compared to a 1 mg dose as active placebo [45]. These four studies all showed clear evidence that buprenorphine is more effective than placebo. There were considerable variations in dose, the form of buprenorphine (with or without naloxone) and the degree of psychosocial treatment provided, but despite these variations the results are very consistent.

There have also been a number of comparisons of buprenorphine with methadone. These have been summarized in various reviews and meta-analyses [5, 9, 51]. The conclusions of these reviews are consistent in suggesting that buprenorphine and methadone are equivalent in reducing illicit opioid use. However, buprenorphine maintenance is associated with slightly lower retention rates than methadone. There may be a number of reasons for this, including use of relatively slow induction dose increases in early studies with buprenorphine.

Problems Associated with Buprenorphine Maintenance Treatment

Some of the adverse effects associated with chronic opioid administration were described in the section above titled "Problems associated with methadone maintenance treatment". As an opioid agonist, buprenorphine will have similar effects. However, as a partial agonist there is evidence that for at least some of these problems of long-term treatment, risk may be lower for buprenorphine than for methadone. There is some suggestion that hypogonadism in men may be less likely in individuals maintained on buprenorphine [31] and that they have lower rates of erectile dysfunction [33]. There is also some evidence that buprenorphine is associated with less QT_c prolongation than methadone [77]. Buprenorphine may be associated with a lower level of cognitive and psychomotor impairment than methadone [64, 65].

For many of these adverse effects a considerably larger body of research is needed to make definitive conclusions on the relative advantages of buprenorphine versus methadone. To date, the lower risk of respiratory depression has been seen as the main advantage of buprenorphine over methadone. However, if continued research on long-term effects reveals increasing problems associated with administration of full agonists such as methadone, and lesser problems with buprenorphine administration, then these advantages of buprenorphine may prove to be equally or more important.

Other Opioid Agonists

While methadone and buprenorphine are the most widely used opioid maintenance medications, other drugs have been used or are currently being used for this purpose. This section will briefly review three of those medications: levo-alpha-acetylmethadol, slow-release morphine, and heroin.

Levo-Alpha-Acetylmethadol

Research on the use of levo-alpha-acetylmethadol as a maintenance medication began in the 1970s in the United States. As a long-acting opioid, it had obvious appeal as a maintenance medication. However, final approval for registration in the United States did not occur until 1993. Subsequently, it was approved also in Europe, but by 2001 there was concern over cases of Torsades de pointes [14]. This adverse effect of levo-alpha-acetylmethadol was associated with increased QT_c interval and resulted in withdrawal of the medication by the manufacturer. As a consequence of these findings, a more thorough investigation revealed that methadone was also associated with these risks, but possibly less risk than levo-alpha-acetylmethadol.

Pharmacology

Levo-alpha-acetylmethadol is structurally similar to methadone. It differs in having two active metabolites, nor-levo-alpha-acetylmethadol and

dinor-levo-alpha-acetylmethadol, each of which has a very long half-life and contributes to the effects of the drug. The result is a long duration of action, meaning that levo-alpha-acetylmethadol can be administered every second or third day [43, 61].

Like methadone, levo-alpha-acetylmethadol is normally administered as an oral solution and is well absorbed from the gastrointestinal tract. Peak plasma concentrations of levo-alpha-acetylmethadol are reached approximately 2–4 h of administration and several hours later for nor- levo-alpha-acetylmethadol and dinor-levo-alpha-acetylmethadol. Like methadone and buprenorphine, CYP3A4 plays the primary role in the metabolism of levo-alpha-acetylmethadol.

Evidence of Effectiveness

In randomized controlled trials, levo-alpha-acetylmethadol has been shown to be about equally as effective as methadone [42, 44]. In a comparison with methadone and buprenorphine, levo-alpha-acetylmethadol showed outcomes at least as good methadone [38].

Problems

In large part, problems associated with use of levo-alpha-acetylmethadol are similar to those associated with methadone use. However, the prolongation of the QT_c interval and life-threatening cardiac arrhythmias have had a much greater impact on the use of levo-alpha-acetylmethadol. There is some evidence that the effect of levo-alpha-acetylmethadol may be due principally to the parent medication, rather than the active metabolites [40].

Slow – Release Oral Morphine

Morphine is regarded as the prototype μ-opioid receptor agonist. It is also the main active metabolite of heroin and much of the action of that illicit opioid is due to the activity of morphine. It would seem logical, therefore, to consider morphine as a maintenance medication. The main reason it was not considered at the time methadone was introduced was because of its short duration of action. However, since then a number of slow-release preparations of morphine have been developed for the relief of pain that have potential for opioid maintenance medication. There is also a slow-release morphine formulation available in eastern Europe that is marketed specifically for treatment of opioid dependence.

Pharmacology

Morphine is an opioid agonist that is highly selective for the μ-opioid receptor but has lower intrinsic efficacy than methadone. It has low oral bioavailability due to extensive first-pass metabolism and a short, variable half-life of approximately 2 h. It has two major metabolites, morphine-3-glucuronide and morphine-6-glucuronide. Both are pharmacologically active, with morphine-6-glucuronide exhibiting opioid effects and morphine-3-glucuronide excitatory effects through an unknown mechanism. Slow-release formulations of morphine developed for chronic pain treatment show varying durations of action and only some allow once daily administration.

Evidence of Effectiveness

In the one double-blind trial comparing slow-release oral morphine to methadone [20], retention in treatment and use of illicit opioids was comparable for the two medications, but morphine recipients had significantly lower depression and anxiety and fewer physical complaints. Variable outcomes have been obtained with quality of life measures [26, 78]. Morphine was shown to be an effective alternative for clients who experienced breakthrough withdrawal when maintained on methadone [58].

Problems

Use of slow-release oral morphine as a maintenance treatment is associated with two problems in addition to those resulting from long-term administration of any opioid. The first is that routine urine testing for illicit opioid use normally relies on detection of morphine. For individuals maintained on morphine, the strategy is not appropriate, and if urine testing is to be used, alternatives need to be developed. Some efforts have been made in this direction [63]. The second problem is the risk of diversion of the medication. While other opioids are associated with such risk, it is somewhat increased because of the low oral bioavailability of morphine. When a dose intended for oral administration is used intravenously, the effect may be particularly pronounced, placing the user at high risk of overdose. Individuals who are taking slow-release morphine need to be aware of this difference in bioavailability between oral and intravenous routes.

Diacetyl Morphine

While diacetyl morphine or heroin has been the main illicit opioid used, there has been interest in using it as a maintenance medication. The drug has significant disadvantages because of its short duration of action requiring multiple daily administrations. In addition, even in treatment it has been administered by the intravenous or inhalation route, resulting in rapid onset of action. Thus, heroin maintenance does not change the usual cycle of peaks and troughs of opioid effect through the day. However, the main rationale for heroin maintenance has not been to provide the maximum stability to clients, but to engage in treatment those who would otherwise be refractory or who have proven to be refractory. Thus, this treatment is intended for the minority of individuals who have not achieved substantial reductions in illicit opioid use despite multiple episodes of engagement with treatment programs.

Pharmacology

Diacetyl morphine is rapidly metabolized to 6-monoacetyl morphine and then to morphine. Both diacetyl morphine and 6-monoacetylmorphine have very short half-lives of 8 and 22 minutes respectively. 6-monoacetylmorphine and morphine are μ-opioid receptor agonists. Diacetyl morphine had been believed to be a pro-drug, but there is evidence suggesting that it may bind to a variant of the μ-opioid receptor [68]. Diacetyl morphine also differs from morphine in being considerably more lypophilic and therefore it more readily crosses the blood-brain barrier.

Evidence of Effectiveness

There have now been a number of trials of heroin maintenance, but the interpretation of the results is made difficult by the variability in trial design. Generally, methadone maintenance has been the usual comparator treatment, but in different studies this has been compared to heroin maintenance alone or heroin maintenance plus methadone maintenance. Heroin has been administered by both intravenous and inhalation routes and the frequency of administration per day has varied.

It is not surprising, therefore, that there has been considerable variability in outcomes from these trials [23]. While they have shown that heroin maintenance can be implemented safely and the results have been largely positive, heroin maintenance cannot be recommended for treatment with the same confidence as methadone or buprenorphine [79].

Adjunctive Treatment in Agonist Maintenance Programs

Maintenance treatment with methadone or buprenorphine can be little more than appropriate assessment and provision of a prescription

with periodic review. However, other aspects of treatment may be included as part of the maintenance program. This may include specific treatment focused on comorbidities such as psychiatric problems, infectious diseases, dental treatment and pain management. Psychosocial treatment may also be a significant part of the package and in many countries such psychosocial treatment is mandated.

Counseling may form part of general medical management. This is generally focused on issues of relevance to illicit drug use, such as recent drug use or abstinence, attendance in self-help groups, provision of support or efforts to reduce drug use or remain abstinent, advice for successful abstinence and feedback on urine results [24]. Two other more focused types of interventions have also been evaluated. Cognitive behavioral therapy is typically centered on drug use, the cues that lead to relapse and ways to cope with these, adjusting to the absence of drug reinforcement, drug refusal skills, and coping with withdrawal. Contingency management is a behavioral based treatment in which individuals receive rewards for drug-free urines. The reinforcers can include money, goods, or additional privileges such as take home doses.

There are a relatively small number of studies evaluating different psychosocial approaches and hence definitive conclusions are not possible. Nevertheless, it has been suggested that psychosocial treatments are effective in reducing use of illicit opioids, but have little effect on retention in treatment [1]. It should be recognised that with the small number of studies, this conclusion should be regarded as tentative only.

Maintenance Antagonist Treatment

An alternative to the use of opioid agonists is maintenance treatment with the μ-opioid receptor antagonist naltrexone. The aim of this approach is to prevent the client from experiencing opioid effects. While it is possible to overcome the effects of naltrexone with a sufficient dose of agonist, the usual dose of naltrexone makes this difficult to achieve. Naltrexone was first approved for use in opioid dependence treatment in the United States in 1984. Despite this relatively long period of clinical use, uptake of naltrexone treatment is generally low.

Pharmacology of Naltrexone

Naltrexone is an antagonist at μ-, κ-, and δ-opioid receptors, with particularly high affinity for the μ receptor. Over the range 20–200 mg naltrexone has been shown to produce dose-dependent antagonism of the euphoric effects of intravenous heroin for up to 72 h [66]. It has been suggested that the minimum plasma naltrexone concentration associated with a significant blockade of opioid effects is 1–2 ng/ml.

Naltrexone is almost completely absorbed following oral administration, but undergoes first-pass metabolism. Estimates of bioavailability have varied considerably, ranging from 5 to 60%. Naltrexone has a relatively short half-life of 2–6 h. The major metabolite, 6-β naltrexol, is a less potent antagonist but with a much long half-life. As a result, in stable maintenance clients, concentrations of 6-β naltrexol are usually higher than those of the parent medication naltrexone and 6-β naltrexol may contribute significantly to the antagonist effects of naltrexone.

Evidence of Effectiveness

While there is clear evidence that naltrexone is a potent antagonist able to block the effects of illicit opioids, outcomes from studies of effectiveness in maintenance treatment have generally been poor. Reviews of these studies have concluded that it should not be a recommended treatment option [36, 57]. A major problem with naltrexone is the low rate of retention in treatment. It is clearly an effective medication when taken on a daily basis for at least 3 months, but few individuals adhere to this treatment regimen. Clinical experience suggests that in a limited

group of highly motivated individuals, naltrexone can be very effective.

Problems Associated with the Use of Naltrexone

Naltrexone treatment is made difficult by the risk of precipitated withdrawal associated with the use of this medication in opioid-dependent individuals. Generally, individuals need to undergo withdrawal prior to administration of naltrexone. There have been attempts to shorten this process through administration of naltrexone while a person is heavily sedated or anesthetized, but there are significant safety concerns with this type of procedure (see below).

The reasons for the high dropout rate with naltrexone are not clear; however, it is possible to speculate on several possible sources. Withdrawal is not alleviated in an individual maintained on an antagonist, and indeed may made worse by administration of the antagonist medication. Naltrexone also has side effects that some individuals find uncomfortable, including nausea, headache, and dizziness. Recent evidence also suggests that naltrexone may not be a pure antagonist. Rather, in common with many other antagonists it may have inverse agonist properties that become evident in people who have been chronically exposed to opioids.

Depot and Implant Formulations

One approach to the low retention rates associated with naltrexone treatment is the development of implant and depot formulations of naltrexone. The aim is to produced sustained therapeutic plasma naltrexone concentrations for periods of weeks to months. To date, one such formulation has been approved in the United States for treatment of alcohol dependence. It produces plasma concentrations in the range 0.6–2 ng/ml and is effective over a 3–6 week period. Thus, if used for opioid dependence treatment, repeated administration would be required. Other longer acting formulations are also under development and, while not yet approved, have been widely used. These include surgically inserted implants that have a duration up to 6 months [35, 75]. While there are encouraging results from early studies with these naltrexone formulations [8], there are issues that need to be addressed, including the inter-individual variability in the plasma concentrations of naltrexone that are achieved.

Management of Opioid Withdrawal

While the main treatment option for opioid-dependence individuals is maintenance treatment with methadone or buprenorphine, some individuals have a preference or need for abstinence-oriented treatment. The major component of this may be a residential program or outpatient counseling based on relapse prevention methods. However, in order to reach abstinence, the client has to undergo withdrawal, and the discomfort associated with the acute phase of opioid withdrawal may lead to a high risk of relapse to illicit opioid use. In order to facilitate the transition to opioid abstinence, medications may be used to relieve withdrawal symptoms and psychosocial treatments may also be provided. In different contexts these may be applied on an inpatient or outpatient basis.

Management of Opioid Withdrawal with Opioid Agonists

As a result of cross-tolerance, any μ opioid agonist can potentially be used for treatment of opioid withdrawal. In practice, methadone was the most widely used opioid agonist for treatment of withdrawal, with buprenorphine becoming more common in recent years.

Protocols for methadone management of withdrawal from short-acting opioids vary

considerably. Peak doses are frequently in the range 30–40 mg/day reached in the first few days after cessation; doses are then gradually tapered at a rate of 5 mg/day or more. On an outpatient basis the tapering process may be considerably longer.

With buprenorphine, peak doses are frequently in the range 8–10 mg/day, with reductions around 2 mg/day for inpatients.

Comparisons of methadone and buprenorphine for treatment of withdrawal suggest that outcomes are similar [27]. Withdrawal symptom severity is approximately equivalent, but withdrawal symptoms may be of shorter duration with buprenorphine. This could be due to some additional withdrawal occurring following cessation of methadone treatment that does not appear to occur following cessation of short-term buprenorphine treatment.

More recently, other opioid agonist have been assessed for their efficacy in treatment of withdrawal, including tramadol [47] and dihydrocodeine [3]. Limited research to date suggests that both medications may have some role, but there is no evidence that they are superior to methadone or buprenorphine in this regard.

Use of α-2 Adrenergic Agonists

Early research on the nature of opioid withdrawal revealed that a significant component of the withdrawal syndrome is due to noradrenergic overactivity. This is manifested, in part, by signs and symptoms of sympathetic arousal, such as elevated heart rate, blood pressure and sweating. The action of α-2-adrenergic agonists in reducing this overactivity makes them potential medications for treatment of opioid withdrawal. Two such medications have been used: clonidine has been used in a number of countries over many years, while lofexidine has been used principally in the United Kingdom. The pharmacology of these medications is slightly different, with clonidine binding in a non-specific way to all three subtypes of α-2-adrenergic receptors and lofexidine binding to one subtype only. The consequence is that lofexidine has less hypotensive effect that clonidine. As hypotension is the main adverse effect from clonidine, lofexidine potentially has advantages in safety.

Comparisons of clonidine-based treatment with use of opioid agonists suggest that clonidine is considerably less effective than agonist treatment. For example, in a multi-site trial, buprenorphine + naloxone was clearly superior to clonidine for management of opioid withdrawal, whether this was carried out on inpatients or outpatients [46]. The major difference is that clonidine suppresses fewer symptoms than does methadone or buprenorphine. In clinical practice, clonidine is usually used in combination with other symptomatic medications because of its failure to alleviate symptoms such as diarrhoea and stomach cramps.

Lofexidine has recently been shown in a placebo-controlled trial to be more effective than placebo in amelioration of withdrawal [80]. In a review of earlier studies it was concluded the lofexidine had similar outcomes to clonidine, but with less effect on blood pressure [28].

Antagonist-Precipitated Withdrawal

When the goal for treatment of the individual is maintenance with naltrexone, the acute withdrawal phase may prove to be a barrier to treatment. As a means of addressing this, anesthesia and heavy sedation have been used to reduce withdrawal distress and the client is administered the first dose of naltrexone while under sedation or anesthesia. Several studies have compared anesthesia-assisted withdrawal with more conventional withdrawal management followed by naltrexone treatment. These studies show that short-term retention may be slightly higher for the anesthesia-based procedures, but at the cost of significantly higher risk of adverse events. After the first 3 months, differences in retention between groups tend to dissipate [7, 22, 53].

Conclusions and Future Directions

Compared to treatments of other types of drug dependence, development of pharmacotherapies for opioid treatment has had several advantages: a clearly defined receptor target in the μ-opioid receptor and a history of research in opioid pharmacology that has produced a range of agonist, partial agonist, and antagonist medications. Today, this has resulted in varied options for treatment of opioid dependence.

Compared to many other pharmacological treatments for a range of disorders, methadone and buprenorphine can be shown to be extremely successful. There are repeated demonstrations of marked declines in illicit drug use and increases in health status associated with treatment with these drugs. Treatment of withdrawal can also be shown to be effective with a choice between the partial agonist buprenorphine and α2 agonists, such as lofexidine and clonidine.

Despite a substantial body of research, there are many questions that remain unresolved. Further research is needed on the optimal range of psychosocial and ancillary treatments provided to individuals. While outcomes are extremely positive with methadone and buprenorphine treatment, there is significant room for improvement as a substantial minority of participants drop out during the first year of maintenance therapy. The duration of treatment is also an issue that is likely to receive increased attention with greater recognition of the potential adverse health effects of long-term opioid treatment.

One way in which the opioid treatment is likely to develop in future years is through the use of different formulations, particularly long-acting formulations. To date, naltrexone has not proven effective as a once-a-day oral medication. However, the development of depot and implant formulations may render naltrexone a much more effective medication that has a significant role in treatment of opioid dependence. Longer acting formulations are also being developed for buprenorphine, and these may result in significant changes in the way that drug is used.

Future attention will also focus on the diversity of opioid-dependent individuals. While illicit heroin users have formed the greatest number of people presenting for treatment of opioid dependence, there is an increasing number of people dependent on prescription opioids. It has yet to be determined whether standard treatments developed for heroin users will be as appropriate for prescription opioid users or whether they need to be adapted in some way. In addition, there is increasing recognition of the frequency of chronic pain problems among opioid-dependent individuals [67], who may also require some differences in approach.

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Methamphetamine

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Contents

Clinical Use of Methamphetamine

Methamphetamine is still available on the market as a controlled substance. Manufactured under the brand name Desoxyn® (Ovation Pharmaceuticals, Deerfield, IL), it has the same control II designation and restrictions that other stimulant medications such as amphetamine and methylphenidate have [65, 66]. Methamphetamine can be used for the treatment of attention-deficit hyperactivity disorder, for short-term weight loss in obese individuals, and for narcolepsy. The Food and Drug Administration has approved its use in the treatment of attention-deficit hyperactivity disorder in children aged 6–12. (Food and Drug Administration approval in adolescents and adults with attention-deficit hyperactivity disorder has not been pursued by any company.) The parameters for Food and Drug Administration approval in treating exogenous obesity include only short-term (i.e., a few weeks) usage only in the context of a weight reduction plan of a structured diet with exercise, and only for patients in whom obesity is refractory to alternative therapy, e.g., repeated structured diets, group programs, and other medications. Also, methamphetamine use in obesity is discouraged if the patient is below age 12. Interestingly, if one reviews the current treatment guidelines from the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry, methamphetamine is not listed as a recommended therapy for the treatment of attention-deficit hyperactivity disorder [1, 70]. Not surprisingly, its use among practicing physicians remains sparse to nonexistent.

The dosage recommendation by the package insert for attention-deficit hyperactivity disorder starts with 5 mg given in the morning, and proceeds with weekly 5-mg increases until optimal clinical response has been achieved [65]. The usual dosing for childhood attention-deficit hyperactivity disorder is 20–25 mg given as a once- or twice-daily dose. The recommended dosage in short-term obesity treatment is 5 mg taken 30 min before meals. Desoxyn® is only available in 5-mg tablets, and no generic manufacturer

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_52,

currently exists. Abbott Pharmaceuticals produced Desoxyn® since its introduction in 1942 and sold its rights to Ovation Pharmaceuticals in 2002, although Abbott still has the facilities that manufacture the product. Abbott also produced a sustained-release form of methamphetamine named Desoxyn® Gradumet, utilizing a plastic matrix for gradual release of the methamphetamine. This product was available in 5, 10, and 15-mg dosages. Manufacturing of the Desoxyn® Gradumet was discontinued in 1999 due to "manufacturing difficulties".

No clinical trials are available by PubMed search for the use of methamphetamine in attention-deficit hyperactivity disorder or obesity. Interestingly, l-deprenyl (selegiline), a common medication for Parkinson's disease that is now used for treatment of depression in a patch delivery form, has been evaluated in clinical trials, the results of which suggest that it may be a good medication for children with attention-deficit hyperactivity disorder [2, 58]. This is relevant because selegiline has two major metabolites: amphetamine and methamphetamine [32].

Although methamphetamine has not received official Food and Drug Administration approval for use in narcolepsy, this appears to be the main use for which it is prescribed in North America [59]. Methamphetamine is used along with the other stimulants and l-deprenyl to treat the excessive sleepiness symptom of narcolepsy. The last trial evaluating methamphetamine in the treatment of narcolepsy was reported in 1993 and found that daytime sleepiness was successfully treated in adults with doses of 40–60 mg/day [57].

Although methamphetamine may have proven efficacy and safety in the treatment of childhood attention-deficit hyperactivity disorder and obesity, the risks of abuse and divergence along with its current negative reputation among health care workers and the public as a drug of abuse make it unlikely that many physicians will endorse its clinical use for these indications.

Diagnosis of Methamphetamine Abuse

Similar to the abuse of other drugs, methamphetamine abuse is characterized generally as a psychological and/or physiological dependence on the drug. The diagnosis is restricted to cases in which there has been long-term abuse leading to impaired social and/or occupational functioning. Based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision nomenclature, methamphetamine or amphetamine abuse and dependence disorders can be primary diagnoses, or the use of methamphetamine can be associated secondarily with the induction of psychotic disorders, intoxication delirium, mood disorders, anxiety disorders, sleep disorders, or sexual dysfunction. There is some controversy about the taxonomy of substance-induced psychosis [47], which likely requires some adjustments in the symptom checklist for diagnosis.

Escalation of Methamphetamine Use

As is the case with other drugs of abuse, methamphetamine is often used in binge-like patterns that are characterized by periods of high intake, followed by "crashes" after the drug is depleted. Individuals often show a developmental trajectory from experimentation with low doses, followed by escalation to higher binge intake, although the various patterns of intake that capture methamphetamine abuse across different individuals are difficult to characterize fully due to the clandestine nature of use within the population [6, 54]. Interviews with chronic methamphetamine abusers suggest that most individuals initiate methamphetamine use by self-administering the drug at long intervals, a so-called "recreational" pattern [12]. Many individuals subsequently progress into dose escalation, with shorter intervals between

successive self-administrations, thus manifesting as a "binge and crash" pattern. The escalation into higher dose intake may reflect, at least in part, tolerance to many of the peripheral and central effects of methamphetamine [14, 22].

Animal models have been developed to characterize the nature of escalation in methamphetamine use with repeated administration. Escalation of methamphetamine use occurs when rats are given extended access to intravenous methamphetamine in an operant conditioning chamber [42]. With this procedure, rats are first trained to press a lever to self-infuse methamphetamine intravenously during daily 1-h sessions. When subsequently shifted to 6-h daily sessions, rats will escalate their intake pattern across sessions. This escalation is typically noted when comparing the intake of methamphetamine within rats across 6-h sessions, as well as when comparing the intake of methamphetamine during the first hour of the 6-h session with the intake of rats maintained on daily 1-h sessions. Escalation of methamphetamine use enhances the ability of methamphetamine to prime reinstatement of extinguished lever-pressing [74], suggesting that the development of an escalating pattern of intake may exacerbate the rate of relapse in abstinent humans.

Escalation of methamphetamine use has a host of deleterious neurobehavioral effects. Compared with non-escalating use, escalating use of methamphetamine impairs performance on the novel object recognition test in rats [74], which parallels the type of neurocognitive impairments observed in abstinent methamphetamine abusers [54]. Escalation of methamphetamine use in rats also decreases the birth of glia (astrocytes and oligodendrocytes) and neurons in the medial prefrontal cortex, as well as promoting cell death [46]. The medial prefrontal cortex is part of a complex frontal neurocircuitry known to be involved in response inhibition and self-control [40]. Damage to the medial prefrontal cortex and related frontal structures may disinhibit behavior, thus yielding a compulsive escalation of methamphetamine intake. In addition, since the medial prefrontal cortex is involved in the processing of stimulant reward [27], it may be that damage to this region reduces the rewarding effect of methamphetamine, thus leading to a compensatory escalation of intake.

With extremely high doses of methamphetamine, profound hyperthermia and neurotoxicity are observed. In rats, neurotoxic effects can be observed following 1 day of high-dose methamphetamine treatment (10 mg/kg; 4 injections at 2-h intervals), an effect characterized by a marked depletion of monoamine levels across various cortical and subcortical structures [10, 23, 93]. This neurotoxicity parallels the reductions in dopamine markers measured with positron emission tomography or with postmortem sampling in human methamphetamine abusers [11, 49, 91, 94]. However, the effects observed in rats following a single 1-day treatment may be somewhat artificial, since human methamphetamine abusers do not typically reach high levels of use until long-term use leads to escalation of intake. In particular, a recent study by O'Neil et al. [64] demonstrated that the neurotoxic effects of a methamphetamine 1-day "binge" noted earlier in rats was blunted substantially when an escalating dose procedure was used. This decrease in neurotoxicity is not related to altered pharmacokinetics, as no changes in brain or plasma methamphetamine levels were observed following a methamphetamine binge in rats treated previously with escalating doses of methamphetamine.

Pharmacokinetics of Methamphetamine

While methamphetamine is used clinically as an oral formulation, illicit use of methamphetamine more typically involves self-administration via the inhalation, intranasal, or intravenous routes.

Unfortunately, information about the precise pharmacokinetics of methamphetamine use via these latter routes is sparse. Bioavailability via the intravenous route is 100%, whereas bioavailability via the intranasal route is 79% and via the inhalation route is 67% [28]. Although there is little opportunity to obtain blood samples from methamphetamine abusers during a binge, one study reported on blood concentrations taken from individuals arrested for suspicious behavior [52]. Among individuals in which methamphetamine was detected, the blood levels were found to range between ~0.5 and 10 μM. In controlled laboratory studies, the plasma half-life of methamphetamine was found to be approximately 10 h in humans, which is considerably longer than the plasma half-life of 70 min observed in rats [28]. In rats, the plasma concentration of methamphetamine reaches a maximum level faster following intraperitoneal administration (5–10 min) than following subcutaneous administration (20–30 min); however, ~42% of methamphetamine administered via intraperitoneal injection is subject to significant first-pass metabolism, which reduces bioavailability to ~52% [24].

The major inactive metabolite of methamphetamine is p-hydroxymethamphetamine, which can be detected readily in the urine of methamphetamine abusers [31]. Methamphetamine is p-hydroxylated to p-hydroxymethamphetamine in liver microsomes. Interestingly, in both rats and humans, a significant portion of methamphetamine is N-demethylated into amphetamine [8]. Amphetamine is also a potent psychostimulant that is p-hydroxylated to the inactive metabolite p-hydroxyamphetamine [34]. Because the conversion of methamphetamine to amphetamine is faster than the elimination of amphetamine from the blood, the concentration of amphetamine can actually exceed the level of methamphetamine when sampled at a long interval following a single bolus injection of intravenous methamphetamine [12]. In humans, the plasma half-life is slightly longer for l-methamphetamine than for d-methamphetamine (~14 h vs. 10 h) [53].

Human Studies in the Treatment of Methamphetamine Abuse and Dependence

A much greater portion of recent research in methamphetamine use pertains to treatment of abuse and dependence, and not its clinical usage. Methamphetamine abuse has increased to epidemic levels globally during the last two decades (and has not been completely abolished by the restrictions on pseudoephedrine purchasing), and the need for outcome-based studies on treatment has increased greatly [48, 71]. Although many scientists and practitioners seem to assume that the more extensive experience and literature on the treatment of cocaine abuse can be extrapolated to methamphetamine, the mechanisms of action between cocaine and methamphetamine are sufficiently different, along with differences in the surrounding drug culture, to warrant independent trials and the unique treatment of people who abuse methamphetamine and wish to quit [73].

A wide range of neuropharmacological strategies are being pursued in the search for an efficacious pharmacotherapy for methamphetamine addiction. Recent evidence can be found with a search of registered clinical trials (clinicaltrials.gov), which is now required for all institutional review board-approved clinical trials. A search of “methamphetamine dependence” and “methamphetamine abuse” yielded 40 to 48 listed studies. Although many of these studies were no longer active or not testing medications, a few representative Phase II and Phase III trials are currently ongoing to evaluate the effectiveness of pharmaceutical interventions for methamphetamine abuse and dependence.

The initial stage of treatment of methamphetamine abuse for some users is the medical management of withdrawal, particularly if the user is a binge user or heavy user. This phase is characterized by increased sleep, eating, depressive symptoms, anxiety, poor concentration, and craving-related symptoms [50]. The other common scenario for withdrawal is when the user is incarcerated and unable to obtain the drug [3].

A randomized, double-blind, placebo-controlled trial of mirtazapine in 31 outpatients undergoing treatment for methamphetamine withdrawal showed no benefit in terms of withdrawal symptoms or retention [15]. Mirtazapine did improve time of sleep in the 2-week period during which it was evaluated. An open-label comparison of modafinil (400 mg/day; $n = 14$) and mirtazapine (60 mg/day; $n = 13$) with treatment as usual with pericyazine (2.5–10 mg/day) demonstrated less withdrawal severity with modafinil and mirtazapine [51]; however, these results must be interpreted with caution since this study lacked a placebo-controlled, double-blind design.

While very few double-blind, randomized, placebo-controlled trials of pharmacotherapy for methamphetamine are available in the literature, there is no doubt that the number of controlled trials will increase in the near future with the establishment of the National Institute on Drug Abuse Methamphetamine Clinical Trials Group [19]. Carefully controlled and adequately powered clinical trials are extremely expensive. Human laboratory studies have been conducted in an effort to evaluate more efficiently the efficacy of potential pharmacotherapies for the treatment of methamphetamine abuse.

Early clinical studies have pointed to the potential pharmacotherapeutic benefit of bupropion, modafinil, and baclofen in treating aspects of methamphetamine dependence including memory function [45, 90]. Initial safety studies indicated that methamphetamine administration during bupropion treatment was safe [62] and that bupropion reduced acute methamphetamine subjective effects and cue-induced craving for methamphetamine, supporting the evaluation of bupropion for the treatment of methamphetamine dependence [63]. Subsequently, perhaps the largest placebo-controlled trial thus far evaluated the use of bupropion for the treatment of methamphetamine dependence [20, 80]. Twelve weeks of treatment with sustained-release bupropion (150 mg twice daily) versus placebo followed by a 30-day follow-up in five outpatient treatment facilities ($n = 152$ participants) showed some benefit when combined with behavioral interventions. In this study, bupropion treatment increased the number of weeks abstinent, although only the male subgroup that was ranked as low-to-moderate for methamphetamine usage showed statistically significant improvement over placebo.

A recently reported open-label study evaluated a sequential dosing algorithm consisting of hydroxyzine (a sedating antihistamine), flumazenil (a benzodiazepine antagonist), and gabapentin (an anticonvulsant) to treat methamphetamine dependence [88]. In that study, 50 adults with a diagnosis of methamphetamine dependence were administered hydroxyzine (50 mg), followed 1 h later by flumazenil (0.1–0.3 mg intravenously over 30 min) and gabapentin (initial dose 300 mg/day up to 1,500 mg/day), for 4 weeks, and were followed up for 8 weeks. Results showed a 47% reduction in methamphetamine use for the entire subject sample and a 65% reduction for the 36 subjects who completed the 8-week evaluation, suggesting efficacy of the sequential medication regimen [88]. Caution is needed, however, due to the open-label design employed and the fact that a placebo comparison was not included in the study design. In contrast, a previously reported study evaluating 16 weeks of treatment with either gabapentin (800 mg twice daily; $n = 26$), baclofen (20 mg 3 times daily; $n = 25$), or placebo ($n = 37$) using a randomized double-blind, placebo-controlled design showed that neither medication was superior to placebo, indicating a lack of efficacy in the treatment of methamphetamine abuse [33].

A recent placebo-controlled, cross-over study investigating the effects of another anticonvulsant, topiramate, showed that acute administration (up to 200 mg) enhanced, rather than attenuated, the positive subjective effects of methamphetamine [37]. More recently, a Phase II double-blind, placebo-controlled trial proof-of-concept study determined the safety and efficacy of chronic topiramate for the treatment of methamphetamine addiction [21]. Subjects ($n = 140$) meeting the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition criteria for methamphetamine dependence were

randomized to receive topiramate or placebo at 50 mg, escalating to 200 mg daily during weeks 1–5 and 200 mg daily during weeks 6–12. The primary outcome measure was abstinence from methamphetamine during weeks 6–12. Results showed that generally topiramate was well-tolerated and safe, although no significant topiramate treatment effect was found. However, exploratory data analyses indicated that subjects ($n = 35$) whose baseline use was less than 18 days out of the previous 30, or who had negative urine prior to randomization ($n = 26$), experienced a topiramate treatment effect ($p = 0.03$ and 0.02, respectively). Thus, despite the failure of the primary protocol outcome variable, a subset of "light" methamphetamine users were identified as positive responders to treatment.

A small open-label study of 11 methamphetamine-dependent veterans showed decreased use with risperidone (average dose, 3.6 mg/day) over a 4-week treatment period [55]. A randomized, double-blind trial evaluating 80 participants with concurrent *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition-defined bipolar I or II and methamphetamine or cocaine dependence showed that both quetiapine and risperidone, serotonin-2 and dopamine D2 receptor antagonists, improved the manic, mixed, and depressive symptoms, as well as reducing drug craving; however, this interpretation is limited by the lack of a placebo control group [60].

A recent small preliminary, randomized, double-blind, placebo-controlled trial of ondansetron, a serotonin-3 receptor antagonist, has been reported for participants seeking treatment for methamphetamine dependence [36]. This 8-week trial evaluated ondansetron (0.25, 1, or 4 mg twice daily) vs. placebo along with cognitive behavioral therapy and found no benefits of ondansetron on any measured markers of methamphetamine use, withdrawal, or craving. Another trial demonstrated that sertraline, a serotonin transporter inhibitor (50 mg twice daily), actually worsened some parameters of methamphetamine abuse treatment over placebo [81].

Aripiprazole, a dopamine D2 receptor partial agonist approved by the Food and Drug Administration for the treatment of schizophrenia, has been evaluated in human laboratory studies in which volunteers learned to discriminate the interoceptive effects of 15 mg of d-amphetamine [84]. Aripiprazole at 20 mg, but not at 10 mg, attenuated the discriminative stimulus effects of d-amphetamine; however, the high dose alone also produced performance decrements. The low dose of aripiprazole attenuated some of the subject-rated effects of d-amphetamine and did not impair performance, suggesting that aripiprazole may have therapeutic benefit [84]. In a subsequent double-blind inpatient study employing 16 methamphetamine-dependent subjects, treatment with aripiprazole (15 mg orally) was associated with significantly higher ratings on the Addiction Research Center Inventory subscales, reflecting euphoria and amphetamine-like effects following the administration of methamphetamine (15 and 30 mg intravenously) [61]. Further, aripiprazole was found to have no effect on abstinence-induced and cue-induced craving over the time course of treatment, suggesting that this dopamine D2 receptor partial agonist is not likely to be an effective treatment for methamphetamine dependence.

A double-blind, placebo-controlled, between-groups study employing a human laboratory model of intravenous methamphetamine self-administration evaluated the effect of rivastigmine, an acetylcholinesterase inhibitor, as a treatment of methamphetamine abuse [17]. In this study, 0 or 30 mg of intravenous methamphetamine or placebo was sampled initially. Subsequently, subjects chose either to self-administer a 3-mg dose of methamphetamine or placebo or to receive a monetary alternative ($0.05–$16). The number of choices for methamphetamine infusion was greater than for placebo, and the number of money choices was greater when placebo was available than when methamphetamine was available. Rivastigmine (1.5 or 3 mg; $n = 6–9$) did not alter the total number of methamphetamine infusions compared with placebo ($n = 7$); however,

the higher dose of rivastigmine reduced the positive subjective effects of self-administered methamphetamine. Thus, as has been reported previously for other drugs of abuse, a reduction in methamphetamine-induced subjective effects does not necessarily predict a reduction in drug self-administration.

There is a general consensus that any medication for methamphetamine abuse will be most effective in the context of concomitantly delivered behavioral therapies, much like other drugs of abuse [77]. The most common therapies employed and studied have included cognitive behavioral therapy, contingency management, or both [43]. Outcome-based studies on cognitive behavioral therapy have shown reductions in methamphetamine abuse and relapse of abuse [9]. Contingency management procedures, though effective when individuals are actively in drug treatment, have not been shown to have benefits once the individuals are "on their own" [75].

Mechanisms of Methamphetamine Reward

In addition to the clear evidence of abuse on the "street", methamphetamine has been shown to be a potent reinforcer in humans tested under highly controlled laboratory conditions. Methamphetamine reward is manifest both as a subjective report of "liking" and as a behavioral choice of methamphetamine self-administration over placebo. (We use the term "reward" to refer to both subjective and behavioral effects, whereas "reinforcement" is a more specific term that refers to behavioral effects only.) Hart et al. [30] evaluated healthy research volunteers in a residential laboratory facility for their response to oral methamphetamine (5 or 10 mg) or placebo. Over an 8-day choice procedure, subjects had the opportunity to self-administer the dose of methamphetamine that they most recently sampled or to receive a $1 voucher. As expected, methamphetamine was chosen significantly more than placebo, and the sampled methamphetamine (10 mg) increased subjective ratings indicative of drug liking, demonstrating that oral methamphetamine is rewarding in humans. In another study from this same laboratory, Comer et al. [13] evaluated the effects of repeated oral methamphetamine or placebo administration in humans in a residential laboratory. Relative to placebo baseline, tolerance developed to methamphetamine's positive subjective effects across repeated administrations, which may be a factor leading to escalating use among at-risk individuals.

Methamphetamine reward may be dependent to some extent on the pharmacokinetics of the drug. As discussed by Lile [44], drug reward is enhanced when there is a rapid onset of effect, which may explain why methamphetamine abusers tend to prefer the inhalation and intravenous routes of delivery over the oral route. In addition, the rate of self-administration may be determined by the offset (elimination half-life) of the drug effect, with longer offset durations leading to less frequent self-administrations. These general principles may be important points to consider in attempts to develop effective pharmacotherapies for methamphetamine abuse. In particular, therapeutic agents designed to substitute for or block the rewarding effect of methamphetamine should ideally have a slow onset of action and a prolonged duration of action in order to minimize their potential for abuse. Nonetheless, it may be desirable for pharmacotherapeutic agents to have some rewarding effect because this will enhance patient compliance.

To better understand the neurobiological basis of methamphetamine reward and to develop new potential pharmacotherapies, a number of laboratory animal models have been developed. One widely used model is drug self-administration, which is based on fundamental principles of operant conditioning. In this model, rodents or non-human primates are trained to make an operant response (e.g., lever press) in order to receive a drug infusion. Responding is reinforced typically on a fixed ratio schedule in which a fixed number of responses lead to an

infusion. Alternatively, a progressive ratio schedule can be used in which the number of responses required to earn an infusion increases incrementally after each infusion until a "break point" (cessation of responding) is achieved; the progressive ratio schedule is thought to estimate the relative effectiveness of the drug to serve as a reinforcer. As expected based on human literature, both rats and non-human primates self-administer methamphetamine avidly and in a dose-dependent manner [4, 29, 72].

Another model for measuring methamphetamine reward in rodents is the conditioned place preference preparation. This is a Pavlovian procedure in which the drug is paired with one distinct context and placebo is paired with a different context. When allowed to choose between the two different contexts in a drug-free state, rats show a preference for the drug-paired context. This preference is thought to reflect a secondary rewarding effect of the context due to its association with the drug, and it may be a model of contextual control of drug seeking, rather than a direct measure of the primary reinforcing effect of the drug per se [5]. Similar to self-administration, methamphetamine conditioned place preference has been demonstrated in both rats and mice [23, 26, 41].

A third animal model for evaluating methamphetamine reward is the brain stimulation reward preparation. In this model, a bipolar stimulating electrode is implanted chronically into the lateral hypothalamus, a region through which courses the medial forebrain bundle. The medial forebrain bundle connects dopaminergic cell bodies in the ventral tegmental area to the limbic terminal fields of the nucleus accumbens and prefrontal cortex, and stimulation of this pathway is highly reinforcing. Rats are first evaluated for their brain stimulation reward threshold by adjusting the frequency of stimulation pulses in a series of ascending and descending increments. When a drug of abuse is subsequently administered, the brain stimulation threshold is lowered, thus providing an index of rewarding strength. Corroborating the findings with self-administration and conditioned place preference, methamphetamine has been shown to decrease the threshold for brain stimulation reward [83].

Animal models, coupled with neuroimaging technologies in humans, have uncovered some of the basic neural mechanisms that underlie methamphetamine reward. While the reward circuitry is complex, involving multiple circuits and neurochemical systems [39], dopaminergic neurotransmission in the mesocorticolimbic dopamine pathway undoubtedly plays a critical role in the psychostimulant effects of methamphetamine [35, 68, 79]. Methamphetamine reward results from increased dopamine release in limbic terminal fields, which is regulated by the vesicular monoamine transporter [87]. Methamphetamine increases extracellular dopamine concentrations by inhibiting the action of the vesicular monoamine transporter, which sequesters dopamine into vesicular stores, as well as by inhibiting monoamine oxidase, which diminishes dopamine metabolism, thereby making cytosolic dopamine more available for methamphetamine-induced reversal of the plasmalemma dopamine transporter [18, 85]. In addition to these dopamine-regulating cellular targets in the limbic terminal fields, a number of other systems impinge on reward-relevant dopamine neurons, including gamma-aminobutyric acid (GABA)-ergic, glutamatergic, and nicotinic acetylcholine receptors localized within the midbrain ventral tegmental area region [16]. In addition, prefrontal cortical regions are thought to provide descending input into both the dopaminergic cell body and terminal regions [39]. Consistent with this latter view, functional magnetic resonance imaging analyses in humans indicate that, in addition to increasing neural activity in the nucleus accumbens, methamphetamine increases activity in the orbitofrontal and anterior cingulate cortices [92]. Further, using functional magnetic resonance imaging and positron emission tomography imaging, abnormalities in brain structure and chemistry are observed in individuals using methamphetamine, including reductions in the density of dopamine transporters, dopamine D2 receptors, serotonin transporters, and vesicular

monoamine transporters, particularly in the striatum [11].

A greater understanding of the components of the neurocircuitry involved in methamphetamine reward has provided new opportunities for targeting the development of medications to treat methamphetamine addiction [89]. As mentioned previously, the dopamine transport inhibitor bupropion has been shown to be effective in a double-blind, placebo-controlled clinical trial [20]. However, since bupropion also is a nicotinic acetylcholine receptor antagonist [56, 82], it is not clear whether its efficacy is due to blockade of the dopamine transporter, blockade of nicotinic receptors, or blockade of both mechanisms concomitantly. Preclinical studies have also provided evidence that blockade of the vesicular monoamine transporter with lobeline or related synthetic analogs may be a useful new approach [18, 29]. Moreover, although direct blockade of dopamine D2 receptors is not a likely approach to treat methamphetamine abuse due to the induction of extrapyramidal side effects, effort has focused on atypical antipsychotics that work at either serotonin-2 receptors [86] or dopamine D3 receptors [83].

In addition to the direct effects of medications on the plasmalemma and vesicular dopamine transporters and receptors, an alternative approach is to target systems that modulate mesocorticolimbic dopamine neurons. For example, preclinical work has indicated that medications that enhance gamma-aminobutyric acid transmission by blocking the metabolic enzyme gamma-aminobutyric acid transaminase may be useful to treat methamphetamine abuse [25]. At least one study has shown that the gamma-aminobutyric acid transaminase inhibitor, γ-vinyl gamma-aminobutyric acid, is safe in human abusers, even among those who continue to use methamphetamine [7]. Gamma-aminobutyric acid receptor selective agonists are also under investigation [26, 72], as are glutamate receptor antagonists [38].

Several other novel, albeit unproven, approaches for treating methamphetamine abuse are in the pipeline. For example, novel congeners of the iboga plant alkaloid ibogaine may be useful [67], although the potential utility of these alkaloids awaits characterization of their neuropharmacological mechanisms of action. Additionally, a recent study indicates that medications that suppress the endogenous opioid peptide nociceptin may attenuate methamphetamine reward [78]. Another approach is a therapeutic vaccine to treat methamphetamine addiction [69]. Regardless of the mechanism, however, any pharmacotherapeutic approach for treating methamphetamine abuse should be considered an adjunct to behavioral therapies. As mentioned earlier, the utility of contingency management and cognitive behavioral therapy to maintain abstinence rates among methamphetamine abusers has been demonstrated [9, 43, 75, 76], and further work is needed to determine whether the combination of pharmacotherapy and psychosocial interventions has a synergistic effect.

Conclusions

Methamphetamine abuse has increased to epidemic levels during the last 20 years, and the need for outcome-based studies on treatment has greatly increased. Currently, no medications have been approved by the Food and Drug Administration for the treatment of methamphetamine abuse. Recent advances in the understanding of the neurocircuitry involved in methamphetamine reward have provided new opportunities and rational targets that can be exploited for the development of pharmacotherapies to treat methamphetamine addiction. The efficacy and safety of these candidate pharmacotherapies require evaluation in adequately powered, double-blind, placebo-controlled trials; however, human laboratory studies have the potential to evaluate more efficiently candidate treatments and provide information on whether the more expensive clinical trials are warranted. Currently, a wide range of neuropharmacological strategies are being pursued in the search for an efficacious pharmacotherapy for methamphetamine abuse.

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Potential Pharmacotherapies for Cannabis Dependence

Carl L. Hart and R. Douglas Shytle

Contents

Introduction

Cannabis, which comprises Δ^9-tetrahydrocannabinol-containing products including marijuana and hashish, is the most widely used illicit drug in the world [2], with nearly 150 million people reporting annual use [122]. In the United States alone, an estimated 14.8 million individuals report current marijuana use, defined as use within the past 30 days [111]. Most users of cannabis consume the drug infrequently and without apparent negative consequences. There are, however, a small proportion of users who experience problems related to frequent cannabis use. It has been estimated that 9% of cannabis users will become dependent [3]. Although this number is low compared with dependence rates for tobacco consumers (about a third of tobacco users will become dependent), rates of cannabis dependence in several countries have increased substantially over the past decade [11, 111] as well as the number of individuals seeking treatment for cannabis-related problems [109, 112]. The terms "dependence" and "dependent" encompass the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition, text revision) and the International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Although the total number of cannabis-dependent individuals who seek treatment is higher than the number of those who seek treatment for other illicit drugs, the relative proportion of those seeking treatment for cannabis dependence is low. For example, in the U.S., the percentage of regular drug users who received treatment for a cannabis use disorder (includes cannabis abuse and dependence) in 2006 was less than 10%, whereas this number was nearly 40% for cocaine users [111]. There are several possible explanations for the relatively low percentage of cannabis treatment seekers including the fact that many individuals perceive cannabis as a relatively innocuous drug [134]. However, several investigators have reported that heavy, daily cannabis use is associated with an

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_53,

abstinence syndrome upon cessation of the drug (for review, see [19]). Although cannabis withdrawal is not life threatening, the accompanying symptoms such as irritability, anxiety, sleep disruptions, aches, and pains can be quite unpleasant. In addition, many individuals seeking treatment for cannabis dependence reported that these symptoms made it more difficult to maintain abstinence [110, 16, 30].

Heavy cannabis use has also been reported to produce adverse effects on cognitive functioning (e.g., [101, 102, 108]). For example, Bolla and colleagues [12] reported that heavy use of cannabis was associated with poorer cognitive performance on a wide range of tasks (e.g., memory and executive functioning) and that decreased performance persisted as long as 28 days of abstinence. Regular cannabis smoking is also associated with pulmonary dysfunction similar to that which is seen in regular tobacco smokers (for review, see [73, 125]). Finally, recent data indicate that cannabis smoking can precipitate psychosis in individuals susceptible to developing a psychotic disorder (e.g., [5, 64, 92]; see also [4]).

Some investigators have speculated that the low percentage of individuals seeking treatment for cannabis dependence may be related to the fact that there are relatively few specific treatments for cannabis dependence [109], although this issue does not appear to deter treatment-seeking cocaine abusers. Regular cannabis users may also be reluctant to participate in treatment programs dominated by alcohol-, cocaine-, and opioid-dependent individuals. There are data indicating that some cannabis dependence-specific therapies are successful in decreasing drug use and many associated negative consequences (for review, see [85, 88]). Other data, however, show that cannabis-dependent individuals exhibit high rates of relapse similar to those found with other substances of abuse [91]. To date, the majority of treatment studies have investigated behavioral/psychosocial therapies. The high relapse rate and the sheer number of cannabis-dependent individuals, however, underscore the importance of developing pharmacotherapies for those individuals who may be less responsive to other treatments. Pharmacotherapies may be used alone, in combination with behavioral/psychosocial therapies, or in a staged manner following inadequate response to behavioral/psychosocial therapies. In general, the problem in treating substance-dependent individuals has been less that of treating withdrawal and more of preventing relapse. However, treating withdrawal symptoms continues to be an important first step in eventual success and one that clinicians often need to begin this therapeutic endeavor. The treatment of cannabis dependence in this regard is similar to efforts under way for decades for opioids, cocaine, and alcohol dependence.

This chapter represents an update of Hart [61]. It reviews findings from recent research on cannabinoids (a group of compounds related to $\triangle^9$-tetrahydrocannabinol, the primary psychopharmacologically active constituent of marijuana smoke) that may be relevant for the development of pharmacotherapies for cannabis dependence. Data from studies that assessed the ability of medications to attenuate cannabinoid-related abstinence symptoms in laboratory animals and in humans will be reviewed. In addition, results from studies that have investigated the effects of pharmacological agents on response to cannabinoids are reviewed because these data may prove useful in informing the development of cannabis relapse prevention medications. The review begins with a brief overview of the different phases of the dependence cycle that cannabis pharmacotherapies might target as well as cannabinoid relevant neuropharmacology.

Detoxification and Relapse Prevention or Maintenance Phase

Medications are typically initiated at two different phases of the dependence cycle: during detoxification and prevention of relapse. Detoxification is usually an *initial and immediate goal* during which medications are administered in order to assuage unpleasant abstinence symptoms that may appear following abrupt

cessation of drug use, e.g., the administration of a benzodiazepine during alcohol withdrawal. Medications used in the detoxification phase are also sometimes used in the relapse prevention or maintenance phase, e.g., nicotine replacement medications. Thus, the distinction between a detoxification medication and a relapse prevention medication is sometimes less clear.

Maintenance medications can be viewed as a *longer-term strategy* used to help the dependent individual avoid relapsing to the abused drug. There are at least three major maintenance strategies. First, agonist or substitution therapy is used to induce cross tolerance to the abused drug. For example, methadone, a long-acting μ-opioid agonist, and nicotine replacement medications have been used for opioid dependence and tobacco dependence, respectively, as agonist maintenance treatments to prevent relapse and cravings in individuals attempting to maintain abstinence. Agonist maintenance agents typically have safer routes of administration and diminished psychoactive effects, relative to the abused drug. Second, antagonist therapy is used to produce extinction by preventing the user from experiencing the reinforcing effects of the abused drug. For example, the naltrexone blocks opioid mu receptors and agonists' associated effects, and is therefore used as an antagonist therapy for opioid dependence. Finally, punishment therapy produces an aversive reaction following ingestion of the abused drug. For example, disulfiram (Antabuse®) is used in the treatment of alcohol dependence. Disulfiram inhibits aldehyde dehydrogenase, a major enzyme involved in alcohol metabolism, thereby preventing the complete breakdown of alcohol, and the resultant accumulation of aldehyde produces unpleasant symptoms including headache, vomiting, and breathing difficulties.

Cannabinoid Neuropharmacology

Over the past two decades, data from basic research have contributed to an increased understanding of neuronal mechanisms involved in the effects of cannabinoids. Although a comprehensive review of cannabinoid neuropharmacology is beyond the scope of the current manuscript and such reviews have already been published (e.g., [42, 70]), a brief overview might be informative for the rationale regarding some of the medications presented in this review. Cannabinoids bind to two types of receptors: cannabinoid receptor 1 and cannabinoid receptor 2 (CB_1 and CB_2). These receptors are much more abundant than opioid receptors [105] suggesting that the potential actions of cannabinoids are widespread. CB_2 receptors are found mainly outside of the brain in immune cells, suggesting that cannabinoids may play a role in the modulation of the immune response. CB_1 receptors are found throughout the body, but primarily in the central nervous system. The regions in which central nervous system CB_1 receptors reside may provide some clues about their functions. For example, the highest density of CB_1 receptors has been found in cells of the basal ganglia, which primary components include the caudate nucleus, putamen, and globus pallidus (for review, see [65, 98]). Cells of the basal ganglia are involved in coordinating body movements. Other regions that also contain a larger number of CB_1 receptors include: the *cerebellum*, which coordinates fine body movements; the *hippocampus*, which is involved in aspects of memory storage; the *cerebral cortex*, which regulates the integration of higher cognitive functions; and the *nucleus accumbens*, which is involved in drug reinforcement. This suggests that endogenous cannabinoid activity modulates a broad range of behaviors.

Data from microdialysis studies have revealed that dopaminergic transmission is increased in the nucleus accumbens following acute administration of cannabinoid agonists [26, 114], and this effect is blocked by the CB_1 antagonist rimonabant (SR 141716A). While it is possible that cannabinoid-induced dopamine elevations are a result of direct stimulation of dopamine neurons, accumulating evidence suggest a more likely mechanism of action is via disinhibition of dopamine-containing neurons that are under tonic gamma-aminobutyric

acid-ergic inhibition [113]. Consistent neurochemical correlates during withdrawal from cannabinoids include reduced dopaminergic activity along the ventral tegmental area-nucleus accumbens pathway [34, 115] and upregulated expression and release of corticotropin-releasing hormone in the central nucleus of the amygdala [22, 104]. This growing body of knowledge, coupled with increasing numbers of individuals seeking treatment for cannabis dependence, has prompted research on the effects of cannabinoid antagonism on cannabis-associated reinforcement and research on the effects of cannabinoid agonists, as well as medications that decrease the stress response, on cannabis withdrawal.

Abstinence Symptoms Treatment Medications

Studies of Laboratory Animals

Prior to the availability of a cannabinoid antagonist, findings from investigations of cannabinoid-related withdrawal symptoms in laboratory animals were inconsistent. Some researchers found evidence of withdrawal symptoms upon abrupt cessation of drug administration [9, 77], while others failed to observe signs of withdrawal when drug administration was terminated (e.g., [33, 57]). Administration of the cannabinoid antagonist rimonabant, however, produces a reliable withdrawal syndrome in laboratory animals undergoing chronic cannabinoid treatment (e.g., [8]). Behaviorally, this syndrome is most consistently characterized in rodents by wet-dog shakes, paw tremors, piloerection, and increased grooming.

The fact that cannabinoid-related withdrawal symptoms are reliably produced in laboratory animals not only provided evidence for physiological cannabinoid dependence, but it also provided an opportunity to examine systematically pharmacological agents for effectiveness in attenuating these symptoms. Table 1 summarizes selected studies that have employed laboratory animals to evaluate medication effects on precipitated cannabinoid withdrawal symptoms. Although the number of studies conducted evaluating potential cannabinoid treatment medications continues to grow, compared with medications development research for other drugs of abuse, this number is conspicuously low. In one earlier study, Verberne et al. [127] administered intravenous Δ^9-tetrahydrocannabinol in escalating doses for five consecutive days to rats; on day six, an acute dose of Δ^9-tetrahydrocannabinol or placebo was given 30 min prior to an intraperitoneal injection of clomipramine, a serotonin reuptake inhibitor. The investigators reasoned that clomipramine would precipitate withdrawal in animals chronically exposed to Δ^9-tetrahydrocannabinol because fluoxetine,

Table 1 Published studies that have employed laboratory animals to evaluate medication effects on precipitated cannabinoid withdrawal symptoms

Investigators	Species	Medication (dose)	Precipitant (dose)	Outcome
Verberne et al. [127]	Rat	Δ^9-THC (6 mg/kg, i.v.)	Clomipramine (15 mg/kg, i.p.)	Δ^9-THC reduced withdrawal symptoms.
Lichtman et al. [83]	Mouse	Δ^9-THC (30 mg/kg, i.v.)	Rimonabant (10 mg/kg, i.p.)	Δ^9-THC reversed withdrawal-related paw tremors.
Lichtman et al. [83]	Mouse	Clonidine (0.125 – 1 mg/kg, i.p.)	Rimonabant (10 mg/kg, i.p.)	Clonidine reversed withdrawal-related paw tremors and head shakes.
Anggadiredja et al. [1]	Mouse	Prostaglandin E_2 (1, 3.2 μg, i.c.v.)	Rimonabant (10 mg/kg, i.p.)	Prostaglandin E_2 lessened withdrawal symptoms.
Cui et al. [31]	Rat	Lithium (4, 8, 16 meq/kg)	AM281 (3 mg/kg, i.p.)	Lithium blocked withdrawal symptoms.

Δ^9-THC Δ^9-tetrahydrocannabinol, *i.v.* intravenously, *i.p.* intraperitoneally, *i.c.v.* intracerebroventricularly

another serotonin reuptake inhibitor, precipitated withdrawal in animals treated with a similar $\triangle^9$-tetrahydrocannabinol dosing regimen [128]. While clomipramine precipitated withdrawal symptoms in rats that received acute placebo, there were significantly fewer withdrawal symptoms observed in rats that received the acute dose of $\triangle^9$-tetrahydrocannabinol. These findings, together with data from the report showing that fluoxetine also induces behavioral signs of withdrawal in rats chronically administered $\triangle^9$-tetrahydrocannabinol [128], suggest that increased serotonergic activity following abrupt discontinuation of repeated cannabinoid agonist treatment may be an important component in the behavioral expression of cannabinoid withdrawal. More recently, however, Touriño et al [120] reported that the serotonin agonist 3,4-methylenedioxymethamphetamine dose-dependently attenuated rimonabant-precipitated $\triangle^9$-tetrahydrocannabinol withdrawal symptoms in mice. The reasons for these apparent incongruent findings are unclear, but might be related to the fact the tested medications have multiple sites of action. Some of these actions may overlap, while others may not. It is also important to note that there have been no published reports of clomipramine- or fluoxetine-precipitated cannabis withdrawal in humans, so it is not known whether precipitated withdrawal has not occurred. Thus, the impact of increased serotonin activity on cannabinoid-related withdrawal is unclear.

Lichtman and colleagues demonstrated that $\triangle^9$-tetrahydrocannabinol as well as clonidine, an α_2-receptor agonist, lessened rimonabant-precipitated withdrawal symptoms in mice [83]. In that study, mice were administered two daily subcutaneous injections of either $\triangle^9$-tetrahydrocannabinol or vehicle for two days; on the third day, animals were given one injection of their respective treatment, followed four hours later with an intraperitoneal injection of rimonabant or vehicle. Five minutes after the rimonabant challenge dose, mice were administered either an intravenous injection of $\triangle^9$-tetrahydrocannabinol (or placebo) or an intraperitoneal injection of clonidine (or placebo). Both $\triangle^9$-tetrahydrocannabinol and clonidine reversed rimonabant-precipitated paw tremors, and this effect was independent of any generalized effects on movement. While the finding that $\triangle^9$-tetrahydrocannabinol reversed precipitated cannabinoid withdrawal is consistent with previous data [127], these were the first published data to demonstrate that an α_2-receptor agonist was effective in alleviating symptoms of cannabinoid withdrawal. Clonidine has been shown to attenuate some withdrawal symptoms associated with alcohol (e.g., [7, 97]) and opioid dependence (e.g., [40, 45, 121]) in humans and laboratory animals, suggesting some features of withdrawal syndromes associated with drugs of abuse may share common underlying pathophysiological mechanisms. For instance, it is possible that withdrawal symptoms, at least in part, may be mediated by noradrenergic hyperactivity. This view is consistent with the observation that many humans experiencing withdrawal from commonly abused drugs, including alcohol, opioids, and cannabis, often report increased anxiety. One exception to this speculation, however, is the efficacy of bupropion in the treatment of nicotine dependence (see below).

Another interesting line of research aimed at understanding mechanisms underlying cannabinoid withdrawal is the examination of the role of the arachidonic acid cascade. Anggadiredja et al. [1] rendered mice $\triangle^9$-tetrahydrocannabinol-dependent by administering two daily intraperitoneal injections of $\triangle^9$-tetrahydrocannabinol for five days. On the sixth day, mice received one injection of $\triangle^9$-tetrahydrocannabinol, followed four hours later with an intraperitoneal injection of rimonabant to precipitate withdrawal. Mice in an additional treatment group were given an intra-ventricular injection of prostaglandin E_2, an end-product of the arachidonic acid cascade, immediately before the rimonabant challenge dose. Prostaglandin E_2 dose-dependently attenuated rimonabant-precipitated withdrawal symptoms including forepaw tremors, forepaw licking, and facial preening. While the exact mechanism(s) through which prostaglandin E_2

lessened withdrawal symptoms remains to be elucidated, it has been proposed that prostaglandin E_2 reduced symptoms of withdrawal via noradrenergic mechanisms [1].

Convergent evidence supports this hypothesis. In an in vitro study of the effects of prostaglandin E_2 on electrically-evoked tritiated norepinephrine overflow, Exner and Schlicker [37] found that prostaglandin E_2 inhibited the electrically-evoked norepinephrine tritium overflow from mouse and rat brain cortex slices. Data from an earlier, similarly designed study [66] were consistent with those obtained by Exner and Schlicker [37]. In addition, as mentioned above, clonidine, administered 5 min after rimonabant in $\triangle^9$-tetrahydrocannabinol-dependent mice, reversed the precipitated withdrawal [83], providing further evidence for the role of noradrenergic processes in cannabinoid withdrawal.

The effects of lithium, a commonly used mood-stabilizing medication for the treatment of bipolar disorder, have also been assessed on cannabinoid withdrawal symptoms. Examination of lithium was based on the clinical observation that increased irritability, anxiety and depression often accompanies cannabis withdrawal; lithium effectively decreases these symptoms. Cui et al. [31] administered two daily injections of HU210, a synthetic cannabinoid agonist, to rats on five days; on the sixth day, animals were given one injection of their respective treatment, followed four hours later with an injection of AM281, a cannabinoid antagonist. The effects of lithium were examined by administering varying doses 15 min before the AM281 challenge dose. Lithium dose-dependently prevented symptoms of cannabinoid withdrawal. The investigators speculated that their findings were mediated via lithium-enhancing effects on central nervous system oxytocin activity and were not related to lithium-associated mood stabilizing effects. This hypothesis was based on the following observations: (1) oxytocin administration mimicked the effects of lithium on cannabinoid withdrawal; (2) pretreatment with an oxytocin receptor antagonist blocked lithium-related effects on cannabinoid withdrawal; (3) pretreatment with an oxytocin receptor antagonist alone enhanced AM281-precipitated cannabinoid withdrawal [31]; and (4) divalproex, another mood stabilizer used in the treatment of mania, failed to attenuate AM281-precipitated cannabinoid withdrawal (unpublished observations from the same group of researchers). The fact that animals exhibit a stress-like response (e.g., increased grooming behaviors and increased release of corticotropin-releasing hormone) during cannabinoid withdrawal, however, suggests that the mechanisms involved in the stress response may also play a role in the cannabinoid withdrawal syndrome. Given that increased oxytocinergic transmission markedly diminishes the stress response (e.g., [23, 95, 96]), it seems plausible that oxytocin plays an integral role in lithium-related effects on cannabinoid withdrawal symptoms. Nevertheless, the exact mechanism responsible for lithium-associated ameliorating effects on cannabinoid withdrawal is an issue that can only be resolved with further research.

One important factor that might limit the generality of the above results is that cannabinoid drugs were administered to animals non-contingently; that is, they were not self-administered but were administered by the experimenter. Data from studies comparing non-contingent and contingent drug administration indicate that substantial differences (e.g., mortality rate and neurochemical) exist that are related to context of drug presentation [36, 63]. Future studies should assess the utility of medications to alleviate cannabinoid withdrawal symptoms in animals undergoing abrupt discontinuation of self-administered cannabinoids.

Despite this potential limitation, the above results suggest that the administration of oral $\triangle^9$-tetrahydrocannabinol might be a useful strategy to treat cannabis withdrawal. Additionally, the data showing that clonidine mitigates cannabinoid withdrawal are encouraging and suggest that pharmacological agents that decrease noradrenergic output are excellent candidate medications to test in humans undergoing cannabis withdrawal. Although side effects, such as

hypotension and sedation, associated with clonidine may limit its clinical use for cannabis dependence, other α_2-receptor agonists such as lofexidine, which has a more favorable side effect profile, may hold promise in treating cannabis withdrawal. Indeed, this strategy was investigated in a recent study employing human marijuana abusers (see below). Data indicating that lithium, as well as oxytocin, prevented cannabinoid withdrawal provide potentially novel treatment strategies, although the clinical use of systemic oxytocin for anti-cannabinoid withdrawal effects might be limited because high doses may be required, which increase the likelihood of unpleasant peripheral side effects. Because oxytocin has been shown to produce similar effects as benzodiazepines [123], an alternative approach might be to evaluate the effects of a benzodiazepine on cannabinoid withdrawal symptoms. Clinicians however, may be wary about the potential for abuse associated with the use of some benzodiazepines, e.g., alprazolam, particularly in sedative abusing populations [131, 132], thus others such as clonazepam or oxazepam may be more likely candidates. Finally, the data regarding the role of serotonergic activity in cannabinoid withdrawal are less clear: findings from two studies indicate that medications that augment serotonin activity may precipitate or worsen withdrawal, while results from another suggest that increased serotonin activity dampens withdrawal.

Studies of Human Research Participants

Although the majority of cannabis users may not experience symptoms of withdrawal, data from a variety of human laboratory and clinical studies demonstrate that an abstinence syndrome can be observed following abrupt cessation of heavy, near-daily use of smoked cannabis [17, 18, 50, 59, 81, 90] or oral $\triangle^9$-tetrahydrocannabinol [49, 71, 72]. Cannabinoid withdrawal syndrome in humans may include a variety of symptoms including increased negative mood states (e.g., increased anxiety, restlessness, depression, and irritability), disrupted sleep, decreased food intake, and in some cases, aggressive behavior [52, 80]. These symptoms have been reported to begin 1 day after cannabinoid cessation, peak effects are observed on days 2–6, and most effects persist from 4 to 14 days, depending on an individual's level of cannabis dependence [18]. Because cannabis withdrawal may be one factor maintaining continued cannabis use (i.e., frequent marijuana smokers may continue their use not only for marijuana-related intoxicating effects, but also to avoid undergoing withdrawal symptoms), medications that would alleviate cannabis withdrawal symptoms could be useful.

Table 2 summarizes the studies that have employed human research participants to evaluate the potential of medications to alleviate marijuana withdrawal symptoms. As can be seen, the majority of the published research in this area has been conducted in our laboratory. Our group at Columbia University/New York State Psychiatric Institute has conducted a series of carefully-controlled, within-participant design, residential laboratory studies. During these studies non-treatment seekers, frequent marijuana smokers smoked active marijuana cigarettes on several consecutive days, five times per day, followed by several days of marijuana abstinence. During abstinence, placebo marijuana cigarettes were smoked and the effectiveness of potential treatment medications to attenuate marijuana withdrawal symptoms was examined. The first medication tested in these studies was bupropion (0, 300 mg/d), a Food and Drug Administration-approved tobacco smoking cessation aid and antidepressant [51]. The rationale for the use of this medication was related to the observation that bupropion had been shown to maintain tobacco smoking abstinence, in part, because of its ability to decrease negative mood symptoms (e.g., increased anxiety, depression, and irritability) associated with nicotine withdrawal. Given that similar negative mood symptoms are also associated with marijuana withdrawal, bupropion was expected to improve symptoms of

Table 2 Published studies that have employed human research participants to evaluate medication effects on marijuana withdrawal symptoms

Investigators	Medication (dose, p.o.)	Outcome
Haney et al. [51]	Bupropion (0, 300 mg/d)	Bupropion worsened symptoms during withdrawal.
Haney et al. [52]	Nefazodone (0, 50 mg/d)	Nefazodone decreased some withdrawal symptoms, but it had no effect on most symptoms.
Haney et al. [54]	Divalproex (0, 1500 mg/d)	Divalproex worsened mood and psychomotor performance during marijuana consumption and during marijuana withdrawal.
Haney et al. [54]	Δ^9-THC (0, 50 mg/d)	Δ^9-THC reduced marijuana withdrawal symptoms and reversed the withdrawal-associated psychomotor performance decrements and weight loss associated with marijuana withdrawal.
Budney et al. [21]	Δ^9-THC (0, 30, 90 mg/d)	Δ^9-THC dose-dependently attenuated marijuana withdrawal symptoms.

Δ^9-*THC* Δ^9-tetrahydrocannabinol, *p.o.* by mouth

marijuana withdrawal. The data, however, indicated otherwise: bupropion worsened several ratings of mood, including irritability, restlessness and depression, and self-reported sleep quality. The mechanism(s) mediating bupropion-worsening effects on marijuana withdrawal is unclear, but the mechanism of action most commonly attributed to bupropion is inhibition of dopamine reuptake and, to a lesser extent, norepinephrine reuptake inhibition ([6]; see also [106]). Thus, bupropion-associated effects on marijuana withdrawal symptoms could be related to enhanced norepinephrine activity. This suggestion is consistent with the above-cited data showing that clonidine, a medication that decreases noradrenergic activity, lessened precipitated Δ^9-tetrahydrocannabinol withdrawal symptoms [83] as well as the withdrawal symptoms associated with alcohol and opioid dependence (for review, see [58]).

Another study conducted by our team investigated the effects of nefazodone (0, 450 mg/d) on symptoms of marijuana withdrawal [52]. Nefazodone, an atypical antidepressant, is thought to exert its major therapeutic effects via antagonistic actions at the serotonin-2a receptor [32, 118], although it has also been shown to produce relatively weak inhibition of norepinephrine and serotonin uptake sites in vitro. A major reason for investigating nefazodone-related effects on marijuana withdrawal symptoms was that it had been demonstrated to treat effectively depression, agitation, and anxiety (symptoms also associated with marijuana withdrawal) in clinical populations [39, 133]. Data from the study by Haney et al. [52] revealed that nefazodone decreased a few symptoms associated with marijuana withdrawal (i.e., ratings of "Anxious" and "Muscle Pain"), but it had no effect on most symptoms (e.g., ratings of "Irritable" and "Trouble Sleeping"). Because nefazodone did relieve some discomfort associated with marijuana withdrawal without worsening other symptoms and because only one active dose was tested, further study of this agent, using a broader dosing range, in the treatment of marijuana withdrawal could be warranted but may not occur because of the "Black box" warning (i.e., the highlighted portion of the package insert) about hepatoxicity.

Divalproex (0, 1500 mg/d), approved for the treatment of epilepsy, mood disorders, and migraine headaches, was evaluated for effectiveness in decreasing marijuana withdrawal symptoms [54]. Divalproex's precise neurochemical mechanism of action remains unknown, although some divalproex-related therapeutic effects have been attributed to its ability to dampen sustained repetitive neuronal firing via modulation of Na^+ channel activity [84]. Other therapeutic effects might be related to its ability to increase central nervous system gamma-aminobutyric acid activity [24, 99]. The rationale for testing the effects of divalproex on marijuana

withdrawal symptoms was not based on a proposed neurochemical mechanism of action, but instead was based on clinical evidence indicating that the medication had been used successfully to treat some symptoms commonly associated with marijuana withdrawal (e.g., irritability and mood lability [35, 44]). Unfortunately, divalproex did not reduce marijuana withdrawal symptoms. In fact, many withdrawal symptoms, including anxiety and irritability, were significantly increased when participants were maintained on divalproex compared to when they were maintained on placebo [54]. Divalproex not only worsened marijuana withdrawal-associated mood, but it also produced psychomotor performance disruptions during marijuana consumption and during marijuana abstinence. The results are in agreement with data from the aforementioned unpublished study using rodents, which showed that divalproex had no effect on AM281-precipitated withdrawal. In short, these data do not support the use of divalproex as a marijuana treatment medication.

Two other groups of researchers have examined lithium carbonate, another mood stabilizer, for effectiveness in decreasing cannabis withdrawal symptoms. The rationale for testing lithium carbonate was based on encouraging data collected using laboratory animals in which the medication decreased cannabinoid-associated withdrawal symptoms [31]. Bowen et al. [13] and Winstock et al. [130] conducted open-label trials of the effects of lithium carbonate (500–900 mg/d) on cannabis withdrawal. In general, the researchers reported that the medication reduced withdrawal severity for most study participants, but both studies contained important limitations that decrease the generality of the findings. For example, the non-controlled nature of these experiments may have increased expectancy effects, i.e., the researchers' and the participants' knowledge that participants were receiving an active treatment medication influenced participants reported cannabis withdrawal intensity

Another strategy tested for efficacy in attenuating human marijuana withdrawal is the administration of oral $\triangle^9$-tetrahydrocannabinol. In a recently reported study, Haney and coworkers [54] investigated the effects of oral $\triangle^9$-tetrahydrocannabinol (0, 10 mg), administered five times per day, on marijuana withdrawal symptoms. The primary reason for evaluating the effects of oral $\triangle^9$-tetrahydrocannabinol on marijuana withdrawal was based on the idea of substituting a longer-acting pharmacologically equivalent drug for the abused substance, stabilizing the individual on that drug, and then gradually withdrawing the substituted drug. In this way, the likelihood of precipitating abstinence symptoms is decreased. Nicotine replacement therapies have been used extensively in this capacity for the treatment of tobacco-related withdrawal, as has methadone for opioid withdrawal. Haney et al. [54] found that oral $\triangle^9$-tetrahydrocannabinol markedly reduced symptoms associated with marijuana abstinence including self-reported ratings of marijuana craving, anxiety, misery, and sleep disturbance. The medication also reversed the withdrawal-associated psychomotor performance decrements as well as the anorexia and weight loss associated with marijuana withdrawal. It is important to note, too, that these effects occurred at an oral $\triangle^9$-tetrahydrocannabinol dose indistinguishable from placebo (i.e., like placebo, active $\triangle^9$-tetrahydrocannabinol produced no apparent subjective effects), highlighting the pharmacological specificity of marijuana withdrawal. Budney and colleagues [21] replicated and extended these findings by demonstrating that oral $\triangle^9$-tetrahydrocannabinol (30 and 90 mg/d) dose-dependently suppressed cannabis withdrawal in an outpatient environment. Together, these results are consistent with findings that showed acute $\triangle^9$-tetrahydrocannabinol administration substantially assuaged precipitated cannabinoid withdrawal in laboratory animals [83, 127]; more importantly, they indicate that oral $\triangle^9$-tetrahydrocannabinol might be beneficial in the treatment of marijuana dependence.

Several limitations of the above studies should be noted. First, most of the studies employed only one active dose of the treatment medication. Perhaps more cannabis-related

withdrawal symptoms would have been alleviated if a wider range of medication doses were examined. This point is particularly relevant for the study that examined nefazodone because the tested active dose (450 mg/d), which was lower than doses regularly used clinically to treat anxiety and depression, showed a trend toward improved withdrawal symptomatology. Second, most study participants were seeking treatment to abstain from cannabis use. Because the study of cannabis-related effects in humans requires the administration of carefully controlled doses of smoked marijuana, ethical considerations dictate that research volunteers not only have current cannabis use histories, but that they are also not seeking treatment for their cannabis use [41]. Thus, it is possible that the above results may not generalize to persons who are requesting treatment for cannabis dependence. A related limitation is that although adolescents are more likely than adults to exhibit clinical features of cannabis dependence and experience difficulties abstaining from cannabis use [25], none of the above studies included participants younger than 21 years of age. This was done because the studies involved the administration of smoked marijuana (a drug of abuse); thus it was believed inappropriate to expose children to smoked marijuana in the laboratory, even if the potential participant had reported previous use. Nonetheless, in light of the fact that a large proportion of cannabis-dependent persons under the age of 21 report using cannabis to alleviate withdrawal symptoms [27], it may be important study the effects of potential treatment medications in older adolescents.

There are at least two issues of potential concern related to treating cannabis-dependent adolescents with medications such as oral $\triangle^9$-tetrahydrocannabinol: (1) administration of a psychoactive drug to individuals whose brains are still developing can potentially hamper development, especially in areas like the prefrontal cortex, which is slower to develop than other cortical regions [69]; and (2) replacement of one psychoactive drug with abuse potential with another drug that has abuse potential. While these concerns deserve serious consideration, it is important to note that the route of administration is a critical determinant of neurochemical consequences associated with drug administration, in part because neurochemical effects depend on the rate of rise of drug concentrations and the maximum drug concentrations achieved [43]. Thus, administration of $\triangle^9$-tetrahydrocannabinol via the oral route would be expected to produce less deleterious neuronal consequences than smoked marijuana. Regarding concerns about the abuse potential of oral $\triangle^9$-tetrahydrocannabinol, data from a recent study completed in our laboratory showed that the drug produced low rates of self-administration in a sample of marijuana smokers, suggesting that the abuse potential of oral $\triangle^9$-tetrahydrocannabinol is limited [62]. Note also that oral $\triangle^9$-tetrahydrocannabinol, unlike smoked marijuana, is not associated with an increased risk of lung toxicity. Hence, from a risk-benefit perspective, oral $\triangle^9$-tetrahydrocannabinol appears to be a safer therapeutic option. It should be noted that Gray et al. [47] recently assessed oral $\triangle^9$-tetrahydrocannabinol (0, 2.5, 5, 10 mg/d) for tolerability in older adolescents (ages 16–21 years). They found that the drug produced dose-related increases in euphoria without producing significant effects on cardiovascular measures, psychomotor performance, or "negative" subjective-effect ratings. Another limitation worth noting is that the same group of researchers has collected most of the published data in this research area, which highlights the need for replication of previous results and additional data.

The above limitations notwithstanding, the data obtained in human research participants demonstrate that while a growing number of medications have been tested, few show promise as potential treatment strategies for the amelioration of cannabinoid withdrawal symptoms. Findings from studies of bupropion and divalproex were discouraging, as these medications failed to assuage many marijuana withdrawal symptoms. In some cases, symptoms were worsened by the medication. Of the agents tested, clearly, oral $\triangle^9$-tetrahydrocannabinol produced

the most promising results. In addition, the limited results obtained in adolescents indicate that oral Δ^9-tetrahydrocannabinol is well tolerated and suggest further study of this medication in adolescent marijuana abusers. Although no study has investigated the effects of benzodiazepines on human cannabis withdrawal symptoms, data obtained in laboratory animals suggest that future studies should examine the ability of agents such as clonazepam or oxazepam to lessen severity of the withdrawal syndrome.

Relapse Prevention Medications

Drug self-administration procedures provide a reliable method for evaluating the reinforcing effects of psychoactive agents. Under these procedures, laboratory animals are provided an opportunity to self-administer intravenously doses of a drug contingent upon an operant response (e.g., lever pressing). These procedures have been used extensively not only to assess drug-related abuse liability, but they have also been used to evaluate the usefulness of potential pharmacotherapies in treating substance use disorders. If a potential treatment medication, for example, decreases self-administration of the abused drug in laboratory animals, then perhaps the treatment medication would be effective in curtailing human abuse of the drug. Although data from the majority of earlier studies showed that cannabinoids did not reliably maintain self-administration behavior in laboratory animals tested (e.g., [57, 78, 86, 100]; for review, see also [117]), findings from recent studies demonstrate clearly that cannabinoids produce dose-related reinforcing effects in rats and squirrel monkeys [38, 74, 116]. The success of recent attempts to obtain reliable self-administration in laboratory animals has been attributed to the employment of lower Δ^9-tetrahydrocannabinol doses that were injected more rapidly than those previously investigated.

Because of the demonstration that Δ^9-tetrahydrocannabinol reliably serves as a reinforcer, Goldberg and colleagues have begun testing the ability of potential marijuana treatment medications to alter marijuana self-administration in squirrel monkeys. In the first study, monkeys were given an opportunity to self-administer Δ^9-tetrahydrocannabinol (2, 4 μg/kg) during sessions [116]. Both doses robustly maintained self-administration; when active Δ^9-tetrahydrocannabinol was substituted with vehicle, responding significantly decreased. Following the demonstration of Δ^9-tetrahydrocannabinol self-administration, the researchers then assessed the effects of the cannabinoid antagonist rimonabant, administered one hour before experimental sessions, on Δ^9-tetrahydrocannabinol as well as cocaine self-administration. The administration of rimonabant markedly reduced Δ^9-tetrahydrocannabinol self-administration, but had no effect on cocaine self-administration, indicating the selective involvement of the cannabinoid system in Δ^9-tetrahydrocannabinol reinforcing effects. These findings were recently extended when this group of investigators demonstrated that rimonabant blocked cue- and Δ^9-tetrahydrocannabinol-induced reinstatement of Δ^9-tetrahydrocannabinol self-administration by squirrel monkeys [76]. The finding that rimonabant suppressed Δ^9-tetrahydrocannabinol self-administration is an important one with respect to cannabis treatment medications development efforts. It suggests that cannabinoid antagonism might be a useful strategy for decreasing cannabis dependence in humans. In fact, Huestis et al. [67] reported that rimonabant (90 mg, by mouth) blocked the acute subjective and cardiovascular effects of smoked marijuana in human research volunteers. An important caveat to the above findings is that an acute rimonabant dosing regimen was employed in those studies. Because individuals undergoing treatment for cannabis dependence may require repeated administration of pharmacological agents, the clinical utility of rimonabant is unclear. In addition, while rimonabant-like medications may present an alternative option for individuals who do not want to be maintained on cannabinoid agonists, it is important to note that lack of compliance has been a major problem

with antagonist therapy used in treating other substance use disorders (e.g., naltrexone for opioid dependence). Despite these concerns, the above data suggest that further study of rimonabant-like medications in the treatment of marijuana dependence is warranted.

In another study by this group of researchers, Justinova et al. [75], using similar procedures, evaluated the effects of naltrexone, an opioid antagonist, on $\triangle^9$-tetrahydrocannabinol self-administration behavior in monkeys. The rationale for the use of naltrexone stemmed from accumulating evidence obtained in laboratory animals, which suggests a reciprocal functional interaction between central nervous system cannabinoid and opioid systems [87]. Opioid antagonists, for example, have been demonstrated to precipitate withdrawal symptoms in rats dependent on cannabinoids [79, 93]. Moreover, pretreatment with the opioid antagonist naloxone has been shown to decrease self-administration behavior maintained by cannabinoid agonists in rodents [14, 15, 94]. Justinova et al. [75] replicated and extended the self-administration data by demonstrating that $\triangle^9$-tetrahydrocannabinol self-administration behavior in monkeys was significantly decreased in the presence of naltrexone. The dampening effect of naltrexone on $\triangle^9$-tetrahydrocannabinol self-administration behavior was not as robust as those produced by the cannabinoid antagonist (described above). While these data are congruent with the hypothesis that the endogenous opioid system modulates central nervous system cannabinoid effects and are suggestive of the idea that naltrexone might be useful in preventing relapse to marijuana use, data obtained using human research participants indicate that naltrexone does not alter marijuana-associated antinociceptive or subjective effects (e.g., [48, 129]). Indeed, Haney et al. [53] reported that naltrexone pretreatment (50 mg, oral) significantly increased "positive" subjective effects (e.g. ratings of "Good Drug Effect") of oral $\triangle^9$-tetrahydrocannabinol (30 mg). Naltrexone also produced a moderate increase in choice to self-administer $\triangle^9$-tetrahydrocannabinol, although this effect was not significant. More recently, Haney [55] investigated the effects of a lower, more selective dose of naltrexone (12 mg, oral) on response to oral $\triangle^9$-tetrahydrocannabinol (0–40 mg) in non-marijuana and marijuana smokers. Naltrexone-related effects varied as a function of marijuana use history: in non-marijuana smokers, $\triangle^9$-tetrahydrocannabinol-associated intoxicating effects (2.5 mg) were enhanced and $\triangle^9$-tetrahydrocannabinol-associated anxiety (10 mg) was decreased, whereas, in marijuana smokers, $\triangle^9$-tetrahydrocannabinol-associated intoxicating effects (20 mg) were reduced and $\triangle^9$-tetrahydrocannabinol-associated anxiety (40 mg) was increased. The apparent lack of correspondence between data obtained using laboratory animals and those obtained with human research participants emphasize the importance of not only testing potential marijuana pharmacotherapeutic agents in laboratory animals, but also evaluating the utility of these medications in human research participants.

In contrast to the large database describing the effects of relapse prevention medications in treating human alcohol and cocaine dependence (for review, see [58]), research evaluating potential cannabis pharmacotherapies is scarce. Of the few studies that have been published, most have focused primarily on the ability of the test medication to alter physiological and subjective effects of marijuana. Cone et al. [29], for instance, showed that clonidine pretreatment reduced marijuana-related increase in heart rate, but had no effect on marijuana-related subjective effects, and as mentioned above, Huestis et al. [68] found that rimonabant pretreatment attenuated both the increased heart rate and intoxicating effects associated with smoked marijuana. Maintenance on a cannabinoid agonist has also been reported to decrease the intoxicating effects and increase heart rate following smoked marijuana [68, 72]. These data indicate that some of marijuana-associated effects can be altered by various medications.

While modification of subjective and cardiovascular effects produced by marijuana provides important information, the behavior of major

interest for the treatment of cannabis dependence is drug-taking. To date, only a few published studies have measured cannabis-taking behavior by human research volunteers while being maintained on a potential pharmacotherapeutic agent. The first study was a within-participant design, residential laboratory study during which the influence of oral Δ^9-tetrahydrocannabinol maintenance (0, 10, 20 mg four times daily, each dose administered for three consecutive days) on choice to self-administer smoked marijuana was evaluated [60]. Hart et al. [60] reasoned that because Δ^9-tetrahydrocannabinol had been demonstrated to play an integral role in the behavioral effects of smoked marijuana (e.g., [59]) and because agonist therapies have been demonstrated to be effective in decreasing self-administration of other drugs of abuse (e.g., [10, 28]), marijuana-related reinforcing and subjective effects could be significantly attenuated during oral Δ^9-tetrahydrocannabinol maintenance. Yet, choice to self-administer marijuana was not significantly altered by either of the two active Δ^9-tetrahydrocannabinol maintenance conditions, although some marijuana-associated "positive" subjective effect ratings (e.g., "Good Drug Effect") were reduced when participants were maintained on oral Δ^9-tetrahydrocannabinol. There exist several possible reasons why oral Δ^9-tetrahydrocannabinol maintenance did not alter marijuana self-administration, but two are of particular importance. First, the Δ^9-tetrahydrocannabinol maintenance regimen involved only three consecutive days of active treatment, which may have been an insufficient time frame to reduce marijuana self-administration by frequent marijuana users (prior to study enrollment, participants reported smoking an average of 7 marijuana cigarettes per day). Second, none of the study participants were seeking treatment to abstain from marijuana use, further decreasing the likelihood of observing alterations in marijuana self-administration behavior. Given these observations, as well as the fact that some of marijuana's subjective effects decreased, the effect of longer oral Δ^9-tetrahydrocannabinol maintenance on self-administration of marijuana by different populations of marijuana-dependent individuals warrants further investigation.

In another laboratory study, Haney et al. [56] determined the effects of oral Δ^9-tetrahydrocannabinol (60 mg/d), lofexidine (2.4 mg/d), and the combination on symptoms of marijuana withdrawal and relapse, defined as a return to marijuana use after a period of abstinence. Oral Δ^9-tetrahydrocannabinol decreased most withdrawal symptoms, which replicates previous findings (e.g., [20, 54]), but did not decrease marijuana relapse. Lofexidine was sedating and did not lessen withdrawal, but improved sleep and decreased marijuana relapse. The Δ^9-tetrahydrocannabinol-lofexidine combination most robustly improved sleep and attenuated marijuana withdrawal, craving, and relapse. These findings argue that the Δ^9-tetrahydrocannabinol-lofexidine combination should be examined further for its potential as a marijuana dependence treatment medication.

In a pilot outpatient trial, Levin et al. [82] tested divalproex as a marijuana abuse relapse prevention medication. This 12-week study utilized a double-blind placebo-controlled, crossover design, during which 25 individuals were initially randomized to either divalproex (average dose: 1673 mg/d) or placebo. Self-reported marijuana use and quantitative Δ^9-tetrahydrocannabinol urine levels were the primary outcome measure. Divalproex was not found to be more efficacious at curtailing marijuana use than placebo. In addition, divalproex, at doses tested, did not appear to be well tolerated, as compliance on the medication was poor. Together with the finding that divalproex was ineffective at decreasing symptoms of marijuana withdrawal [54], these results suggest that divalproex is not a viable therapeutic option for marijuana dependence.

McRae et al. [89] used an open-label design to test buspirone (10–60 mg/d) as a potential marijuana dependence treatment medication. The rationale for testing buspirone was based on its ability to decrease anxiety, a symptom sometimes associated with cannabis withdrawal. This 12-week study enrolled 11 participants, but only

two completed. The researchers reported that buspirone produced moderate reductions in self-reported marijuana craving and irritability and urine samples positive for marijuana metabolites. A major limitation associated with this study is that it was conducted under non-blind conditions. As a result, the generality of the findings is limited.

In another open-label trial, the attention deficit hyperactivity disorder medication atomoxetine was investigated [119]. Tirado et al. [119] reasoned atomoxetine would be an excellent candidate medication because impairments in attention, memory, executive function and response inhibition seen in marijuana smokers resemble deficits seen in individuals with attention deficit hyperactivity disorder. During this 11-week trial, 13 cannabis dependent treatment seekers were administered a flexible dose of atomoxetine (from 25 to 80 mg/day) depending upon individual tolerability and self-reported cannabis use and use verified via urine toxicology were assessed. Self-reported cannabis use was decreased during medication treatment, but this was not confirmed by urine toxicology as the number of tetrahydrocannabinol-positive urine screens did not vary as a function of treatment condition. In addition, atomoxetine was associated with significant adverse gastrointestinal symptoms (nausea, vomiting, dyspepsia and diarrhea).

A growing number of clinical laboratory studies have demonstrated that the physiological and subjective effects of cannabis can be reduced by different classes of medications. Cannabis-related effects on heart rate are attenuated by the α_2-receptor agonist clonidine and by the cannabinoid antagonist rimonabant; cannabis-related intoxicating effects are dampened by rimonabant and by the cannabinoid agonist $\triangle^9$-tetrahydrocannabinol. Such findings are encouraging, but clearly more research is needed to determine the clinical utility of these medications for cannabis dependence. Of the limited number of studies evaluating the effects of relapse prevention medications on cannabis-taking behavior by humans, one has shown a medication to decrease marijuana relapse; the $\triangle^9$-tetrahydrocannabinol-lofexidine combination seems to be the most encouraging. The finding might ultimately prove beneficial in decreasing relapse to cannabis use in a treatment seeking population of cannabis-dependent individuals, but further studies using different doses are needed to confirm data from the single available study.

Future Directions in Medication Development for Cannabis Dependence

In recent years, there has been an increase in the popularity of smoking "blunts," marijuana wrapped in tobacco paper from inexpensive cigars such as Phillies Blunts or Dutch Masters [46]. Anecdotally, blunt smokers report that the combination of nicotine, derived from the tobacco wrapping, and marijuana enhances the psychoactive pleasurable effects of marijuana. Although there is currently a lack of scientific evidence substantiating this claim in humans, Valjent et al. [124] found that $\triangle^9$-tetrahydrocannabinol-induced hypothermia, antinociception and hypolocomotion were markedly facilitated by nicotine in mice. Consistent with these results, Solinas et al. [107] demonstrated that selective alpha7 nicotinic acetylcholine receptor antagonists disrupted the discriminative stimulus and reinforcing effects of cannabinoid receptor 1 agonists. They also found that selective alpha7 nicotinic acetylcholine receptor antagonists decreased $\triangle^9$-tetrahydrocannabinol-induced dopamine elevations in the shell of the nucleus accumbens. In general, the above results are in line with a recent report indicating that symptoms of cannabis dependence are worsened by the combination of tobacco and marijuana smoking [103]. Together, these findings suggest that endocannabinoid and acetylcholinergic activity may produce synergetic effects and should be target for future medication development efforts for cannabis dependence.

Several new nicotinic acetylcholine receptor agonists are now in human clinical development for a variety of cognitive disorders and smoking cessation. Recently, varenicline, a nicotinic acetylcholine receptor partial agonist, was approved for smoking cessation with efficacy superior to nicotine replacement therapies and bupropion. Because of the overlap between nicotine and cannabis in terms of dependence and similarity in withdrawal symptoms [126], pharmacotherapies, like varenicline and transdermal nicotine, may reduce the withdrawal effects associated with cannabis, particularly if the cannabis-dependent individuals are also dependent on tobacco.

In summary, research investigating the use of pharmacotherapies for cannabis use disorders continues to be refined. A growing number of medications have been shown to alleviate cannabinoid withdrawal symptoms in laboratory animals and may provide clues to the underlying neuronal mechanisms of cannabinoid dependence. The majority of these findings, however, have not been tested in humans, as only $\triangle^9$-tetrahydrocannabinol and the $\triangle^9$-tetrahydrocannabinol-lofexidine combination have been demonstrated to ameliorate substantially human symptoms of cannabis withdrawal. Fewer studies have assessed the effects of potential cannabis treatment medications on cannabinoid-related physiological, subjective, and reinforcing effects. In laboratory animals, only rimonabant has been shown to be particularly promising; in humans, a small number of medications have been demonstrated to decrease physiological and subjective effects of cannabis (clonidine, oral $\triangle^9$-tetrahydrocannabinol, and rimonabant), and the $\triangle^9$-tetrahydrocannabinol-lofexidine combination has been demonstrated to most effectively reduce relapse to cannabis use.

Acknowledgements This research was supported by the National Institute on Drug Abuse grant #DA-03746. We gratefully acknowledge the efforts of Michaela Bamdad and Catalina Saldaña, who read an earlier version of the manuscript and made helpful suggestions.

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Hallucinogens

John H. Halpern, Joji Suzuki, Pedro E. Huertas, and Torsten Passie

Contents

Historical Perspectives

Psychoactive substances derived from botanicals have been ritualistically used for millennia [63, 73]. Developments during the second half of the twentieth century in neuroscience and in synthetic organic chemistry recast natural and synthetic intoxicants into a new biological and clinical light [52]. These chemicals, referred to improperly as "hallucinogens", alter psychoneurobiological behavior in ways both subtle and overt. The term "hallucinogen" suggests the induction of hallucinations, a symptom of psychosis well-known within clinical psychiatry, but this is not the case with most hallucinogens and some closely related substances (i.e., entactogens such as 3,4-methylenedioxymethamphetamine), which do not induce major sensory alterations. The terms "psychotomimetics" (psychosis-mimicking) and "psychedelics" have also been used. "Psychotomimetic" only rarely appears anymore in the scientific literature, since, much like with "hallucinogen", these substances are not primarily psychotogenic, whether mimicking or otherwise, though hallucinogens can exacerbate or contribute to worsening the mental health of those vulnerable to a formal thought disorder. The term "psychedelic", first offered by the psychiatrist Humphrey Osmond [55], may be the most commonly used lay term for hallucinogens, and it used to be an accepted alternate descriptor in the scientific literature.

Albert Hofmann first synthesized lysergic acid diethylamide in 1938 and accidentally ingested it in 1943. Publishing on these findings heralded much research in the 1950s where hallucinogens became the focus of intense interest in psychiatric research and stimulated the discovery of the neurotransmitter systems and their functions in the brain [39].

Over 10,000 subjects received lysergic acid diethylamide (and other hallucinogens) in controlled research settings in studies published from 1951 to the late 1960s, resulting in more than 1,000 clinical papers, dozens of books, and six international conferences on their use as aids in psychotherapy [11, 24, 48, 56].

A number of substances have been categorized as hallucinogens or hallucinogen-like:

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_54,

(1) the classical hallucinogens (e.g., mescaline, psilocybin, lysergic acid diethylamide, dimethyltryptamine), (2) the entactogenic phenethylamines (3,4-methylenedioxyamphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxyethylamphetamine, methylbenzodioxolylbutanamine), (3) the anticholinergic delirants (atropine, hyoscyamine, scopolamine), and (4) dissociative anesthetics/miscellaneous (N_2O, ketamine, phencyclidine, salvinorin A). This chapter focuses on the more commonly used classical and entactogenic hallucinogens, but will mention the other substances where appropriate or necessary.

Epidemiology

The Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health estimated that among Americans aged 12 or older in 2006, close to 4 million used hallucinogens that year, with 1.1 million trying one for the first time ever, and some 35.3 million Americans have tried one at least once in their lifetime [60]. 380,000 Americans over age 12 were estimated to meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria for hallucinogen abuse or dependence in 2006 (out of a total of 23.6 million persons classified with any substance abuse or dependence that year) [60]. The Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network data estimated that 16,408 emergency room visits for the entire United States in 2005 involved a hallucinogen (not including phencyclidine: 7,535), with 10,752 for the entactogen 3,4-methylenedioxymethamphetamine and less than 1,900 for the classical hallucinogen lysergic acid diethylamide (out of a total of 1.45 million drug-related visits) [61].

Among high school students, the Monitoring the Future data have shown a continuous decline since the late 1990s in the lifetime, annual, and past-month use of hallucinogens [43]. In 2006, 8.3% of 12th graders in the United States reported lifetime use of hallucinogens, a drop from 15.1% in 1997 [43].

Taken together, these numbers indicate that the prevalence of hallucinogen use still is lower compared with other substances of abuse in the United States and is significantly lower in morbidity and mortality. The prevalence of the various hallucinogen-related disorders is not known.

Basic Pharmacology

Table 1 lists some of the more commonly known hallucinogens. As shown by the table, the various hallucinogens are wide-ranging in dosage and duration. In general, hallucinogens exert their effects by sympathomimetic actions on the central nervous system. This activation may be due to agonist properties on different neurotransmitter-modulated brain systems that are adrenergic, dopaminergic, and, perhaps most importantly, serotonergic. The brain contains approximately 40,000 serotonergic neurons, mainly located in the dorsal raphe nucleus of the mid-brain. This tiny population of neurons maintains a widely distributed network throughout the brain, which modulates nearly every kind of brain activity.

Despite heterogeneity, most classical hallucinogens appear to exert pharmacologic action through agonist effects on 5-HT_{2A}/c receptors [52]. Hallucinogens have high affinity for serotonin receptors [21, 59], and genetic or pharmacologic inactivation of 5-HT_{2A} receptors blocks behavioral effects in preclinical models as well as subjective effects in humans [16, 21, 22, 72]. Rapid tolerance develops due to receptor down-regulation, and repeated administration leads to markedly diminished effects within several days [52].

It remains unclear as to whether a specific pattern of alterations of brain functioning is involved in hallucinogens' psychoactive effects. Neurometabolic studies to date point to activation of the frontal cortex, limbic/paralimbic structures, and the right hemisphere [23, 38, 58, 71].

Table 1 The common hallucinogens (partial list)

Class	Chemical name	Common or street name	Source	Dosage	Route	Duration of action	Major neurobiological target	Notes
Indole-alkylamines	Lysergic acid diethylamide	LSD, Acid, Blotter	Synthesis	50–200 μg	By mouth	8–14 h	5-HT_{2A} partial agonist	Distributed on small squares of blotting paper, drops of liquid, gel-caps, small pills
	Psilocybin	Magic mushrooms, Shrooms	Psilocybe cubensis, Psilocybe azurescens, and many other subspecies, Synthesis	10–50 mg, 1–5 g dried mushroom; quite variable	By mouth	4–8 h	5-HT_{2A} partial agonist	Psilocybin is converted in the body to psilocin, the actual active hallucinogen. Continued shamanic use in Mexico. Bruising of mushroom turns blue.
	Dimethyltryptamine	DMT, Yopo, Cohoba	Psychotria viridis, Anadenanthera peregrina, Mimosa hostilis, and many other natural sources, Synthesis	5–40 mg	Smoked, inhaled snuff	30–60 min	5-HT_{2A} partial agonist	Continued Amazonian shamanic use
	Dimethyltryptamine + monoamine oxidase inhibitors (harmala beta-carbolines)	Ayahuasca, yaje, Hoasca, Daime, "vine of the soul"	Psychotria viridis (dimethyl-tryptamine) + Banisteropsis caapi (monoamine oxidase inhibitor)	Variable	By mouth	2–4 h	5-HT_{2A} partial agonist	Brewed as a tea; religious sacrament
	Ibogaine	Ibogaine	Tabernathe iboga	200–300 mg	By mouth	12+ h	Likely 5-HT_{2A} partial agonist	Religious sacrament; long-acting metabolites may contribute to purported anti-opiate withdrawal benefits.
Phenyl-alkylamines	3,4,5-trimethoxy-phenylethylamine	Mescaline, Peyote, San Pedro	Lophophora williamsii, Echinopsis panachoi, other cacti, Synthesis	200–500 mg, 10–20 g or 5–10 dried peyote buttons, 1 kg fresh E. pachanoi	By mouth	6–12 h	5-HT_{2A} partial agonist	Religious sacrament

Table 1 (continued)

Class	Chemical name	Common or street name	Source	Dosage	Route	Duration of action	Major neurobiological target	Notes
Entactogenic phenyl-alkylamine	3,4-methylenedioxy-methamphetamine	MDMA, Ecstasy, X, XTC, Rolls, Molly	Synthesis	80–150 mg	By mouth	4–6 h	Serotonin release and depletion	Mildly hallucinogenic at high doses
	3,4-methylenedioxy-amphetamine	MDA, Love drug, Adam	Synthesis	75–160 mg	By mouth	4–8 h	Serotonin release and depletion	
	4-bromo-2,5-dimethoxy-phenethylamine	2C-B, Nexus	Synthesis	5–30 mg	By mouth	4–8 h	Unknown	
	4-chloro-2,5-dimethoxy-amphetamine	DOC	Synthesis	1–5 mg	By mouth	4–8 h	Unknown	Has been found on blotting paper
	4-methyl-2,5-dimethoxy-amphetamine	DOM, STP	Synthesis	1–10 mg	By mouth	14–20 h	Unknown	Higher doses used in the 1960s resulted in many ER visits then.
Dissociative	Ketamine	Ketamine, Special K, Vitamin K, K hole	Synthesis	25–50 mg (intramuscularly), 50–100 mg (by mouth or snorted)	Intramuscularly, by mouth, snorted	1–2 h (intramuscularly), 1–4 h (by mouth)	*N*-methyl-*D*-aspartate antagonist	Sub-anesthetic dose: lost sense of time, space, verbal skills, balance, drooling
	Dextromethorphan	DXM, Robo, DM	Synthesis	100–600 mg	By mouth	4–8 h	*N*-methyl-*D*-aspartate antagonist	
	Phencyclidine	PCP, Angel dust	Synthesis	3–10 mg	By mouth	8–24 h	*N*-methyl-*D*-aspartate antagonist	

Table 1 (continued)

Class	Chemical name	Common or street name	Source	Dosage	Route	Duration of action	Major neurobiological target	Notes
Other	Salvinorin A	Salvia, Sally D, Diviner's sage	Salvia divinorum	250–750 mg (smoked), 2–10 g dried leaves (by mouth)	Smoked, by mouth	30–60 min (smoked), 1–3 h (by mouth)	Kappa-opioid selective agonist	Atypical hallucinogen; no longer found in the wild
	Scopolamine and atropine	Datura, Jimson weed, loco weed, Thorn apple, Angel's trumpet, belladonna, deadly nightshade	Datura stramonium, Atropa belladonna, many related species	Highly variable	By mouth	12–48 h	Competitive muscarinic acetylcholine antagonist	Plants of the Solanaceae family contain various ratios of scopolamine to atropine; blurred vision
	Muscimol (5-(aminomethyl)-3-isoxazolol)	Fly agaric, Amanita	Amanita muscaria, Amanita pantherina	1–30 g dried mushrooms	By mouth	5–10 h	Gamma-aminobutyric acid-A agonist glutamate	Shamanic use in eastern Siberia; over 600 species of agarics—easy to misidentify. Some are extremely poisonous, such as "death cap" A. phalloides; mushrooms also contain ibotenic acid—as it dries/ages, decarboxylation of ibotenic acid creates muscimol.

Entactogenic substances, such as 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine, differ from classical hallucinogens by inducing a marked release of serotonin from serotonin-containing neurons and (to a lesser extent) dopamine release from dopamine-containing neurons [70]. Their neurometabolic actions show minor deactivation of cortical regions and limbic activation [23] as well as deactivation of the left amygdala [18]. The latter may be responsible for their most prominent effect: the decrease of emotional tension and anxiety.

Psychological and Biological Effects

Intoxication with hallucinogens, commonly referred to as "tripping", may induce some physiologic effects quite subtle to observation and a wide variety of behavioral, emotional, and cognitive effects (Table 2) [29, 42]. The visual images experienced are usually not true hallucinations but illusions, such as the perception of geometric patterns or scenic dream-like visions appearing before closed eyes, perception of movement in stationary objects, and synesthesias. The content of visual and most emotional phenomena most often reflects the psychodynamics of the user [27, 45]. Colors may appear intensified, and humans (self and others) and animals may be viewed as altered or exaggerated directly or in mirrored reflection [69]. Hallucinogens amplify affectivity and may cause significant changes of mood, with possible rapid changes from euphoria to depression or anxiety or vice versa [67]. In extreme cases, especially with higher order overdoses, psychotic-like reactions may be experienced. In short, the psychological effects of hallucinogens are highly variable and strongly influenced by the individual's psychological state at the time

Table 2 Hallucinogen[a] physical and psychological effects

Intoxication may include a cluster of the following	
Physical effects[b]	Psychological effects
Regular (mild to very mild): Tachycardia, palpitations, hypertension or hypotension, diaphoresis, hyperthermia, motor incoordination, tremors, hyperreflexia, altered neuroendocrine functioning *Regular (mild to strong):* Mydriasis, arousal, insomnia *Occasional:* Nausea, vomiting, diarrhea, blurred vision, nystagmus, piloerection, salivation	Intensification and/or lability of affectivity with euphoria, anxiety, depression, and/or cathartic expressions Dream-like state Sensory activation with illusions, pseudo-hallucinations, hallucinations[c], synesthesias Altered experience of time and space Altered body image Increased suggestibility Acute neuropsychological/cognitive impairments with loosening of associations, inability for goal-directed thinking, memory disturbances Paranoid/suicidal ideation Impaired judgment Megalomania, impulsivity, odd behavior Lassitude, indifference, detachment Psychosomatic complaints Derealization, depersonalization Mystical experiences Sense of profound discovery/healing

[a] Indolealkylamine and phenylalkylamine hallucinogens only (see Table 1)

[b] Some effects are reactionary to psychological content (e.g., increased heart rate and nausea due to anxiety), and complaints can be dependent on factors such as mindset, setting, dose, and supervision. Intoxicated individuals may also deny physical impairment and/or claim increased energy, sharpened mental acuity, and improved sensory perception

[c] A subject experiencing "pseudo-hallucinations" retains the capacity to recognize that these perceptions are transient and drug induced, as opposed to true hallucinations in which no such discernment from reality is possible

of ingestion (mind-set) as well as the social and physical setting [75].

Toxicity of lysergic acid diethylamide, psilocybin, and other classical hallucinogens is very low. Overdosing leads to psychological complications to psychological crises or (rarely) psychotic symptoms. However, no case of lethal overdose is known, and there is no evidence of toxicity beyond the acute state of intoxication [33]. A recent review of the harmful consequences of drugs of abuse found that the classical (and the most used, by far) hallucinogen lysergic acid diethylamide is near the bottom in a ranking of risk to users and society [53].

Hallucinogen Use Disorders

Hallucinogen abuse and hallucinogen dependence are organized in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition much like most other listed substance use disorders. Both are characterized by patterns of compulsive and repeated drug use despite the knowledge of significant harm caused by this use. Hallucinogen use only virtually never leads to the development of classic dependence syndromes as seen with opiates or alcohol [54]. By far the most typical pattern is for users to experiment with a few doses of a hallucinogen and then discontinue further use [41]. Users do not experience withdrawal symptoms as seen with other substances of abuse, and so this symptom is not a criterion in diagnosing hallucinogen dependence. Note that tolerance rapidly increases, in general, when hallucinogens are used with frequency, which strongly limits their use on a regular basis.

Hallucinogen-Induced Disorders

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition allows for the diagnosis of numerous substance-induced disorders. Specific to hallucinogens are: hallucinogen intoxication, hallucinogen persisting perception disorder, and hallucinogen-induced psychotic, mood, anxiety, delirium, or "not otherwise specified" disorder. These disorders arise in the context of substance use and may manifest during intoxication, during withdrawal, or long after the drug has been ingested and the acute effects have subsided [7]. The diagnosis of a hallucinogen-induced psychotic, mood, anxiety, or delirium disorder is made only if the symptoms are in excess of what is expected from intoxication or withdrawal [7].

Assessment and Treatment

Hallucinogen Intoxication

The *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, Fourth Edition criteria for hallucinogen intoxication are presented in Table 3.

Assessment

An individual will most often present for treatment because he or she is experiencing an acute panic and/or depressive reaction (sometimes combined with temporary delusional ideation), commonly referred to as a "bad trip". Symptoms begin any time after the onset of effects and may include marked anxiety or fears of "going insane" [17, 65]. Paranoid ideation, feelings of being manipulated, or feelings of being in a situation without any escape may also occur. Hallucinogen intoxication should be suspected when a patient or his or her friends report recent ingestion of a hallucinogen and the patient presents with a characteristic constellation of sympathomimetic findings with a clear sensorium. Since laboratory testing is generally not available in most acute settings, obtaining an accurate history and clinical examination is critical in establishing this diagnosis. Since illicit drugs often contain various substances, the actual identity of the offending substance ingested may not be known. However, hallucinogens in general produce similar effects, which

Table 3 *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, fourth edition criteria (292.89): Hallucinogen intoxication

A. Recent use of hallucinogen
B. Clinically significant maladaptive behavior or psychological changes (e.g., marked anxiety or depression, ideas of reference, fear of losing one's mind, paranoid ideation, impaired judgment, or impaired social or occupational function) that developed during or shortly after, hallucinogen use.
C. Perceptual changes occurring in a state of full wakefulness and alertness (e.g., subjective intensification of perceptions, depersonalization, derealization, illusions, hallucinations, synesthesias) that developed during, or shortly after, hallucinogen use.
D. Two (or more) of the following signs, developing during, or shortly after, hallucinogen use:
(1) pupillary dilatation
(2) tachycardia
(3) sweating
(4) palpitations
(5) blurring vision
(6) tremors
(7) incoordination
E. The symptoms are not due to a general medical condition or are not better accounted for by another mental disorder.

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should be carefully assessed. Signs and symptoms of hallucinogen intoxication are reviewed in the previous section (see Table 2). Physical examination will also provide important clues that can help support the diagnosis of hallucinogen intoxication (in particular, widely dilated pupils that do not rapidly/tightly constrict to accommodate bright light). Although duration of action can vary considerably among hallucinogens, the acute reaction typically lasts less than 12–24 h; persisting reactions will require further investigation to rule out other etiologies.

Differential Diagnosis

Since polysubstance ingestion is common, history should be sought on whether other substances were also recently consumed. Urine toxicology should also be performed, but tests for specific hallucinogens are specially ordered and results typically will not be available for a few days. Anticholinergic intoxication should be considered in individuals with a suggestive history (i.e., ingestion of jimson weed, or Datura) and findings of hyperthermia, delirium, dry mouth, urinary retention, headache, and blurred vision. Delirium due to alcohol, sedative, or hypnotic withdrawal will present with sympathomimetic findings, but will also present with confusion, seizures, tremors, and visual, auditory, or tactile hallucinations. Stimulant psychosis, a psychosis in the setting of a clear sensorium induced by chronic stimulant abuse, presents with paranoid delusions and visual or auditory hallucinations, and the stimulant abuser may report compulsive fascination with and performance of complex, stereotyped repetitive behaviors known as "punding" [15]. Phencyclidine, ketamine, or dextromethorphan intoxication may present similarly to hallucinogen intoxication, but differentiates with additional symptoms, including ataxia, horizontal nystagmus, rage, erythema, amnesia, and dry skin [19, 20]. Dextromethorphan intoxication will also produce a distinctive, plodding "zombie-like" gait abnormality [10]. In addition, phencyclidine overdose can prolong the toxic effects to 3 days owing to its long half-life [3].

If mood, anxiety, and psychotic symptoms warrant clinical evaluation, then hallucinogen-induced mood, anxiety, or psychotic disorder, respectively, should be considered. Psychiatric diagnoses, including affective psychoses, schizophrenia, anxiety, and dissociative disorders, also can present with varying degrees of acute dysphoria, depersonalization, and hallucinations. Medical causes of perceptual disturbances and mental status change should

be ruled out, including adverse medication reaction, metabolic disturbance, infection, dementia, stroke, seizure, central nervous system tumor, and Charles Bonnet syndrome. Collection of a careful history and physical, collateral information from family and friends, where appropriate, as well as laboratory data, will be needed for narrowing to the correct working diagnoses.

Treatment

The "talk down" (more accurately the "talk through") is usually the only intervention indicated in these situations [68]. Recommendations include placing the patient in a low-stimulus environment—i.e., a quiet space with dimmed lights and minimal distractions—and providing emotional support. Arrange for a reliable sitter (a non-intoxicated family member or friend) to remain with and attend to the patient. The sitter can help keep him or her calm and oriented by providing a sympathetic presence. In addition, provide reassurance to the patient that the experience is generally non-hazardous, drug-induced, and time-limited and will resolve with full recovery. The patient should not be left alone until the effects of the drug wear off [67].

Hallucinogens rapidly absorb in the gastrointestinal tract. Therefore, unless ingestion occurred within 30 min of presentation, gastric lavage is unlikely to remove additional undigested drug. The patient's mental state will invariably worsen if gastric lavage is forcefully attempted; therefore, it should be avoided.

If severe agitation does not respond to redirection and if concerns of safety remain for the patient and/or others, benzodiazepines are quite effective in reducing anxiety and panic [3]. Many authorities recommend diazepam or lorazepam as drugs of choice, by mouth if possible, but intramuscular and intravenous administrations are more effective [13]. In any case, avoid physical restraints, if possible, and limit the use of neuroleptics since paradoxical effects have been reported with chlorpromazine [65], and hallucinogen persisting perception disorder symptoms have been reported to worsen after receiving phenothiazines [1, 64] and 5-HT_{2A} antagonists such as risperidone [2, 50]. Haloperidol may be considered in rare cases of severely agitated patients who require further acute interventions after benzodiazepines have not proven to be sufficient. Great caution must be exercised, however, since neuroleptics lower the seizure threshold and may also induce hypotension [67].

Once acute symptoms subside, patients usually are able to return home accompanied by a family member or friend [65]. It is important to advise patients that subsequent ingestion of hallucinogens may precipitate similar reactions and (especially after bad trips) the risk for uncontrolled re-experience ("flashback") of some element(s) of the altered state is heightened. These flashbacks usually last for seconds, but may be longer if an actual hallucinogen (or cannabis) is re-ingested (see below). If symptoms persist for longer than 24 h or there are accompanying severe mood or psychotic symptoms that warrant further clinical attention, hospitalization may be appropriate [66].

Hallucinogen Abuse and Dependence

The *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, Fourth Edition criteria for hallucinogen abuse are presented in Table 4.

Assessment

For hallucinogen abuse and dependence, evaluation and treatment should proceed similar to those of patients diagnosed with hallucinogen intoxication. Hallucinogen abuse should be diagnosed when individuals report using hallucinogens despite evidence and knowledge of related harm. Hallucinogen dependence should be considered when the pattern of use appears to be out of control, such as when using larger amounts than intended or when there is an inability to cut down on the frequency of use [7].

Table 4 *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, fourth edition criteria (305.30): Hallucinogen abuse

A. A maladaptive pattern of hallucinogen use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:
  (1) recurrent hallucinogen use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to the substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
  (2) recurrent hallucinogen use in situations in which it is physically hazardous
  (3) recurrent hallucinogen-related legal problems
  (4) continued hallucinogen use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
B. The symptoms have never met the criteria for Substance Dependence for this class of substance.

Overall rates of abuse and dependence are estimated to be low compared with other substances [43, 74]. In clinical settings, individuals often present as polydrug users; therefore, a complete history is always needed to assess for other drug use.

Differential Diagnosis

With polydrug use being common, a differential diagnosis must always list other substance use or substance-induced disorders. In addition, a significant portion of illicit drugs sold as lysergic acid diethylamide (or some other hallucinogen) may contain other substances such as amphetamines or phencyclidine [67]. Therefore, diagnosis of amphetamine or phencyclidine abuse and dependence should be included for consideration and further data gathering. Alcohol is likely the drug that is most commonly abused comorbidly, and this should be assessed especially carefully in this population [14]. Schizophrenia, schizophreniform disorder, bipolar disorder, and schizoaffective disorder should be ruled out in these individuals by assessing the longitudinal course of the constellation of symptoms and their temporal relation to hallucinogen ingestion.

Treatment

General principles of substance abuse and dependence treatment apply to treating these individuals [14]. Motivational interviewing, detoxification, relapse prevention, intensive outpatient counseling, and family therapies are examples of interventions that may be individualized to the person presenting. Treatment should target all other substance abuse and dependence, whether or not they are thought to be contributing to the presenting disturbances. Moreover, treatment should be provided with a dual diagnosis approach, such that any underlying psychiatric disorder(s) will receive concurrent attention. No controlled trials have been conducted to evaluate the efficacy of pharmacotherapies.

Hallucinogen Persisting Perception Disorder

The *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, Fourth Edition criteria for hallucinogen persisting perception disorder (i.e., flashbacks) are presented in Table 5.

Assessment

Diagnosis of hallucinogen persisting perception disorder requires differentiation into two kinds of phenomena. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision, describes symptoms as the re-emergence of fragments, scenarios, and/or altered states of consciousness and mood that are similar to those experienced during the hallucinogen intoxication. This implies a re-experience ("flashback") of the initial

Table 5 *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, fourth edition criteria (292.89): Hallucinogen persisting perception disorder (flashbacks)

A. The re-experiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g., geometric hallucinations, false perception of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia, and micropsia).
B. The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The symptoms are not due to a general medical condition (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better accounted for by another mental disorder (e.g., delirium, dementia, schizophrenia) or hypnopompic hallucinations.

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intoxication. These "flashbacks", as they are often nonspecifically called, may (in some rare cases) occur intermittently over weeks, months, or years after the hallucinogen intoxication. Some people intentionally try to induce these re-experiences (with specific music/surroundings), describing them as "free trips". Flashback episodes are very short-lived (usually seconds) but may extend longer with additional cannabis intoxication. There is no documented case in the literature of a flashback leading to real danger or suicide [40].

Different from flashback phenomena is the hallucinogen persisting perception disorder phenomena as described by Abraham [1] and specified in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. They are nearly all visual in nature (including flashes of color, geometric images, and afterimages of moving objects, or "trails") [14], and appear to be continuous phenomena starting in the days to weeks after hallucinogen consumption. Hallucinogen persisting perception disorder is a rare disorder that may afflict individuals who, in particular, report anomalous visual disturbances (such as "floaters" or episodes of micropsia/macropsia) premorbid to hallucinogen exposure and who did eventually try lysergic acid diethylamide [14]. One Web-based survey of purported hallucinogen users estimated hallucinogen persisting perception disorder prevalence at 0.17–4.1% of users [9].

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition diagnostic criteria require that the individual not be intoxicated with other substances [34]. As such, urine toxicology screens should be performed routinely.

Differential Diagnosis

Hallucinogen-induced psychotic disorder should be considered in patients experiencing significant psychotic symptoms shortly after their use of hallucinogens, but it is important to note that the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition does not list a diagnosis for hallucinogen-induced *persistent* psychotic symptoms. However, very rare cases of a prolonged post-lysergic acid diethylamide psychosis have been reported but also, tellingly, have been more likely in patients with schizophrenia [65]. Psychotic disorders, including schizophrenia and bipolar disorder, should be ruled out by careful psychiatric examination and review of history. Medical causes of intermittent perceptual disturbances should also be considered, including adverse medication reaction, metabolic disturbance, migraine, temporal lobe epilepsy, ocular disease, stroke, or primary or secondary cancer of the central nervous system.

Treatment

Simple reassurance that symptoms do not reflect brain damage, and that the complained-about symptoms typically resolve over more time, can prove tremendously effective in an anxious patient with hallucinogen persisting perception disorder. A variety of treatments have been

reported in several case series to ameliorate symptoms as well as the distress associated with hallucinogen persisting perception disorder, including the use of benzodiazepines, clonidine, haloperidol, olanzapine, carbamazepine, psychotherapy, behavior modifications, and sunglasses [34]. Some case reports note worsening hallucinogen persisting perception disorder symptoms after trials of risperidone [2], phenothiazines [1], and selective serotonin reuptake inhibitors [47]. Clearly, avoiding further hallucinogen use is recommended. In addition, other substances, particularly cannabis, may also trigger hallucinogen persisting perception disorder symptoms. Avoiding triggering drugs (e.g. cannabis) is an important element of treatment. Those providing treatment should take into account the need for symptom relief while also remaining vigilant for benzodiazepine abuse and dependence (when such drugs are chosen for pharmacological intervention), as polysubstance abuse and dependence is common in this patient population [14].

Hallucinogen-Induced Psychotic Disorder

The *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, Fourth Edition criteria for substance-induced psychotic disorder are presented in Table 6.

Assessment

Hallucinogen-induced psychotic disorder is considered in individuals with recent ingestion of a hallucinogen who also present with marked psychotic symptoms and who are often lacking insight that their symptoms are related to this hallucinogen use. While this reaction may be a more severe form of the "bad trip", the diagnosis is made in the setting where a patient's psychotic symptoms are more severe than what would be expected to extend from hallucinogen intoxication. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition lists modifiers to indicate whether hallucinations or delusions are prominent features [7]. Hallucinogen-related psychotic reactions usually end once the effects of the drug wear off.

Differential Diagnosis

Differential diagnosis includes diagnoses considered for any acute psychosis. Since toxicology screens do not routinely test for hallucinogens, obtaining a thorough history and physical examination is critical. Collateral information from families and friends will aid in narrowing the possible diagnoses. As is stressed several times above, evaluation must include a careful review of the use of other substances of abuse and their frequency of ingestion, including information gained from sources other than the patient. Formal thought disorders and affective psychoses should be considered, with relevant historical information sought to help rule in or out a primary psychiatric illness for the presenting condition. Any evidence for delirium needs careful continued evaluation and management, including infection, adverse medication reaction, metabolic disturbance, central nervous system tumor, stroke, and head injury. Finally, diagnosis should be distinguished from hallucinogen persisting perception disorder, which represents a re-experiencing of the perceptual disturbances of past hallucinogen intoxication (see above).

Treatment

Procedures for the treatment of recent hallucinogen intoxication should be followed as described above, and underlying etiologies for psychosis should be further investigated. In rare occurrences, the patient may require hospitalization as the prolonged reaction can persist for days.

Hallucinogens as Treatment Tools for Addiction?

Past research indicated a use for lysergic acid diethylamide in the treatment of alcoholism and drug dependence [4, 5, 8, 28, 37, 44, 51, 62].

Table 6 *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, fourth edition criteria: Substance-induced psychotic disorder

A. Prominent hallucinations or delusions, Note: Do not include hallucinations if the person has insight that they are substance induced.
B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
(1) the symptoms in Criterion A developed during or within a month of substance intoxication or withdrawal
(2) substance use is etiologically related to the disturbance
C. The disturbance is not better accounted for by a psychotic disorder that is not substance induced. Evidence that the symptoms are better accounted for by a psychotic disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced psychotic disorder (e.g., a history of recurrent non-substance-related episodes).
D. The disturbance does not occur exclusively during the course of delirium.
Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.
Code specific substance-induced psychotic disorder.
292.11: amphetamine (or amphetamine-like substance), with delusions;
292.12: amphetamine (or amphetamine-like substance), with hallucinations;
292.11: hallucinogen, with delusions;
292.12: hallucinogen, with hallucinations.
Specify:
With onset during intoxication: if criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome.
With onset during withdrawal: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, a withdrawal syndrome.

This promising research collapsed under the weight of federal de-funding, decreased access to test compounds, and political hostility to research involving drugs thought to foment the public unrest of the era [25].

In the 1980s, the indolealkylamine hallucinogen ibogaine was patented as a treatment of addiction [46], but it has remained an "underground" tool in America and elsewhere, with only limited research published to date [6, 49]. Ayahuasca, which contains dimethyltryptamine, has been proposed to help those seeking recovery within the religious practices of the União do Vegetal [26] and the Santo Daime Church [36], as well as to possibly "inoculate" teen members from engaging in the addictive use of drugs of abuse [12]. Similarly, anecdotal evidence exists that sacramental peyote taken within the prayer ceremonies of the Native American Church by Native Americans may assist in recovery from drug dependence and alcoholism [30, 31, 32, 35].

There is an ongoing, desperate need for effective treatments for alcoholism and other drug abuse and dependence disorders. The long-standing and continued religious use of hallucinogens suggests that some hallucinogens (combined with psychotherapeutic and socio-therapeutic procedures) may well be an effective psychopharmacologic intervention for these disorders. As research to evaluate hallucinogens for therapeutic use is no longer a major area of investigation, the few legitimate research groups in the United States and elsewhere will hopefully re-evaluate hallucinogens' potential for addictions as well as continue to encourage more colleagues to return to this field. It is also hoped that future research will avoid methodological flaws, which unfortunately made the studies of the 1950s and 1960s less reliable from today's perspective [5, 32, 57]. Without current, clearly favorable clinical research findings, hallucinogen "treatments" for drug dependence hold only aging speculative "promise"

and are not accepted for any medical indication, including for those seeking treatment for their problematic drug use.

Acknowledgments The authors greatly appreciate the editing assistance of medical student Sean Doherty of Cardiff University School of Medicine.

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Part IX
Molecular Genetics, Alternative Therapies, and Other Topics in the Treatment of Addiction

Molecular Genetics and the Treatment of Addiction

Lara A. Ray and Kent E. Hutchison

Contents

Overview

Substance use disorders represent complex phenotypes that result from the intricate interplay of genetic variation, neurobiological mechanisms, psychosocial variables, and environmental variables. To date, one of the least studied factors has been genetic variation. However, basic research on the human genome is progressing at a rapid pace, and investigations of genetic factors that influence the etiology and treatment of substance use disorders are now much more common. The promise of this research is that it may help scientists optimize the success of treatments by matching specific treatments with individuals who have specific genetic vulnerabilities. The ability to match a specific treatment with an individual who is most likely to benefit from that treatment is especially exciting because, while a number of treatment alternatives exist, the overall effectiveness of these treatments is quite modest and there are currently no objective criteria that can be used to match an individual with the treatment that is most likely to be effective. It is only a matter of time before much of the genetic variation that contributes to the risk of addiction is uncovered and, likewise, only a matter of time before clinicians begin to utilize genetic information to match individuals with the treatment that is safest and most likely to benefit them.

This chapter provides a critical review of the expanding literature with respect to molecular genetics and the treatment of addiction. First, we present a brief overview of key concepts in the genetics of addictions. Second, we provide a more extended review and discussion of pharmacogenetics and pharmacogenomics applied to addiction medicine. Recent studies of genetic differences and responses to pharmacological, and to a lesser degree psychosocial, treatments for addictions will be reviewed for various substances of abuse, including alcohol, nicotine, cocaine, and opiates. Third, we discuss practical

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_55,

and ethical issues in the translation of pharmacogenetics science into clinical practice. Fourth, we outline several future directions for the field of molecular genetics applied to the treatment of addictions. Finally, we present a summary and some concluding remarks.

Genetics and the Treatment of Addictions

Twin and adoption studies have suggested that approximately 50% of the variance in risk for developing alcohol dependence can be explained by genetic factors [24, 44]. Likewise, studies have demonstrated that genetic factors account for a significant portion of variance in drug use, abuse, and dependence [7, 27, 28, 45, 48, 92, 93]. The progression from initial use to abuse or dependence for substances such as marijuana and cocaine also appears to be largely due to genetic factors [46, 47].

Just as the etiology of substance use disorders appears to be under moderate genetic control, so does the response to pharmacotherapies. Broadly speaking, evidence for heritability of medication effects in psychiatry dates as far back as 1967, when heritable variation in plasma concentration of the tricyclic antidepressants, desipramine and nortriptyline, were first shown in twin and family studies [2, 30]. More recent research has also documented the heritability of response to typical antipsychotics [98], including differences in antipsychotic response among ethnic groups [1, 21]. As discussed in detail below, genetic factors also seem to play a role in response to pharmacotherapies, and perhaps psychosocial treatments, for substance use disorders.

After determining that genetic variation plays a substantial role in the etiology of addictive disorders and the response to treatment through family, twin, and adoption studies, the next step in genetics research often consists of identifying specific genetic variations that contribute to the etiology and response to treatment for these disorders. In many ways, research on genetics of addiction has already transitioned from establishing that genetic variables contribute to the variance in a disorder to identifying the specific genetic variables that actually contribute to the disorder.

Currently, there are two basic approaches to the identification of genetic variations that influence substance use disorders and/or treatment outcomes. The first is a hypothesis-driven approach, in which investigators develop a priori hypotheses based on what is known about the genetic variation and the neurobiology of the disorder or the mechanism of action for a specific treatment. For example, one might hypothesize that a specific genetic variation that influences the mu-opioid receptor expression might also predict acute responses to alcohol [8, 74] and the effects of a medication (e.g., naltrexone) that targets this receptor [3, 66, 78].

In many cases, it is more common to work with a gene for which function variations have yet to be identified. In this situation, a variation on the approach described above is to hypothesize that a gene is related to a specific aspect of a substance use disorder or the effects of a medication and then use special analytic approaches to probe genetic variation across the entire gene. This approach is commonly known as a haplotype-based approach, and is designed to capture most of the genetic variation across the gene even when the function variations have not been identified. To that end, "tag single nucleotide polymorphisms" are often used as they allow scientists to capture genetic variation in various loci by genotyping fewer, but informative, markers. More specifically, tag single nucleotide polymorphisms are selected on the basis of patterns of linkage disequilibrium that indicate whether several polymorphisms are highly correlated, in which case, instead of having to genotype all markers, scientists can identify a few that strongly predict genetic variation in a given area or locus. This approach has become increasingly accessible due to the availability of bioinformatics resources, most notably results from the International HAPMAP Project, which have been made publicly available in the user-friendly HAPMAP Project Web site (http://www.hapmap.org/). The next step after

identifying tag single nucleotide polymorphisms for areas of interest is often to build haplotypes, which describe common patterns of DNA sequence variation. In fact, the objective of the HAPMAP Project is to develop a haplotype map of the human genome, which in turn can aid scientists in finding genes affecting health, disease, and responses to medications and environment [22, 41, 90]. A detailed review of haplotype-based techniques in pharmacogenetics is beyond the scope of this chapter and can be found elsewhere [57].

Finally, a more recent approach is to conduct exploratory genome-wide analyses to identify genetic variation that influences substance use disorders or responses to medications. The genome-wide association study is currently in vogue and represents one of the most cutting-edge approaches in terms of identifying sources of genetic variation that may eventually be used to predict response to treatment. A genome-wide association study utilizes a high-density single nucleotide polymorphism array to generate data on more than one million genetic markers (e.g., using the Illumina 1 M array). This vast array of genetic data can then be analyzed in combination with a set of phenotypes. A number of reviews have been published recently on the advantages, disadvantages, limitations, and recommendations associated with this approach [11, 68, 89]. One obvious problem with this approach is the sheer number of statistical tests and the resulting increase in Type I error that may lead to false positives. A corollary is the requirement of strict statistical corrections and the need for massive sample sizes. To date, there have been a number of genome-wide association study reports in the psychiatric genetics literature, including major depressive disorder [9], bipolar disorder [19], and schizophrenia [65], but only one that involves a substance abuse disorder, namely nicotine dependence [95]. While genome-wide association is the approach du jour and has generated much excitement in the field, it is important to note that genome-wide association studies represent a transition to even more difficult and time-consuming work. Once new genetic variations are identified, models will need to be developed and hypothesis-driven research will be needed to translate the effect of genetic variation uncovered in the genome-wide association studies regarding the effect of the genetic variations from the molecular level, to the cellular level, to the systems level, and to the behavioral level in order to understand the implications of these findings for the etiology, prevention, and treatment of substance use disorders. This translation will likely lead to new findings on as yet unknown neuronal mechanisms that influence the development of substance use disorders and lead to new targets for pharmacotherapies as well as generating information about which individuals will be most likely to respond to those new pharmacotherapies.

Pharmacogenetics and Pharmacogenomics

Pharmacogenetics is a field of research that seeks to understand individual differences in the metabolism and efficacy of medications. As described by Vogel [97], pharmacogenetics is the study of heritable differences in the metabolism and activity of exogenous agents, including medications and environmental toxins. Current pharmacogenetics research focuses on identifying genetic factors that account for variability in pharmacotherapy effects, in terms of both pharmacodynamics and efficacy [16, 61]. In recent years, the term pharmacogenomics has been defined [81] as the application of genomics to the study of pharmacogenetics. In brief, the distinction between the two terms refers to the methodological and theoretical approach such that pharmacogenetics investigations are generally hypothesis driven and focus on a few loci at a time. Conversely, pharmacogenomics investigations include the use of high-throughput genotyping and genome-wide association approaches to understanding genetic determinants of pharmacotherapy response. In essence, the objective of pharmacogenomics is the same as pharmacogenetics, which is to elucidate genetic variants that influence the efficacy and safety of

pharmacotherapies. For simplicity, we will refer simply to pharmacogenetics in this chapter.

The field of pharmacogenetics has grown rapidly and has greatly benefited from advancements in molecular genetics tools for identifying gene polymorphisms, developments in bioinformatics and functional genomics, and new findings from the human genome project. The foremost goal of this line of research is to optimize pharmacotherapy by identifying genetic factors that predict who is more likely to respond to certain pharmacotherapies and who will not respond, thereby matching individuals to medications on the basis of genetic factors. Genetic factors can account for individual differences in medication toxicity and response in many ways. Genetic polymorphisms may lead to functional differences in medication metabolism and disposition, such as functional differences in enzyme activity or medication transporters. Alternatively, genetic polymorphisms may impact the target of a medication, such as a particular receptor. An example of the first case is a polymorphism of the CYP2D6 gene, which is involved in the availability of specific medication-metabolizing enzymes associated with one's response to opioid painkillers, such as codeine or morphine. Individuals who are homozygous for the nonfunctional CYP2D6 alleles were found to be resistant to the analgesic effects of opioid painkillers [70].

On the other hand, genetic polymorphisms involved in a medication's target may also impact one's response to pharmacotherapy. For example, polymorphisms of the dopamine D4 receptor gene (DRD4) have been associated with differential response to antipsychotic medications [10]. There is also a growing literature on the pharmacogenetics of antidepressant medications [49]. Specifically, research has suggested that the functional polymorphism of the serotonin transporter gene located in the 5′ upstream regulatory region consisting of a 44-base pair insertion/deletion, which results in a long or short variant, predicts response to various selective serotonin reuptake inhibitors, including fluoxetine [71], fluvoxamine [88], and paroxetine [99]. Carriers of the long allele of the serotonin transporter promoter polymorphism have better clinical response to antidepressant medications compared with individuals who are homozygous for the short allele, which results in two-fold decreased expression and transport activity of the receptor in vitro [32]. These results suggest that pharmacogenetics may soon inform a more targeted use of antidepressant medications. In addition to medications' efficacy, pharmacogenetics research has focused on identifying susceptibility loci contributing to adverse effect profiles and medications' toxicity, thereby enhancing the safety profile of pharmacotherapies. Next, we will review pharmacogenetic studies in the field of addictions to various substances of abuse.

Alcohol

Several studies to date have investigated genetic polymorphisms in the context of pharmacotherapies for alcohol dependence. Naltrexone, a mu-opioid receptor antagonist, is one of the very few pharmacotherapies currently approved for the treatment of alcoholism by the United States Food and Drug Administration. From a pharmacogenetics perspective, there has been recent interest in the gene coding for mu-opioid receptors (OPRM1), as they represent a primary target of naltrexone. More specifically, studies have focused on the Asn40Asp mutation of the OPRM1 gene, given evidence that this nonsynonymous mutation leads to an amino acid change, which in turn codes for more potent receptors. Human laboratory studies have shown that the Asp40 allele of the OPRM1 gene is associated with greater sensitivity to the reinforcing effects of alcohol [74] and greater neural activation in the mesocorticolimbic structures following a priming dose of alcohol [20].

In a pharmacogenetic study of naltrexone, Oslin and colleagues [66] found that the Asn40Asp allele of the OPRM1 gene was associated with clinical response to naltrexone for the treatment of alcohol dependence. The relationship was such that individuals with at least one copy of the Asp40 variant showed lower relapse rates and longer time to return to heavy

drinking when treated with naltrexone, as compared with homozygotes for the Asn40 allele [66]. These findings have been recently replicated and extended in the multisite COMBINE Study, such that carriers of the Asp40 allele of the OPRM1 gene had better clinical response to naltrexone, in combination with medication management, as compared with homozygotes for the Asn40 allele [3]. A double-blind, placebo-controlled laboratory trial of naltrexone (50 mg) found that carriers of the Asp40 allele of the OPRM1 gene showed significantly greater naltrexone-induced blunting of the alcohol "high", as compared with individuals who were homozygous for the Asn40 allele [78]. These findings suggest that the differential clinical response to naltrexone may be due to differential blunting of alcohol-induced reward as a function of genotype and propose a mechanism for this important pharmacogenetic relationship. Nevertheless, there have been null findings regarding the association between this functional polymorphism and the efficacy of naltrexone for alcoholism [33] such that further work is necessary before these findings can be translated into clinical practice.

Limitations notwithstanding, the pharmacogenetics of naltrexone and the putative moderating effects of a functional single nucleotide polymorphism of the OPRM1 gene represent an interesting line of work that is both promising and exciting from a pharmacogenetics perspective. In this case, functional variation in a gene coding for a medication (i.e., naltrexone) target, namely mu-opioid receptors, may be used to predict the efficacy of a pharmacotherapy. This case most likely represents an exception, rather than the rule, in pharmacogenetics research as most pharmacotherapies do not have such targeted neurobiological effects and the functional significance of most single nucleotide polymorphisms are not well characterized.

Using a similar hypothesis-driven approach, a series of pharmacogenetic studies have tested the association between olanzapine, a medication that targets dopamine receptors, alcohol craving, and a polymorphism of the dopamine D4 receptor gene (DRD4 variable number tandem repeat) [37–39]. One study found an association between the 7-repeat allele of the DRD4 variable number tandem repeat polymorphism and increased craving for alcohol after a priming dose of alcohol [36]. Another study found that olanzapine decreased craving after a priming dose of alcohol in a non-clinical sample of college drinkers [39]. Finally, results from a recent clinical trial revealed that the efficacy of olanzapine in the treatment of alcohol dependence was moderated by this genetic variation, such that individuals with at least one copy of the long allele showed greater reductions in cue-elicited craving and greater decreases in alcohol consumption during the 12-week clinical trial, as compared with individuals who were homozygous for the short allele [37]. This genetic variation has also been associated with increased activation of mesocorticolimbic regions during the presentation of alcohol cues [20]. Together these series of laboratory and clinical trials have established a relationship between a polymorphism of the DRD4, craving for alcohol in the laboratory, and response to a medication that targets dopamine receptors.

The approach in this series of studies of olanzapine for alcoholism was theory driven and focused on intermediate phenotypes for alcoholism, in this case alcohol craving, rather than the diagnostic phenotype of alcohol dependence per se. There are important advantages to a theory-driven pharmacogenetics approach, such as the ability to answer more specific questions about the mechanisms of action of pharmacotherapies, genetic variants, and biobehavioral risk makers of complex disorders, such as alcoholism. Importantly, theory-driven approaches can be complementary to data-driven pharmacogenomics investigations, which are likely to become increasingly accessible given recent advances in DNA genotyping technology.

Nicotine

Currently, there are two non-nicotine pharmacotherapies approved by the United States

Food and Drug Administration for the treatment of nicotine dependence, namely bupropion hydrochloride and varenicline. In addition, there are five Food and Drug Administration-approved nicotine replacement therapies, which vary mostly in terms of their delivery kinetics; these include transdermal patch, gum, lozenge, inhaler, and nasal spray. Several candidate genes have been subjected to pharmacogenetic studies, mostly those of nicotine replacement therapies and bupropion as described in recent reviews of the pharmacogenetics of smoking cessation [6, 64, 80]. Specifically, pharmacogenetic studies of nicotine dependence have examined genes underlying the metabolism of nicotine, focusing primarily on the cytochrome P450 2A6 gene (CYP2A6). This gene codes for the primary enzyme that converts nicotine to cotinine and cotinine to 3-hydroxycotinine. In a study of transdermal patch and nasal spray nicotine replacement therapies, at the same levels of nicotine replacement, carriers of CYP2A6 alleles coding for a slower metabolism were found to have higher plasma nicotine concentrations following 1 week of the nicotine patch than normal metabolizers [59]. Those differences were not seen using the nasal spray, and at 6-month follow-up, slow metabolizers had higher quit rates in the transdermal patch condition, as compared with normal metabolizers [54]. However, the results have not been consistent, and a study found that slow metabolizers had higher relapse rates when treated with the nicotine patch [67].

Nicotinic receptor genes have also been subjected to pharmacogenetic investigations. Nicotine binds to nicotinic acetylcholine receptors, which are ligand-gated ion channels for which there are several subunits. Allelic variation in the gene coding for the nicotinic acetylcholine receptor's α4 subunit (CHRNA4) has been associated with nicotine dependence [18, 56]. More recent molecular work has suggested that certain single nucleotide polymorphisms in the CHRNA4 gene are functional and related to smoking cessation during nicotine replacement therapy [35]. Although promising, these findings await replication. Likewise, a series of studies have examined the role of functional genetic variation in the DRD2 in response to bupropion and nicotine replacement therapy [42, 52]. Results revealed that the DRD2–141C Ins/Del genotype was associated with treatment response to bupropion, such that smokers homozygous for the Ins C allele had a more favorable response to treatment compared with those carrying the Del C allele. Conversely, regardless of nicotine replacement therapy type, those carrying the Del C allele had higher quit rates from nicotine replacement therapy compared with those homozygous for the Ins C allele [52]. Additional polymorphisms that have received attention as putative genetic moderators of smoking cessation in response to nicotine replacement therapies and bupropion include dopaminergic genes (e.g., the Val/Met single nucleotide polymorphism of the catechol-*O*-methyltransferase gene) [53], opioidergic genes (e.g., Asn40Asp single nucleotide polymorphism of the OPRM1 gene) [55, 79], and serotonergic genes (e.g., the serotonin transporter promoter polymorphism) [63].

Perhaps one of the more exciting new developments in the pharmacogenetics of smoking cessation is a series of genome-wide association studies of smoking cessation with bupropion and nicotine replacement therapy [95]. These studies revealed that genetic variants in quit-success were likely to alter cell adhesion, enzymatic, transcriptional, structural, and protein-handling functions. The genes identified through these genome-wide association studies had modest overlap with genes associated with addictions and memory processes. Clearly, as noted above, there are limitations to the genome-wide association approach, and these results should be interpreted with caution until replicated in an independent sample.

Cocaine

Currently, there are no Food and Drug Administration-approved pharmacotherapies for the treatment of cocaine dependence; nor have there been any compelling findings with respect to specific genetic variations that influence the

trajectory of cocaine dependence or treatment outcomes. However, several pharmacotherapies are currently under study for stimulant use disorders, and some of the most promising ones include gamma-aminobutyric acid agents (e.g., topiramate, tiagabine, baclofen, and vigabatrin) and agonist replacement agents such as modafinil and methylphenidate [43]. Nevertheless, much work has yet to be done in identifying efficacious pharmacotherapies for cocaine and stimulant dependence before pharmacogenetic investigations can take place.

Opiates

Opiate addiction is treated pharmacologically through opiate agonists, antagonists, and partial agonists; for a review see [29]. The first medication for opioid addiction was methadone, a selective synthetic opioid agonist [12]. Buprenorphine is another synthetic opiate that functions as a partial agonist at mu-opioid receptors and an antagonist at kappa-opioid receptors [51]. Both methadone and buprenorphine are equally effective for maintenance treatment of heroin dependence [60]. Methadone and buprenorphine are metabolized by CYP3A4; however, buprenorphine is metabolized to a much lesser degree than methadone by CYP2D6. Studies have found that Caucasians who lack CYP2D6 function have a poor metabolizer phenotype, which in turn is protective against opiate dependence [94]. Nevertheless, when slow opioid metabolizers go on to develop opioid addiction, they tend to respond well to methadone treatment, whereas opioid-dependent individuals with the CYP2D6 genotype coding for the "ultra rapid" opioid metabolism are less responsive to the withdrawal relief afforded by methadone maintenance therapy [69] and respond better to buprenorphine, which is not as significantly metabolized by CYP2D6. The case of pharmacogenetics of opioid addiction is an interesting one in that what was learned about the pharmacogenetics of responsiveness to opiates for pain management purposes (described above) has informed the clinical literature on the use of opiates for the treatment of opiate addiction and has ultimately led toward the optimization of pharmacotherapy for opioid dependence.

An Intermediate Phenotype-Driven Pharmacogenetics Approach

Recent research has increasingly recognized the heterogeneity of diagnostic phenotypes and argued for the development of more discrete and homogeneous phenotypes, or intermediate phenotypes, for psychiatric disorders of complex genetics [25, 26], including addictions [13, 34]. Recently, intermediate phenotypes have been further refined as translational phenotypes, which emphasizes the role of the phenotype in translating the effect at the genetic level to the clinical level [40]. An ideal translational phenotype is one that is narrowly defined and biologically based with a plausible link to the gene as well as the clinical presentation of the disorder. The use of intermediate phenotypes for disorders of complex genetics has allowed for progress in genetic association studies, and importantly, this approach not only increases power to detect genetic effects but also allows scientists to ask different research questions about the neurobiology and mechanisms underlying disease processes and pharmacotherapy response. When applied to pharmacogenetics research, intermediate or translational phenotypes often involve examining mechanisms of medication response that go beyond clinical outcomes. Examples of intermediate phenotypes for substance use disorders include craving for a substance, withdrawal mechanisms, substance-induced reward, reinforcing value of the substance, and response inhibition processes, to name a few.

Based on the literature on intermediate phenotypes for addictions and their potential to advance etiological and treatment approaches to these disorders, a conceptual model that integrates translational addiction phenotypes, genetic factors, and pharmacological treatments

for addictions is clearly warranted [77]. In this model, phenotypes, such as subjective responses to alcohol, represent an important translational link between genetic variations and the effects of medications and clinical outcomes. More specifically, this theoretical framework may be used to improve our understanding of pharmacotherapies for addictions in several ways (Fig. 1). First, intermediate phenotypes for alcoholism, such as alcohol craving and subjective responses to alcohol, have been shown to predict drinking behavior and the risk for developing alcohol use disorders [34, 36, 73, 83, 91]. Second, medications found to operate at the level of intermediate phenotypes, such as craving and subjective responses to alcohol [62, 75], may ultimately be effective in reducing drinking. In a recent example of this approach, a laboratory study found that aripiprazole increased the sedative effects of alcohol and decreased its euphoric and stimulant properties; those effects, in turn, are thought to capture the mechanisms of action of aripiprazole for alcoholism [50]. Third, genetic variants appear to underlie the expression of alcohol phenotypes such as craving [36, 58, 96] and subjective responses to alcohol [31, 74, 82]. Fourth, genetic variants associated with alcohol intermediate phenotypes may, in turn, be used to predict responses to pharmacotherapies thought to affect those phenotypes [36, 37, 74, 75].

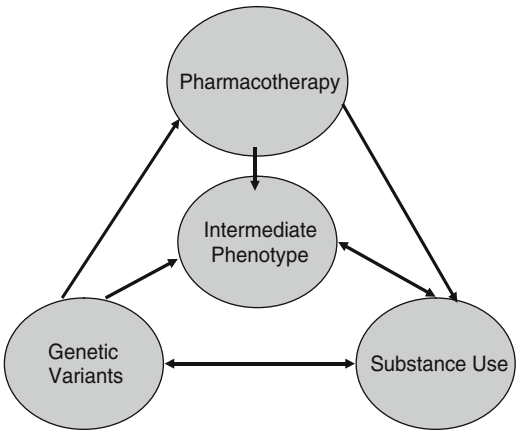

Fig. 1 An intermediate phenotype-driven pharmacogenetics model for addiction treatment

In sum, we have proposed that a theory-driven pharmacogenetic approach can be used to enhance the pharmacological treatment of alcoholism [77]. This approach is interdisciplinary and translational by definition, as it integrates aspects of behavioral genetics, pharmacology, and clinical and experimental science. Focusing on theory-driven addiction intermediate phenotypes and the genetic and neurobiological factors underlying these phenotypes may help us elucidate the mechanisms of action of pharmacotherapies, as well as moderators of response. Most importantly, this approach has the potential to enhance the translation of basic science to treatment, as it more directly connects translational phenotypes and genetic variants to pharmacotherapies for addictions. The intermediate phenotype-driven pharmacogenetics model described herein offers a potentially useful framework for better understanding how addiction phenotypes and genetic factors concomitantly influence responses to pharmacotherapies. Similar approaches may be useful in optimizing psychosocial interventions by targeting more specific and narrowly defined components of the risk for substance use disorders (i.e., prevention efforts) or the clinical syndrome itself (i.e., treatment efforts).

Optimizing Psychosocial Treatments Through Genetics

Molecular genetics may also inform psychosocial treatments for substance use disorders. In a recent example of the application of behavioral genetics to optimizing treatment, Bauer and colleagues [5] reported that variation within the GABRA2 gene, thought to increase the risk for alcoholism [14], predicted the response to the psychosocial interventions tested in Project MATCH. Specifically, the low-risk allele was associated with more robust differences in drinking outcomes in the trial, enhancing the superiority of 12-step facilitation over cognitive behavioral therapy and motivational enhancement therapy [5]. A recent study examined the

DRD4 variable number tandem repeat polymorphism, previously linked to alcohol use and cue reactivity [36], possibly through an underlying impulsivity phenotype [15, 72], and response to a brief motivational intervention [17]. The findings suggested that heavy-drinking college students who were carriers of the long allele of the DRD4 variable number tandem repeat polymorphism were more impulsive and less likely to benefit from the brief motivational intervention for drinking problems. In summary, these results indicate that the assessment of genetic liability may also be important to studies of the efficacy of psychosocial interventions. More broadly, these results allude to the importance of integrating biological and psychosocial variables to capture more fully the clinical phenomenon of addiction and its treatment.

Translating Pharmacogenetic Approaches into Practice

In anticipation of the translation of pharmacogenetic approaches into practice, issues of physicians' attitudes and training have received recent attention, particularly in the field of smoking cessation, a highly prevalent chronic condition and public health concern. In a national mailed survey study of 2,000 primary care physicians in the United States, the self-reported likelihood that physicians would offer a new test to tailor smoking cessation treatment ranged between 69 and 78%, across various scenarios [87]. Describing the test as genetic versus non-genetic decreased the likelihood of physicians offering the test across all scenarios. Moreover, physicians were less likely to offer the test when the scenario indicated that the same genotypes used for treatment tailoring may identify individuals at risk for other conditions (e.g., cocaine or alcohol addiction), differed in allele frequency by race, and may also predict individuals predisposed to become addicted to nicotine [87]. The authors concluded that physicians' responses may reflect an assumption of greater complexity in genetic testing, as compared with other laboratory tests, for example. A broader survey of genetic testing in clinical practice, non-specific to addictions, revealed that physicians serving minority patients were less likely to use, and refer for, genetic testing in their practice [85]. In short, it has been suggested that several steps are necessary to facilitate the translation of pharmacogenetics science to practice, especially in primary care, including issues such as physicians' training and experience, organizational-level policy, and infrastructure, including reimbursement for pharmacogenetic testing and protections of privacy and against discrimination [84, 86]. Those practical and ethical issues warrant further attention as they are critical to the integration of pharmacogenetic treatment strategies for addiction.

Future Directions of Molecular Genetics and Addiction Treatment

In many ways, the future impact of genetic research on addiction medicine will depend on the substance use disorder in question. For example, there are currently no medications approved for cocaine dependence but a number that have been approved for alcohol dependence. The opportunity to make progress with respect to identifying genetic variation that influences treatment effectiveness for cocaine dependence is limited by the lack of approved medications for cocaine dependence. Additional directions for future research include:

a) There is great need and opportunity to develop robust brain-based translational phenotypes for each substance use disorder, thereby examining specific mechanisms of genetic risk and therapeutics for various substances of abuse [40]. Brain-based translational phenotypes may also be informative in investigations of pharmacotherapies for addictions as they can advance the knowledge on the neuropharmacological mechanisms of medications' efficacy as well as help identify

genetic factors that may operate at the neural level, leading to differential clinical response to a given pharmacotherapy.

b) Genome-wide association studies with refined behavioral and brain-based phenotypes are necessary to isolate important sources of genetic variation. These initial findings of genome-wide association studies can lead to more refined genetic analyses, including custom genetic panels designed based on the more consistent findings of genome-wide association studies.

c) Laboratory-based studies of candidate medications using behavioral and brain-based translational phenotypes are needed to inform large-scale clinical trials and address more specific and mechanistic questions regarding medications' efficacy. Specifically, these phenotypes not only enhance power to detect genetic effects, they also allow scientists to answer more nuanced questions regarding the pathophysiology of addictive disorders and their pharmacological treatment [76].

d) According to recent research, genotypes used to tailor the pharmacological treatment of alcohol and nicotine dependence may vary in allele frequencies across populations [23]. For instance, the Asn40Asp allele of the OPRM1 gene, thought to predict clinical response to naltrexone for the treatment of alcoholism, has a minor allele frequency of approximately 20–25% in individuals of European ancestry, 50% in Asians, and <5% in African-Americans [4]. If treatment recommendations are to be developed based on genetic variants, careful attention to issues of allele frequency across racial and ethnic groups is essential in ensuring that appropriate recommendations are made and that the ethical principle of beneficence is upheld across populations.

e) Clinical scientists need to integrate multiple pieces of information to determine which medications have promise, which genetic variables are likely to predict the effectiveness of those medications, and for which population. Clearly, much work has yet to be done before these findings are translated into clinical practice.

f) Educating and training physicians to implement pharmacogenetic treatment strategies in clinical practice is critical to the translation of science into practice. As discussed above, much work remains to be done in the area of physicians' training and education before pharmacogenetic findings for addictions can be disseminated into clinical practice [84, 87].

Summary and Conclusions

Translational approaches such as the ones described in this chapter have the potential to inform clinical practice by identifying individuals who are more likely to benefit from a given pharmacotherapy on the basis of genetic factors. At present, efforts at optimizing pharmacotherapy on the basis of genetic factors, often referred to as personalized medicine, remain incipient, and considerable research is required before these findings can be translated into clinical practice. Important issues such as the differential frequency of certain gene variants among various ethnic groups and the clinical significance of these differential treatment responses must be evaluated carefully in future pharmacogenetic trials and before translating these findings to clinical practice. Likewise, as the technology for high-throughput genotyping becomes increasingly accessible, the use of genomic approaches to the study of pharmacotherapy response will become more widespread, hopefully leading to more consistent findings that can be more rapidly translated into clinical practice. Limitations notwithstanding, research efforts in pharmacogenetics and pharmacogenomics hold considerable promise for optimizing treatment for a host of medical and psychiatric disorders, including addiction.

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Physical Considerations for Treatment Complications of Alcohol and Drug Use and Misuse

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Introduction

The effects of chronic ingestion of alcohol and other substances of abuse vary considerably and depend on the concentration and dose, together with various other factors, such as nutritional status, gender, and ethnicity. The present chapter analyzes the main medical consequences related to substance abuse, particularly alcohol, nicotine, opioids, cocaine, amphetamine, and benzodiazepines. The effects of these substances on the liver, gut, pancreas, nervous system, cardiovascular system, and endocrine system will be discussed. The link between substance abuse disorders and tumors will also be reported, as well as the relationship between substances of abuse and nutrition and body composition.

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_56,

Liver

Alcohol

Alcoholic liver disease is one of the major medical complications of alcohol abuse [185]. In particular, 80% of heavy drinkers develop steatosis, 10–35% develop alcoholic hepatitis, and approximately 10% will develop cirrhosis [185]. Steatosis represents an abnormal retention of lipids accumulated in vesicles that displace the cytoplasm of the hepatocytes. Although liver function is usually normal, if alcohol abuse continues steatosis may progress to cirrhosis [185] (Table 1).

It has been suggested that 15–20 years of alcohol abuse are necessary to develop alcoholic hepatitis, which usually results in cholestasis [185]. When alcohol abuse is persistent for a long period and generally follows a regular pattern, an individual can often develop cirrhosis. Alcoholic liver disease represents the most common cause of liver cirrhosis in the Western world [177, 178]. Liver damage is related to the toxicity of alcohol being linked to its metabolism via alcohol dehydrogenase. Alcohol dehydrogenase converts nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide-reduced form, which contributes to hyperuricemia, hypoglycemia, and hepatic steatosis by inhibiting lipid oxidation and promoting lipogenesis [118]. Another pathway of ethanol metabolism is the microsomal ethanol oxidizing system. The activity of its main enzyme, cytochrome P4502E1 (CYP2E1), and its gene are increased by chronic consumption, resulting in metabolic tolerance to ethanol [118]. Twin studies suggest a genetic component to disease susceptibility [94]. In white people, associations between alcoholic liver disease risk and polymorphisms of the genes encoding the cytochrome P-450 have been shown [185]. The activity of the cytochrome P4502E1 is also associated with the generation of free radicals, with resulting lipid peroxidation and membrane damage as well as depletion of mitochondrial reduced glutathione and its ultimate precursor—methionine activated to *S*-adenosyl-*L*-methionine [118]. The involvement of free radical mechanisms in the pathogenesis of alcoholic liver disease is demonstrated by the detection of lipid peroxidation markers in the liver and the serum of alcohol-dependent individuals, as well as by experiments in alcohol-fed rodents that show a relationship between alcohol-induced oxidative stress and the development of liver pathology [9, 15, 19]. In particular, oxidative stress promotes hepatocyte necrosis as well as a pro-apoptotic action via tumor necrosis factor-alpha. Furthermore, oxidative mechanisms can contribute to liver fibrosis by triggering the release of pro-fibrotic cytokines and collagen gene expression in hepatic stellate cells [19]. From a clinical point of view, alcohol-related damage can be present without any apparent symptoms or signs of liver disease. Otherwise, non-specific clinical features can include nausea, vomiting, or fatigue. When liver cirrhosis is present, typical cirrhosis-related signs and symptoms can include jaundice, ascites, encephalopathy, or upper gastrointestinal bleeding. Although two meta-analyses suggest that corticosteroids are beneficial in improving short-term survival in individuals with severe alcoholic hepatitis [96], the utility of using corticosteroids in the treatment of

Table 1 Main hepatic features in subjects with substance abuse or dependence

Substance	Main feature(s)	Other feature(s)
Alcohol	Enzyme induction; steatosis	Chronic liver disease; acute liver failure; liver cirrhosis
Nicotine	Enzyme induction	Risk factor for: gallstones; PSC; HCC
Opioids	Hepatotoxicity	High risk factor for hepatitis viruses, especially HCV
Cocaine	Hepatotoxicity	Impaired hepatic perfusion
Amphetamine	Hepatotoxicity	Chronic liver disease; acute liver failure
Benzodiazepines	Enzyme induction	Hepatotoxicity

PSC primary sclerosing cholangitis, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus

advanced alcoholic liver disease is still debated. In particular, while the short-term mortality is reduced, the benefits in terms of long-term mortality are still unknown. Propylthiouracil has also been proposed because it abolishes the ethanol-induced increase in liver oxygen consumption after long-term alcohol consumption [38]. S-adenosyl-L-methionine dietary supplement therapy has been used in alcoholic liver disease as it replenishes liver mitochondrial glutathione levels [49]. Acute alcohol hepatitis can be present in some cases of acute alcohol intoxication. Based on the assumption that tumor necrosis factor has a role in the pathogenesis of alcoholic liver disease, some recent studies have suggested a role of infliximab and pentoxifylline in alcoholic liver disease. Infliximab is an anti-tumor necrosis factor antibody [176], while pentoxifylline is a non-selective phosphodiesterase inhibitor that has a moderate anti-cytokine effect attributed to reduced transcription of the gene that encodes tumor necrosis factor [165]. However, further studies are needed to confirm these preliminary results. Orthotopic liver transplantation represents an option when liver cirrhosis is present. Survival after a liver transplant for alcoholic cirrhosis is similar to—or even better than—that for other end-stage liver diseases [176, 185]. Abstinence for at least 6 months before transplantation is required. However, several ethical concerns are still present due to the limited availability of liver transplants and the risk of relapse after the transplantation [176, 185]. Independent of the stage of disease, abstinence from alcohol is the cornerstone of management. Accordingly, total alcohol abstinence can improve the histology and/or survival of individuals with alcoholic liver disease [176] and the clinical outcome of all stages of alcoholic liver disease [59]. Persistent alcohol intake in those with alcoholic cirrhosis is associated with a significant risk ratio of death [150] due to bleeding esophageal varices, infection, renal failure, and/or hepatic failure [191]. In recent decades, several medications able to reduce alcohol craving and, consequently, to increase abstinence and prevent alcohol relapse have been evaluated—i.e., naltrexone, acamprosate, and topiramate [10, 11]. However, trials investigating anti-craving medications typically exclude individuals with high levels of transaminases and/or advanced liver disease [24, 72]. Furthermore, naltrexone is contraindicated in those with liver disease due to its hepatic metabolism and reports of medication-related hepatic injury [27]. A more recent compound that is potentially useful in the treatment of alcohol dependence is the gamma-aminobutyric acid-B agonist baclofen [13]. Baclofen is mainly eliminated by the kidney. No hepatic side effects have been reported in treated individuals. A recent trial demonstrated the efficacy and safety of the gamma-aminobutyric acid-B baclofen in the treatment of alcohol-dependent individuals affected by liver cirrhosis [14]. This last study suggested that baclofen is effective at promoting alcohol abstinence in alcohol-dependent individuals with liver cirrhosis and is well tolerated [14]. Due to the lack of hepatic side effects, baclofen may have an important role in the treatment of these individuals [73].

Nicotine

Several preclinical studies suggest an influence of nicotine on the hepatic enzymatic systems. For example, the chronic exposure of rats to cigarette smoke does not alter hepatic biotransformation processes [81].

However, in a rat model of cirrhosis, a reduction of nicotine metabolism has been observed and linked to the decreases in cytochrome P450 and flavin-containing mono-oxygenase protein expression levels [137]. Clinical studies have often been performed considering both smoking and alcohol consumption. Whitehead et al. [187] evaluated a large population of 46,775 men and showed a joint effect of cigarette smoking and alcohol consumption in increasing the levels of gamma-glutamyl transferase, while alcohol but not cigarette smoking was related to an increase of transaminases [187]. In other words, nicotine is able to modify the hepatic enzymatic system but not to induce liver damage. Consistently, smoking does not appear to be a risk factor for cirrhosis of the liver [25].

On the other hand, a link between smoking and hepatocellular carcinoma has been suggested since constituents of cigarette smoke are hepatic carcinogens in animals [193]. Cigarette smoking has been suggested as an important risk factor for primary sclerosing cholangitis and gallstones, although in the latter case other co-factors should be taken into account, such as gender, alcohol consumption, overweight, etc. [25]. Finally, there is growing interest in the role of nicotine in those individuals with liver disease who are undergoing surgical procedures, particularly orthotopic liver transplantation. In a recent study [62], 60% of orthotopic liver transplantation recipients reported a lifetime history of smoking, with 15% reporting smoking post-orthotopic liver transplantation. Of smokers who quit before orthotopic liver transplantation, 20% reported relapse to smoking post-orthotopic liver transplantation. This observation has been subsequently confirmed by DiMartini and colleagues [60], who showed that individuals with alcoholic liver disease resume smoking early post-orthotopic liver transplantation, increase their consumption over time, and quickly become tobacco dependent.

Opioids

Preclinical studies show that opioid substances, such as morphine, heroin, meperidine, and methadone at therapeutic doses, do not usually produce irreversible damage to human hepatocytes, while opiate doses during tolerance or abuse may be a cause of liver dysfunction [79]. However, it has also been noted that chronic use at therapeutic doses of opioids such as tramadol and, most of all, morphine for the management of chronic pain increases liver damage via oxidative stress and induction of apoptosis [148]. Consistent with the preclinical findings, intravenous drug abusers are commonly found to have altered transaminases [186]. However, from a clinical perspective, the most important implications of opioid abuse and dependence are related to the high prevalence of hepatitis infection. In fact, over 90% of intravenous heroin addicts carry the hepatitis C virus [171]. Accordingly, a hepatitis C virus-related elevation of the liver enzyme can be present, along with several stages of liver damage leading to cirrhosis [171]. Furthermore, several extrahepatic clinical features can be present (e.g., immune suppression, collagen diseases, lymphoma, and leukemia) and included in the so-called "hepatitis C virus syndrome" [171]. The hepatitis B virus may hold a similar chronic and degenerative course [171].

Cocaine

Animal data show cocaine-induced liver damage including periportal and portal damage and elevated transaminases [153]. In subjects using cocaine, acute hepatotoxicity and hepatocellular necrosis have been described [80], perhaps via oxidative stress [163]. However, because cocaine is a sympathomimetic, impaired hepatic perfusion potentially may be a contributing factor together with other conditions (e.g., rhabdomyolysis) that are often present in subjects with cocaine abuse [163]. Interestingly, the concurrent use of cocaine and alcohol produces another psychoactive substance called cocaethylene and can induce significant liver damage [23].

Amphetamine

Methylenedioxymethamphetamine (ecstasy) and amphetamine abuse can be associated with serious liver clinical features. Intoxication with amphetamine or methylenedioxymethamphetamine can be associated with severe hepatotoxicity [100]. Also, chronic abuse of amphetamines/methylenedioxymethamphetamine can be associated with either subclinical liver damage [102] or cholestatic chronic liver damage [100]. Histologic features include confluent necrosis and ballooning degeneration in centrilobular zones [102]. The use of steroids has been suggested according to a possible immune-mediated component of amphetamine-related hepatic damage, while the benefit/risk ratio of

orthotopic liver transplantation for fulminant hepatic failure is still controversial [100].

Benzodiazepines

Liver alterations can be present in subjects abusing benzodiazepines, especially those with a liver metabolism like diazepam and chlordiazepoxide. Subjects with benzodiazepine abuse or dependence can present with an increase of gamma-glutamyl transferase, reflecting the chronic enzymatic induction [91]. With a much lower frequency, benzodiazepines such as diazepam and chlordiazepoxide can induce cholestatic hepatotoxicity by a hypersensitivity mechanism [163]. Furthermore, the use of benzodiazepines needs to be evaluated carefully in those alcohol-dependent individuals with liver damage, taking into account the possibilities of both dual substance abuse (alcohol and benzodiazepines) and the need to administer benzodiazepines to treat alcohol withdrawal symptoms.

Gut and Pancreas

Alcohol

The effects of alcohol on the gastrointestinal apparatus include those on the esophagus, stomach, small bowel, colon, and pancreas. Excess alcohol ingestion at the esophageal level is able to induce the Mallory-Weiss syndrome due to vomiting. In the Mallory-Weiss syndrome, 60–80% of patients are seen to have consumed important amounts of alcohol in the hours before [36]. Gastroesophageal reflux is also facilitated in these individuals for the existence of esophageal peristaltic dysfunction, making easier the development of esophagitis and/or Barrett esophagus [172]. Furthermore, alcohol is able to cause direct damage of the mucosa via alterations in epithelial transport, intercellular junction disorders, and impairment of the mucosal barrier [36]. Both superficial and chronic atrophic gastritis are common in alcoholics. For example, 25.8% of alcohol-dependent individuals enrolled in detoxification programs present with superficial gastritis, and 24.2% have chronic atrophic gastritis. In healthy subjects, the incidence is 10.7% for superficial gastritis and 3% for chronic atrophic gastritis. A recent study indicates that moderate consumption of wine and beer (approximately 7 units/week) protects against *Helicobacter pylori* infection [136]. However, more generally it seems that chronic *Helicobacter pylori* infection, and not alcohol per se, is the major causative agent of chronic gastritis in alcohol-dependent individuals [172]. Consistently, epidemiological studies have concluded that both acute and chronic alcohol consumption are not associated with an increase in the risk for a gastric or duodenal ulcer [172]. In the small intestine, acute and chronic alcohol misuse impairs the barrier function of the gastrointestinal mucosa, resulting in increased permeability and translocation of macromolecules. Bacterial overgrowth in the small intestine has been also demonstrated in individuals with chronic alcohol abuse. These bacteria may cause mucosal damage and contribute to malabsorption [155]. Exposure of the mucosal side of the small intestine to alcohol inhibits the active transport of numerous macro- and micronutrients across the epithelial layer, such as folate and others. Moreover, alcohol affects the metabolism of carbohydrates and lipids in the brush border membrane of the small intestinal mucosa by damaging the villi, where lactase and sucrase are located. The activities of both enzymes are reduced, which may exacerbate lactose intolerance. However, the activities of lactase and sucrase return to normal within weeks of abstinence [155]. Acute alcohol reduces impending wave motility and increases propulsive wave motility; this may result in reduced transit time to the colon and diarrhea [155]. Conversely, chronic alcohol misuse may induce a reversible prolonged orocecal transit time [2]. Both abnormalities could contribute to diarrhea as shortened transit reduces absorption while prolonged transit predisposes to bacterial overgrowth. In contrast to the organs of the upper gastrointestinal tract, the mucosa of

Table 2 Main gastrointestinal and pancreatic features in subjects with substance abuse or dependence

Substance	Main feature(s)	Other feature(s)
Alcohol	Gastric and intestinal motility disorders; malabsorption; pancreatitis	Esophagitis; Mallory-Weiss syndrome; esophageal varicosities; acute and chronic gastritis; peptic ulcer disease; bacterial overgrowth; acute and chronic pancreatitis
Nicotine	Peptic ulcer disease; risk factor for pancreatic carcinoma	Gastroesophageal reflux disease; atrophic gastritis; reduced risk of developing UC; detrimental effect on CD
Opioids	Inhibition of gastric and intestinal motility	Nausea; constipation; increased sphincter of Oddi tonicity; pancreatitis
Cocaine	Bowel ischemia	"Candy-cane" esophagus; intestinal perforations; ischemic colitis
Amphetamine	Decreased gut motility	Constipation; teeth damage
Benzodiazepines	Gastric and gut motility disorders	Vomiting; nausea; diarrhea; epigastric distress; abdominal pain; gaseous distension; dysphagia

UC ulcerative colitis, *CD* Crohn's disease

the large bowel is exposed only to alcohol concentrations corresponding to those in the blood [33]. However, due to the low aldehyde dehydrogenase activity of the colonic mucosa, acetaldehyde accumulates in the colon and may contribute to the pathogenesis of alcohol-induced diarrhea and colon cancer. The morphology of the rectum is altered by chronic alcohol misuse; rectal biopsies often show crypt destruction, inflammation, and proliferation of epithelial cells. Abnormal cellular proliferation is the hallmark of malignant neoplasia [154]. Pancreatitis due to alcohol abuse is a very painful and potentially fatal condition. About one-third of acute pancreatitis cases in the United States are related to alcohol, and 60–90% of pancreatitis patients have a history of chronic alcohol consumption. It is estimated that drinking more than 80 g of alcohol per day for a minimum of 6–12 years is required to produce symptomatic pancreatitis. However, other factors, including environment, genetics, race, and concomitant risk factors such as cigarette smoking, are also involved [46]. Possible mechanisms involved in the pathophysiology of alcoholic pancreatitis include inhibition of secretion from acini, microtubular dysfunction, induction of oxidative stress, production of pro-inflammatory cytokines, alteration of cell permeability, increased lysosomal fragility, inhibition of apoptosis, and enhancement of necrosis [46]. Finally, an increased risk of pancreatitis is present in individuals with acute alcohol intoxication and secondary hyperlipidemia. This hyperlipidemia, together with hemolytic anemia and the consequent increase of bilirubin, is called Zieve's syndrome (Table 2).

Nicotine

Smoking could worsen gastroesophageal reflux disease; specifically, nicotine might be responsible for lower esophageal sphincter pressure [173]. Epidemiological data show that cigarette smoking increases both the incidence and relapse rate of peptic ulcer disease and delays ulcer healing in humans [122]. Nicotine may tilt the balance between aggressive and defensive factors of the gastric and duodenal mucosal integrity, favoring aggressive factors (e.g., gastric acid secretion, *Helicobacter pylori* infection, pepsinogen secretion) and attenuating defensive factors. In particular, *Helicobacter pylori* infection is more common in smokers and eradication therapy is less effective. In fact, nicotine potentiates the vacuolating toxin activity of *Helicobacter pylori* in gastric cells [138]. Regarding the effects of nicotine on the gut, nicotine is an important factor in inflammatory bowel disease, with differing effects in ulcerative colitis and Crohn's disease. Several epidemiological studies show a reduced risk of developing ulcerative colitis in cigarette smokers

when compared with non-smokers. Intermittent smokers often find their symptoms actually improved with smoking. Moreover, a dose-response relationship exists between a decreased risk of ulcerative colitis and increasing amounts of cigarettes smoked [190]. Therefore, nicotine, a major component of tobacco, has been examined as a possible pharmacological agent in the treatment of ulcerative colitis. Various mechanisms have been considered to explain the beneficial effect of nicotine on ulcerative colitis, including effects on the epithelial mucus (increased mucin synthesis), gut motility (reduction of circular muscle activity), eicosanoid metabolism, inhibition of pro-inflammatory cytokine production, and parasympathetic nervous system [173]. On the other hand, smoking has a detrimental effect on the course of Crohn's disease. The reason for the opposite association with smoking status compared with ulcerative colitis is still unclear. A hypothesis is that this opposite effect could be related to smoking's immunosuppressive effects on macrophages, which might further compound any deficiency in the host response to luminal bacteria (a possible mechanism of the pathogenesis of Crohn's disease). Finally, epidemiological evidence shows an association between cigarette smoking and pancreatic diseases. The mechanism is perhaps mediated by signal transduction pathways in the pancreatic acinar cell, leading to enhanced levels of intracellular calcium release and thereby resulting in cytotoxicity and eventual cell death [45]. Also, the induction of pancreatic injury by nicotine may involve the activation and expression of the proto-oncogene H-ras, which may lead to the development of pancreatic carcinoma in cigarette smokers [45].

Opioids

Opioid-induced gastrointestinal dysfunctions are well known. In particular, nausea and vomiting are severe adverse effects of opioids. Among individuals being treated with opioids, 8–35% have reported nausea while 14–40% have suffered from vomiting [128]. Opioids act at the chemoreceptor trigger zone (area postrema in the medulla), triggering emetic mechanisms mediated by the vomiting center in the medulla. By an action on mu receptors, opioids result in inhibition of gastric motility and a delay in gastric emptying, leading to gastroesophageal reflux/heartburn [189]. The inhibitory effect of opioids on the ileocecal sphincter and defecation reflexes contributes to opioid-induced constipation. Opioids do not seem able to induce detrimental effects on the gastrointestinal mucosa. Conversely, it has been suggested that morphine protects against stress-induced gastric ulceration in a dose-dependent manner [44]. Opioids can increase sphincter tonicity and result in sphincter of Oddi dysfunction [134]. Sphincter of Oddi dysfunction may be manifested clinically by alteration of liver tests, pancreaticobiliary pain, and pancreatitis. For example, a study conducted in a group of 91 hospitalized heroin addicts evidenced hyperamylasemia in 19% of the individuals [88]. However, it also has been suggested that hyperamylasemia after heroin usually arises from sources other than the pancreas.

Cocaine

Gastrointestinal complications of cocaine abuse occur less frequently than those in the cardiovascular and nervous systems. Esophageal lesions are characterized by alternating pink and white linear bands imparting a "candy-cane" appearance to the mucosa. The injury produces chest pain, as well as dysphagia, odynophagia, and abdominal pain. However, when individuals with candy-cane esophagus have chest pain, myocardial ischemia should remain the first possible diagnosis. Smoking cocaine has been reported to induce intestinal perforations. These perforations occur in a predominantly male population of drug addicts who are 8–10 years younger than the usual group of individuals with pyloroduodenal perforations. *Helicobacter pylori* infection may be a contributing factor to these perforations [77]. Cocaine injected intravenously has

been shown to cause bowel ischemia without evidence of thrombosis, embolism or atherosclerosis [69]. The intestinal vasculature contains alpha-adrenergic receptors, which are stimulated by norepinephrine, leading to mesenteric vasoconstriction and focal ischemia [77].

Amphetamine

Amphetamines act as an indirect sympathomimetic amine and may include decreased gut motility with consequent constipation [162]. Cocaine- and amphetamine-regulated transcript peptides are found in areas of the intestine and are thought to be responsible for regulating the sympathetic nervous system effects. Typically, misuse of "crystal meth", the smokable form of methamphetamine hydrochloride, can have an important effect on teeth. In a few months, healthy teeth can turn greyish-brown, twist, and begin to fall out. The mechanism is due to the dry mouth caused by amphetamine sympathomimetic action, which in turn makes users thirsty and crave sugary soft drinks. The problem is aggravated by caustic substances used in the drug preparation, such as lithium and red phosphorus [57].

Benzodiazepines

Oral benzodiazepine poisoning produces minimal effects on the gastrointestinal tract. However, vomiting, nausea, diarrhea, epigastric distress, abdominal pain, gaseous distension, and dysphagia can occur after the administration of high doses of benzodiazepines [84]. Conversely, several studies have evidenced possible protective effects of benzodiazepines against ethanol-induced gastric mucosa damage and stress-induced gastric ulcerations for the involvement of central-type benzodiazepine receptors located in the stomach [21]. Finally, peripheral benzodiazepine receptors are expressed also in human pancreatic islets, and prolonged binding to peripheral benzodiazepine receptors may cause human beta-cells functional damage and apoptosis [125].

Nervous System

Alcohol

Alcohol abuse is often related to brain defects and associated cognitive, emotional, and behavioral impairments. Interestingly, it has recently been suggested that the right hemisphere may be more vulnerable to the effects of alcohol than the left [143]. The regions particularly vulnerable to damage and dysfunction in individuals with chronic abuse are the frontal lobes, limbic system, and cerebellum [144]. The alterations of the frontal lobes in alcoholics are related to a decreased neuronal density, a reduction of the regional blood flow, reduced amplitude of event-related potentials, and a low glucose metabolism. These alterations generally determine some aberrations of emotion and personality including disinhibition, impulsivity, and antisocial trait. The alterations of the limbic system in alcoholics are related to dysfunction in the amygdala, a reduction of the hippocampal volume, and damage to the mammillary bodies of the hypothalamus. Clinical consequences include alterations in the control of major emotions, memory deficits (anterograde amnesia), and learning impairments. The alterations in the cerebellum in alcoholics are related to a reduction of the white matter volume of the vermis, a disruption of the fronto-cerebellar circuitry [41]. Clinical consequences include walking alterations, ataxia, and alterations of executive function [41]. Moreover, a 36% reduction in Purkinje cell number in the cerebellar vermis has been correlated to Korsakoff's syndrome in alcoholics [30]. Korsakoff's syndrome is characterized by anterograde and retrograde amnesia, disorientation, and impairment of recent memory coupled with confabulation [16]. This

syndrome is often associated with Wernicke's encephalopathy. The typical signs of Wernicke's encephalopathy are ocular motility disorders, ataxia, and mental changes (confusion, drowsiness, obtundation, clouding of consciousness, pre-coma, or coma) [16, 174]. These two disorders are usually termed the Wernicke-Korsakoff syndrome and considered as a single clinical manifestation [16]. The prevalence of Wernicke-Korsakoff syndrome is 8–10 times higher in alcoholics than in the general population (12.5 and 0.8%, respectively) and is caused by thiamine (vitamin B_1) deficiency in these individuals [174]. Moreover, thiamine deficiency is probably the basis of the cause of polyneuropathy often present in alcoholics, although the pathogenesis of alcoholic neuropathy is still unclear [107]. Alcoholic peripheral neuropathy is characterized by an asymmetric polyneuropathy pattern with greater involvement of the lower extremities, via distal axonal degeneration that involves both myelinated and non-myelinated fibers [107] (Table 3).

Nicotine

Among the 4,700 compounds found in tobacco smoke, many are associated with brain toxicity, including vinyl chloride, a risk factor for brain cancer. Other components are associated with negative effects on the pulmonary system, with secondary effects on the central nervous system. Several animal and human studies demonstrated that chronic nicotine exposure induces an increase in the number of central nervous system nicotinic acetylcholine receptors [157]. Nicotinic acetylcholine receptors are highly represented in the thalamus and cerebellum. Both acute and chronic nicotine exposure can induce changes in the central nervous system. Cerebral responses to acute administration of nicotine or smoking include reduction in global brain activity, activation of the prefrontal cortex, thalamus, and visual cortex during visual cognitive tasks, and increased dopamine concentration in the ventral striatum/nucleus accumbens. Responses to chronic nicotine exposure include decreased monoamine oxidase A and B activity in the basal ganglia and a reduction in alpha-4-beta-2 nicotinic acetylcholine receptor availability in the thalamus and putamen [167]. Ultimately, nicotine is able to induce free radicals, to deplete antioxidants, and to increase markers of oxidative stress in neural cells, inflammatory response, and atherosclerosis [167]. Smoking history represents a reliable risk factor for preclinical brain changes, such as accelerated risk for incident silent brain infarct, reduction of gray matter volumes and densities in the prefrontal cortex, in left dorsal anterior cingulated cortex, and in cerebellar gray matter. From a clinical perspective, it has been reported that continuous smoking is associated with an increased risk of cognitive impairment [26] and dementia [131].

Opioids

Chronic opiate abuse can modify several neurotransmitter systems of the central nervous system. In particular, chronic opiate abuse has been associated with marked changes in the

Table 3 Main neurological clinical symptoms in subjects with alcohol abuse or dependence

Symptoms	Area(s) mainly involved
Disinhibition, impulsivity, antisocial trait	Frontal lobes
Control emotions altered, memory deficits, learning impairments	Limbic system
KS: walking alterations, ataxia, executive function alterations	Cerebellum
Polyneuropathy: nociception alteration, painful symptoms	PNS
WKS: ocular motility disorders, ataxia, confusion, drowsiness, obtundation, pre-coma, coma	Cerebellum, Thalamus, Hypothalamus

KS Korsakoff's syndrome, *WKS* Wernicke-Korsakoff syndrome, *PNS* peripheral nervous system

brain density of mu-opioid receptors [129]. Interestingly, although methadone is used as a substitute for heroin in the treatment of opiate-dependent individuals, the long-lasting effects of these two opiates differ. Methadone administered in a maintenance regimen results in an up-regulation of the mu-opioid receptors, which persists even after detoxification from opiates [55]. Conversely, post-mortem analyses of chronic heroin users have shown a down-regulation of the mu-opioid receptors [70]. Regarding monoamine neurotransmission, chronic opiate abuse has been associated with reduced densities in noradrenaline (α2) and dopamine (D2) receptors [70]. The effects on the dopamine system overall in opiate users are less pronounced than in stimulant users [105]. From a clinical perspective, heroin vapor inhalation induces leukoencephalopathy, or "chasing the dragon" syndrome, characterized by progressive neurological deficits such as altered levels of consciousness, spastic paraparesis, ataxia, bradykinesia, and dysarthria [142]. Intravenous injection of heroin also can induce permanent neuropathies. Rhabdomyolysis and myopathy have been attributed to toxicity and ischemia or a gluteal compartment syndrome, whereas the associated neuropathy could have been caused by compression [139].

Cocaine

Within the central nervous system, frontal lobes represent the areas most affected by cocaine abuse [71]. For example, imaging results show volumetric deficits in multiple frontal areas in cocaine users, including the anterior cingulate and orbitofrontal cortex as well as the insula and temporal cortex [126]. Chronic cocaine users often present with poor performance on experimental and neuropsychological tasks that probe working memory function [71]. This feature is consistent with the observations that many of these compromised cognitive functions involve the dopaminergic neurons of the dorsolateral prefrontal and orbitofrontal regions [71]. In cocaine abusers, some cerebral vascular alterations have also been recognized [139]. In particular, cerebral hemorrhage and ischemic stroke have been reported. Silent ischemia has been suggested as a possible mechanism for the cerebral atrophy and consequent encephalopathy often present in cocaine abusers [147]. Either ischemic or hemorrhagic stroke can lead to *ex novo* seizures or exacerbate a pre-existing seizure disorder [115]. However, seizures can also occur in the absence of vascular disorders when high blood concentrations of cocaine are present, suggesting a direct toxicity [139]. Cocaine can also induce transient movement disorders, characterized by choreoathetosis, akathisia, parkinsonian tremor, and multifocal tics, and can aggravate the symptoms of individuals with Tourette's syndrome [146]. Furthermore, some cocaine abusers experience an acute severe migrainous headache, which can be attributed to either acute use or withdrawal of the drug [58].

Amphetamine

Methamphetamine-induced neurotoxicity involves several neurotransmitter systems, mostly by altering the function of the dopamine fronto-striato-thalamocortical loops [39]. Both high doses and chronic administration of methamphetamine can result in a depletion of dopamine and destruction of dopamine nerve terminals [47]. Several mechanisms have been implicated in methamphetamine-induced neurotoxicity, including production of reactive oxygen and nitrogen species, hyperthermia, and the triggering of an apoptotic cascade dependent upon mitochondria [47]. Acute effects of methamphetamine use are mediated by the sympathetic branch of the autonomic nervous system and include hypertension, tachycardia, hyperthermia, increased breathing rate, and constriction of blood vessels. Cognitive and emotional effects include euphoria, enhanced energy and alertness, a surge in productivity, and an increase in libido

[47]. Chronic methamphetamine use can result in pulmonary hypertension, acute aortic dissection, myocardial infarction, and ischemic and hemorrhagic strokes. In addition, some physical and mental consequences can occur, including sleep deprivation, affective distress, psychiatric disorders, and an increased risk of depression and suicidal ideation [47]. Furthermore, methamphetamine may induce seizures, delirium, and coma, especially if used in combination with other drugs [139]. Either hemorrhagic [192] or ischemic stroke [192] may also occur. Finally, in chronic methamphetamine addicts, a transient movement disorder named "jerking syndrome" has been described. The "jerking syndrome" is probably caused by a basal ganglia disorder and is characterized by constant automatic involuntary choreiform movements, stereotyped dystonic facial movements, and/or chewing-gum movements [139].

Benzodiazepines

In individuals with benzodiazepine abuse, many studies have demonstrated a down-regulation of the benzodiazepine binding sites, although the affinity is usually unchanged [95]. Symptoms of benzodiazepine withdrawal are time-limited, usually occurring for only 1 or 2 weeks after the discontinuation of the drug, but the duration varies according to the drug and the individual subject [141]. During withdrawal, the original anxiety symptoms often return in a more intense form, a phenomenon known as "rebound anxiety" [95]. Rebound anxiety can include psychological and physiological symptoms such as anxiety, apprehension, irritability, insomnia, dysphoria, tremor, palpitations, mild systolic hypertension, dizziness, sweating, muscle spasm, and gastrointestinal disturbances [95] (Table 4).

Cardiovascular System

Alcohol

Alcohol abuse has been associated with several cardiovascular diseases, such as hypertension, cardiomyopathy, coronary artery disease, and stroke [121]. However, low-to-moderate ethanol consumption has been linked to a reduced cardiovascular risk, with a J-shaped dose-response curve. Although red wine consumption and the related compounds (i.e., polyphenols) were considered important in the so-called "French paradox", alcohol itself seems to hold the major benefits [121]. On the other hand, chronic alcohol abuse induces several alterations in the cardiovascular system, including: low-grade systemic inflammation, hyperuricemia, dyslipidemia, hyperhomocysteinemia, increased oxidative stress with enhanced lipid peroxidation,

Table 4 Main neurological clinical symptoms in subjects with substance abuse or dependence

Substance	Neurological features
Alcohol	Disinhibition, impulsivity, antisocial trait, control emotions altered, memory deficits, learning impairments, KS, WKS, polyneuropathy
Nicotine	Atherosclerosis, stroke vigilant, attention and memory, cognitive decline, dementia
Opioids	Neuropathies, rhabdomyolysis, myopathy, altered levels of consciousness, spastic paraparesis, ataxia, bradykinesia, dysarthria
Cocaine	Hemorrhagic stroke, ischemic stroke, encephalopathy, seizure disorder, choreoathetosis, akathisia, parkinsonian tremor, multifocal tics, Tourette's syndrome symptoms, headache
Amphetamine	Ischemic stroke, hemorrhagic stroke, euphoria, enhanced energy, alertness, increase in libido, sleep deprivation, affective distress, psychiatric disorders, increased risk of depression and suicidal ideation, jerking syndrome
Benzodiazepines	Benzodiazepine withdrawal: "rebound anxiety", anxiety, apprehension, irritability, insomnia, dysphoria, tremor, palpitations, dizziness, sweating, muscle spasm, hypersensitivity to light, sound or touch body pains, headache, generalized seizure

KS Korsakoff's syndrome, *WKS* Wernicke-Korsakoff syndrome

impaired glucose tolerance with insulin resistance, endothelial dysfunction, arterial hypertension, and alcoholic cardiomyopathy [121, 151]. From a clinical point of view, all the mentioned mechanisms are able to modify the pathophysiology of atherosclerosis. Atherosclerosis is a diffuse disease, and its clinical presentation varies depending upon the vascular bed in which it occurs. Moreover, long-term heavy alcohol consumption (of any beverage type) is the leading cause of a non-ischemic dilated cardiomyopathy called alcoholic cardiomyopathy [151]. The exact pathogenesis of alcoholic cardiomyopathy is still unclear. Alcohol induces several changes in the myocardial structure by inducing myocyte loss, intracellular organelle dysfunction, and contractile protein alterations, and influencing calcium homeostasis. These changes can alter several aspects of myocyte function and, therefore, may lead to myocyte dysfunction and alcoholic cardiomyopathy. Symptoms often appear late, and the diagnosis could be difficult since the symptoms are close to those of chronic heart failure. Alcohol abstinence often results in at least partial recovery of the myocyte damage, with a consequent improvement in cardiac function. The term "holiday heart syndrome" was coined by Ettinger et al. [63] and defined as "an acute cardiac rhythm and/or conduction disturbance associated with heavy ethanol consumption in a person without other clinical evidence of heart disease and disappearing, without evident residual, with abstinence". In sum, although numerous studies have described a J-shaped or U-shaped curve to describe the relationship between alcohol intake and total and cardiovascular mortality, these studies have been observational and epidemiological in nature. Prescribing alcohol for those who do not drink and the use of alcohol as a cardioprotective strategy are not recommended [106] (Table 5).

Nicotine

Smoking is associated with an increased risk of atherosclerotic vascular disease, hypertension, myocardial infarction, unstable angina, sudden cardiac death, and stroke [188]. Acute and chronic cigarette smoking impairs nitric oxide synthase-mediated relaxation of large blood vessels. Smoked tobacco, in fact, contains high levels of free radicals and pro-oxidant agents. There is considerable evidence that cigarette smoking can result in both morphologic and biochemical disturbances to the endothelium both *in vivo* and in cell culture systems. However, a consensus of the causal relationship between cardiovascular disorders and the consumption of smokeless tobacco has not yet been established [83]. An acute hypertensive effect has been shown, up to 90 minutes after smoking tobacco. In particular, absorbed nicotine stimulates the release of catecholamines; the subsequent activation of alpha-adrenoceptors in vascular smooth muscle cells contracts vascular tissues and elevates blood pressure. Free radicals and aromatic compounds diminish the endothelial synthesis of nitric oxide, causing impaired endothelium-dependent relaxation of arteries, the earliest clinical sign of endothelial dysfunction, and they injure the arterial endothelium, promoting atherogenesis [83]. The increased oxidation of low-density lipoprotein in smokers has synergetic effects to promote

Table 5 Main cardiovascular features in subjects with substance abuse or dependence

Substance	Cardiovascular features
Alcohol	Hypertension, alcoholic cardiomyopathy, coronary artery disease, stroke
Nicotine	Atherosclerosis, hypertension, myocardial infarction, angina, sudden cardiac death, stroke
Opioids	Bradycardia/bradyarrhythmias, hypotension, pulmonary edema, endocarditis
Cocaine	Severe hyper-/hypotension
Amphetamine	Arrhythmias (supraventricular/ventricular), chest pain/myocardial infarction, acute heart failure, dilated cardiomyopathy/chronic heart failure, endocarditis
Benzodiazepines	Bradycardia, myocardial infarction (?)

monocyte adhesion and monocyte migration into the subintimal space. Continued stimulation of intimal cells by oxidized low-density lipoprotein leads to the development of atherosclerosis. Smokeless tobacco use has been linked to impotence [101], acute myocardial infarction, congestive heart failure [156], and ischemic stroke [75]. In particular, diseases of the cardiovascular system and their final or lethal states occur 3 to 4 times more frequently than lung cancer in heavy smokers [83].

Opioids

The cardiovascular effects of opioids are directed to the vasomotor center to increase parasympathetic activity, reduce sympathetic activity, and release histamine from mast cells. These combined effects produce bradycardia and hypotension [119]. Acute cardiac effects of opioid abuse are represented by drug-induced bradycardia [119]. The reduction in the heart rate increases the automaticity in ectopic electrical myocardial activity, leading to atrial fibrillation, idioventricular rhythm, or potentially lethal ventricular tachyarrhythmias [119]. Some opioids (such as dextropropoxyphene) have additional sodium channel-blocking effects, which further contribute to the pro-arrhythmic and myocardial depressant effects, leading to acute left ventricular dysfunction and cardiogenic pulmonary edema. Overdose of narcotic analgesics can also cause acute non-cardiogenic pulmonary edema. This may be related to an anaphylactic reaction to the drug, to an increase in pulmonary capillary hydrostatic pressure resulting from pulmonary vasoconstriction induced by hypoxia, or to disruption of alveolar capillary membrane integrity. Apart from the well described central nervous system and respiratory depressant effects, there also may be profound cardiovascular collapse or arrhythmias after narcotic analgesic overdose [76]. Chronic consequences of intravenous opioids injection include the risk of infection of the injection site, along with the risk of bacterial endocarditis, which usually affects the right-sided heart valves and may be associated with pulmonary abscess formation [164]. Since the abused drug is rapidly metabolized, the majority of arrhythmias are short-lived. Compared with abusers of other drugs, opioids abusers show a low prevalence of coronary artery disease [124]. On this point, the binding of morphine to opioid receptors before induction of an infarction in a rat model results in smaller infarcts, with protection of cardiomyocytes mediated by peripheral opioid receptors [76]. Moreover, in humans, long-term exposure to opioids is associated with decreased severity of coronary artery disease, with a decreased incidence of fatal myocardial infarctions. One possible explanation is that narcotics may decrease inflammation [54], which is associated with atherogenesis and plaque disruption [116].

Cocaine

Cocaine affects the cardiovascular system, predominantly via activation of the sympathetic nervous system [76]. Cocaine acts indirectly as a sympathomimetic drug inhibiting the reuptake of noradrenaline and dopamine at the sympathetic nerve terminals. Cocaine can also act through central pathways to release noradrenaline from the adrenal medulla [43]. At high doses, cocaine can impair myocyte electrical activity and contractility by blocking fast sodium and potassium channels and inhibiting calcium entry into myocytes [133]. Furthermore, cocaine has a short serum half-life of approximately 30–80 minutes, but some of its metabolites are more cardiotoxic than the parent compound [89]. Cocaethylene, for example, is formed when cocaine is taken with alcohol and has an important cardiotoxic effect [89]. The clinical symptoms related to the cocaine-induced sympathetic activation include tachycardia, vasoconstriction, unpredictable blood pressure effects, and arrhythmias, depending on the dose and the possible presence of a coexisting cardiovascular disease. Hypertension is common, but severe hypotension (due to a paradoxical central sympathetic suppression) can also occur [133]. Chest pain, myocardial ischemia, and infarction can be

produced by various mechanisms, such as diffuse or local coronary artery spasms [132]. A pro-coagulant effect that is able to facilitate a thrombotic coronary occlusion can also occur by decreasing the concentrations of protein C and antithrombin III, activating platelets, and potentiating thromboxane production. Chronic use of cocaine can induce repetitive episodes of coronary spasm and paroxysms of hypertension, which may result in endothelial damage, coronary artery dissection, and subsequent acceleration of atherosclerosis. Prolonged administration of cocaine may be associated with an irreversible dilated cardiomyopathy, related to subendocardial ischemia and fibrosis and myocyte necrosis produced by exposure to excessive catecholamine concentrations or repeated episodes of myocarditis. Myocardial cellular injury can also occur in association with exposure to infectious agents or heavy metals, such as manganese, that contaminate street preparations of cocaine. A wide and unpredictable range of supraventricular and potentially lethal ventricular tachyarrhythmias can be precipitated by such a sympathomimetic stimulation. Moreover, cocaine can impair cardiac conduction, inducing a wide range of bradyarrhythmias such as sinus arrest and atrioventricular block. Sudden cardiovascular collapse may occur as a result of myocardial ischemia and infarction, arrhythmias, acute heart failure, or mechanical complications. Benzodiazepines attenuate the cardiac and central nervous system toxicity of cocaine and should be given in sedative dosages, also to manage hypertensive and cardiovascular complications, in addition to nitrates [93]. Cocaine-induced chest pain should be treated initially with oxygen, aspirin, and benzodiazepines. If the ischemia damage continues, then the use of additional vasodilators such as nitrates or phentolamine to reverse residual coronary spasm may be necessary.

Amphetamine

As a consequence of acute amphetamine intoxication, cardiovascular symptoms, including chest pain, palpitations, and dyspnea, are common [20]. Cardiovascular effects of amphetamine are similar to those induced by cocaine and include hypertension, supraventricular tachyarrhythmias, ventricular arrhythmias, myocardial ischemia and infarction, acute heart failure, chronic heart failure, and endocarditis [76]. Similar principles should be applied to the management of the cardiovascular complications associated with these recreational drugs, although the duration of treatment will vary depending on the half-life of the agent taken.

Benzodiazepines

Benzodiazepines, particularly diazepam, are usually considered primarily to exert a cardiodepressant effect, which is a consequence of a centrally mediated decrease in cardioregulatory outflow of the sympathetic nervous system [40]. On the other hand, some studies report that diazepam produces positive inotropic effects on the myocardium, which have been related to catecholamines released from sympathetic nerve terminals located in the heart [17]. Moreover, it has also been shown that diazepam potentiates the positive inotropic effect of both noradrenaline and adrenaline, as well as that of the endogenous noradrenaline-releasing agent tyramine in electrically driven right ventricular strips of rat, by directly inhibiting the enzyme cyclic nucleotide phosphodiesterase [123]. Diazepam overdose can produce cardiac sympathomimetic-like effects on atrioventricular conduction. Recently, it has been shown that peripheral-type benzodiazepine receptors are almost ubiquitous (i.e., platelets, erythrocytes, lymphocytes, and mononuclear cells) and are abundant in the cardiovascular system (endothelium, striated cardiac muscle, vascular smooth muscles, and mast cells) and in intracellular locations (mitochondria) [182]. The exact function of peripheral-type benzodiazepine receptors is still unclear, but they seem to take part in some responses to trauma such as ischemia. The irreversible peripheral-type benzodiazepine receptor

antagonist, SSR180575, was found to reduce the ischemia-related damage [182]. Diazepam is often found to be a substance of abuse that is able to induce a myocardial infarction secondary to coronary spasm, mostly in teenagers.

Oncology

Alcohol

The alcohol-associated risk for the development of cancers varies from low to moderate to high, depending on the type of organ affected as well as the amount of alcohol consumed. Statistically significant relative risks for the development of cancers from the consumption of 100 g of alcohol per day were reported for the oral cavity, pharynx, esophagus, larynx, breast, liver, ovary, colon, rectum, and stomach [29]. Among the possible mechanistic pathways, the formation of acetaldehyde seems to be the most important [99]. Twenty-five percent to 80% of upper aerodigestive tract cancers are attributable to alcohol acetaldehyde. For example, individuals heterozygous for inactive ALDH2 are at increased risk for upper aerodigestive tract cancers because of the accumulation of acetaldehyde after alcohol consumption [154]. The pooled alcohol-associated risks for colorectal cancer range from 1.08 for 25 g of alcohol consumed per day to 1.18 for 50 g/day to 1.38 for 100 g/day [29]. A daily alcohol consumption of $\geq$30 g/day was associated with an increased risk of proximal colon cancer, distal colon cancer, and rectal cancer. An association between alcohol abuse and gastric cancer has not been clearly shown [104]. While the association between cirrhosis and the development of hepatocellular carcinoma is well documented, a direct correlation between ethanol consumption and the development of hepatocellular carcinoma remains debatable. Among individuals with alcoholic cirrhosis, the annual incidence of hepatocellular carcinoma is 1–2% [127]. Similarly, while heavy alcohol consumption represents a major cause of chronic pancreatitis and a risk factor for type 2 diabetes mellitus (both of which are linked to pancreatic cancer), there is little or no support for a direct causal relationship between light and moderate alcohol use and risk of pancreatic cancer [78]. Alcohol consumption is associated with increased risk for breast cancer in both premenopausal and postmenopausal women, regardless of the type of alcoholic beverage consumed. The proportion of breast cancer cases attributable to alcohol consumption among U.S. women is 2.1%, accounting for about 14,000 women per year [181]. The role of alcohol drinking in the etiology of non-Hodgkin's lymphoma is still debatable. Some studies have suggested that alcohol consumption reduces the risk of non-Hodgkin's lymphoma, whereas others have found increased non-Hodgkin's lymphoma risk among alcohol drinkers, or no relationship [169] (Table 6).

Nicotine

Cigarette smoke contains 4,800 identified chemicals, including at least 61 products (e.g., benzene, polonium, polycyclic aromatic hydrocarbons, nitrosamines, aromatic amines, etc.) able to cause cancer [86]. Moreover, tobacco components have been recognized to induce immunosuppression, which may play an important role in the development of malignant cells [169]. The unequivocal role of cigarette smoking in causing lung cancer is one of the most thoroughly documented causal relationships in biomedical research. Using an attributable risk approach, the annual number of deaths caused in the U.S. by smoking-related lung cancer from 1995 to 1999 was 122,800. The risk for lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day. Genetic factors can also contribute. For example, it has recently been shown that a common variant in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 with an effect on smoking quantity confers a risk of lung cancer [175]. Regarding upper

Table 6 Pathways and related effects on the basis of the link between cancers and substances of abuse

Possible pathways involved in alcohol-related cancer	Effects
Alcohol contacts-related local effects	Cancer of: UADT, stomach, colon
Alcohol's solvent effects on tobacco and other carcinogens	Cancer of: UADT, stomach, colon, pancreas
Induction of microsomal enzymes involved in carcinogen metabolism	Cancer of: UADT, stomach, colon, liver, pancreas
Generation of oxygen radicals and lipid peroxidation products	Cancer of: UADT, stomach, colon, liver, pancreas
Nutritional deficiency	Cancer of: colon, breast, blood
Suppressed immune function	Cancer of: UADT, stomach, colon, liver, pancreas, breast, NHL
Acetaldehyde-induced carcinogenesis	Cancer of: UADT, stomach, colorectal, liver
Decreased hepatic retinoic acid	Cancer of: liver
Iron overload	Cancer of: liver
Perturbation of estrogen metabolism and response	Cancer of: breast
Down-regulated BRCA1 expression	Cancer of: breast
Possible pathways involved in tobacco component-related cancer	**Effects**
Increasing mean leukocyte counts Decreasing serum concentration of immunoglobulins Decreasing NK-cells Decreasing CD41/CD81 ratio Altering T-cell function	Cancer of: lung, larynx, mouth, esophagus, bladder, pancreas, kidney, cervix uteri, stomach, breast, blood
Possible pathways involved in opioid-related cancer	**Effects**
Decreased natural and adaptive immunity	Worsening of cancer in animal models
Possible pathways involved in cocaine-related cancer	**Effects**
Vasoconstriction irritating to the respiratory epithelium of the nasal airway	Nasal SFT
Possible pathways involved in amphetamine-related cancer	**Effects**
Suppresses neutrophil phagocytosis Suppresses production of TNF-alpha and IL1 Suppresses circulating lymphocyte numbers Alters T-cell function	Reduced tumor surveillance

UADT upper aerodigestive tract, *NHL* non-Hodgkin's lymphoma, *SFT* solitary fibrous tumor, *NK-cells* natural killer cells, *TNF* tumor necrosis factor, *IL1* interleukin-1

aerodigestive tract cancers, the risk of laryngeal cancer in smokers is on the order of 10 relative to non-smokers and >15 for heavy smokers, and the risk seems stronger for glottic than for supraglottic neoplasms. Smokers are at a dramatically increased risk for oral carcinoma, particularly squamous-cell cancer. Studies also have demonstrated a dose-response effect of intensity and duration of smoking [109] on this risk. Epidemiological studies report a two- to five-fold increase in the risk of esophageal cancer among smokers. A dose-response increased risk of squamous-cell carcinoma of the esophagus with increased intensity and duration of smoking and a decline in risk after smoking cessation have been repeatedly demonstrated. Smoking is also responsible for a two- to three-fold increased risk of adenocarcinoma of the esophagus, and risk relates to the intensity of smoking [109]. Relevant cohort and case-control studies that have examined the relationship between tobacco smoking and stomach cancer show an up to two-fold increase in risk for smokers compared with non-smokers. A positive dose-response relationship with intensity and duration of smoking was demonstrated in most studies. A large number of case-control and cohort studies have reported an increased

risk for liver cancer in smokers. Smoking is associated with an approximate two- to four-fold increased risk of pancreatic cancer. The proportion of pancreatic cancer attributable to cigarette smoking was 29% in blacks and 26% in whites [109]. Furthermore, an increased risk of kidney and renal pelvis cancers has also been reported in smokers compared with non-smokers [109]. During the last four decades, many epidemiological studies and reviews have consistently shown that cigarette smoking substantially increases the risk of bladder cancer. A positive dose-response relationship has been found with both the number of cigarettes smoked per day and the number of years smoking. Age at first exposure and cessation of cigarette smoking were inversely associated with bladder cancer risk. The role of human papillomavirus in cervical tumors in women is well known. Accordingly, recent cohort and case-control studies have investigated the association between tobacco smoking and the incidence of invasive cervical cancer, cervical intraepithelial neoplasia, and cervical cancer in situ using analyses adjusted for human papillomavirus status or restricted to human papillomavirus-positive women. In these studies, the association between tobacco smoking and cervical cancer was present and remained even after adjustment for a series of other potentially confounding factors. The association between smoking and breast cancer risk remains controversial despite >100 epidemiological studies conducted over the past three decades. The results of these studies overall suggest that smoking probably does not decrease risk and indeed suggest that there may be an increased risk with smoking, particularly heavy smoking of long duration. Recent cohort studies found statistically significantly positive associations between smoking of long duration and breast cancer risk among non-drinkers in their populations. Finally, among hematological tumors, the available literature on tobacco smoking and leukemia indicates that there is an association between tobacco smoking and myeloid leukemia, with an increased risk with higher intensity and longer duration of smoking. In recent years, a direct relationship between tobacco smoking and the risk of non-Hodgkin's lymphoma has been suggested. Compared with those who have never smoked, current smokers had a 10–40% higher risk of developing non-Hodgkin's lymphoma. The association seemed stronger for follicular and high-grade lymphomas [169]. On the contrary, Nieters et al. [140] showed an elevated risk of Hodgkin's lymphoma in relation to smoking but did not find any association between tobacco smoking and risk of non-Hodgkin's lymphoma. However, the latter study was based on a small sample size.

Opioids

There are few data on this topic; the most important pertain to the immunomodulatory activities of morphine and the related potential risk of carcinogenesis [158]. Moreover, injecting opioids also exposes an individual to an indirect risk of cancer, considering the impairment of the immune system in human immunodeficiency virus/acquired immune deficiency syndrome subjects [111].

Cocaine

Also in this case, few data are available. Reactive vascular lesions of the nasal septum simulating angiosarcoma have been reported in chronic cocaine abusers [18]. Cocaine that is snorted is vasoconstricting and locally irritating to the respiratory epithelium of the nasal airway. An anecdotal report also described a solitary fibrous tumor of the nasal cavity in an individual with a long-standing history of cocaine inhalation [18].

Amphetamine

Both animal and human studies demonstrated that amphetamine, particularly methylenedioxymethamphetamine, has immunosuppressive actions that can play a role in reducing tumor

surveillance. However, it is difficult to predict the impact of methylenedioxymethamphetamine-induced immunosuppression on disease susceptibility, particularly cancer onset risk [50].

Benzodiazepines

For the majority of benzodiazepines, results of genotoxicity and carcinogenicity tests recommended by current guidelines are difficult to retrieve [34]. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals, together with supporting evidence from other relevant data, may be placed in Group 2B. On the basis of these indications, three drugs might be considered as possibly carcinogenic to humans: oxazepam, already classified by the International Agency for Research on Cancer in Group 2B, and, tentatively, midazolam and zopiclone due to sufficient evidence of carcinogenicity in experimental animals. Three other drugs—brotizolam, quazepam, and zolpidem—might be tentatively classified as probably not carcinogenic to humans (Group 4). All the other benzodiazepines, on the basis of available data, should be considered not classifiable as to their carcinogenicity to humans (Group 3), including diazepam, doxefazepam, estazolam, prazepam, ripazepam, and temazepam [34].

Endocrinology

Alcohol

Alcohol abuse can often be associated with several endocrine disorders. Among them, the thyroid gland seems to be typically affected. Most studies have shown a reduction in peripheral thyroid hormones and/or blunted thyroid-stimulating hormone response to thyrotropin-releasing hormone in alcohol-dependent individuals [90]. Consistently, in these individuals, both ultrasound and autopsy studies have shown a significant reduction of the thyroid gland volume. Decreased thyroid hormones might result from damage to the thyroid gland or from alterations of the hypothalamic-pituitary-thyroid axis due to chronic alcohol intake. Interestingly, thyroid hormone dysfunction has been associated with some behavioral features of alcohol dependence, such as the severity of withdrawal, negative mood status, and an increased risk of alcohol relapse and alcohol craving, especially in its compulsive component [113, 145]. This last feature is of interest and in line with other similar findings found with other hormones and peptides able to modulate food intake, such as leptin [92], ghrelin [12], and insulin [114]. Alcohol-dependent individuals may show a chronic activation of the hypothalamic-pituitary-adrenal axis, with increased concentrations of cortisol during periods of heavy intake [120]. Recent abstinent alcoholics also show a blunted adrenocorticotropin response to corticotropin-releasing hormone, possibly caused by a direct pituitary effect of chronic ethanol exposure. Alcohol-dependent individuals tend to relapse more rapidly when they have smaller cortisol responses to public stress or in response to alcohol cues in a cue exposure procedure. Consistent with these data, the involvement of other stress hormones in alcoholism has been shown. For example, alcohol drinking is known to cause hyperprolactinemia in both humans and laboratory animals after acute and chronic ethanol exposure, with a consequent normalization during abstinence [110]. Accordingly, women addicted to alcohol suffer from menstrual cycle irregularities, amenorrhea, and infertility because hyperprolactinemia is able to increase the dysfunction of the pituitary-ovarian axis, as caused directly by alcohol. Consistent with the involvement of the hypothalamic-pituitary-adrenal axis in alcohol addiction, a significant decrease in aldosterone levels during abstinence, as well as its potential role in mediating alcohol craving, has been suggested [112]. With regard to the link between alcohol and diabetes, a recent meta-analysis showed that a moderate alcohol intake was associated with a reduced risk of type 2

diabetes compared with low consumption or abstinence, while high consumption of alcohol was associated with an increased risk of type 2 diabetes compared with moderate consumption [37]. Chronic moderate use of alcohol has no deleterious effect on metabolic control in individuals with diabetes. The relationship between alcohol use and insulin sensitivity is J-shaped, with the lowest fasting insulin levels and the lowest insulin resistance index values in moderate drinkers and higher values in both abstainers and heavy drinkers. Finally, some sexual dysfunctions also can be present in alcohol-dependent individuals. In fact, alcohol impairs testicular production of testosterone as well as hypothalamic pituitary secretion of gonadotropin-releasing hormone and the two gonadotropins, follicle-stimulating hormone and luteinizing hormone. Also, acute alcohol intoxication increases sexual desire but inhibits sexual performance. On the other hand, chronic alcohol consumption is associated with the risk of an erectile dysfunction, in a J-shaped manner, with moderate consumption conferring the highest protection and higher consumption conferring fewer benefits [42]. In alcoholic females, several gynecologic problems such as gonadal dysfunction, loss of libido, and infertility are frequent. Consistently, various studies have shown that alcohol consumption increases estrogen levels in the pre-ovulation and luteal phases of the menstrual cycle [28] (Table 7).

Nicotine

Smoking is a risk factor for Graves' hyperthyroidism, and especially for Graves' ophthalmopathy, due to both a tissue hypoxia and an immune-mediated effect [183]. Consistently, the response to the treatment in individuals with ophthalmopathy is delayed and markedly poorer in smokers. Furthermore, in individuals with Graves' disease, smoking may promote the development of thyreotoxicosis. Cigarette smoking has been found to be negatively associated with thyroid cancer, a feature probably due to both the lower thyroid-stimulating hormone levels that reduce thyroid cell proliferation and a smoking-related anti-estrogen effect. With regard to hypothyroidism, a meta-analysis has suggested that Hashimoto's thyroiditis, postpartum thyroid dysfunction, and non-toxic goiter are associated with smoking [183]. Smoking acutely increases the plasma levels of prolactin, adrenocorticotropin, cortisol, growth hormone, and arginine vasopressin without significant changes in thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone [103]. These effects are directly proportional to the nicotine content of cigarettes. Four potential mechanisms may cause these effects: nausea induced by smoking via the stimulation of the emetic center; nicotine-stimulated cyclic adenosine monophosphate production; stress per se, and a direct effect of nicotine on the anterior pituitary or hypothalamus. In chronic smokers, however, inhibition of prolactin secretion occurs, and it depends on a nicotinic release of dopamine acting as a prolactin-inhibitory factor [180]. Chronic smoking stimulates plasma renin activity and raises plasma aldosterone levels. Higher levels of androstenedione and dehydroepiandrosterone sulfate are found in smokers. Plasma adrenaline and noradrenaline levels rise after smoking. Cigarette smoking has an anti-estrogenic effect in women. This is probably due to increased production of 2-hydroxyestrogen compounds with minimal estrogenic activity [170]. Some physiological estrogen-dependent processes, such as the menstrual cycle, are affected by the risk of anovulation and the consequent decreased fertility. Menopausal symptoms such as hot flashes are experienced more commonly among smokers. Cross-sectional studies have also shown increased insulin resistance in smokers vs. non-smoking controls [65]. The reduced insulin sensitivity seen in smokers could be due to the increase in counter-regulatory hormones such as growth hormone, cortisol, and catecholamines, which all raise blood glucose levels. Calcium absorption is lower in smokers vs. non-smokers, a feature probably related to the lower parathyroid hormone and serum calcitriol levels seen in smokers. An association between smoking

Table 7 Main endocrine features in subjects with substance abuse or dependence

Substance	HPT axis	HPA axis	HPG axis	Sexual dysfunction(s)	Other(s)
Alcohol	↓ thyroid hormones ↓ TSH response to TRH	↑ Cort ↓ DXT suppression of Cort	↓ FSH, LH ↓ GnRH ↓ TESTO ↑ ESTRO	↑ mci ↓ libido ↓ fertility ↑ risk for ED	↑ PRL ↓ GH ↑ risk of diabetes
Nicotine	↓ TSH ↑ risk of thyroid dysfunction ↓ risk for thyroid cancer	↑ACTH ↑ Cort ↑ Adr & NAdr ↑ Aldo ↑ Andro ↑ DHEAS	↓ ESTRO	↑ mci ↓ fertility ↑ risk for ED ↑ menopausal symptoms	↓ PRL ↑ GH ↑ AVP ↑ Ins ↑ Ins-R ↑ renin
Opioids		↓ ACTH ↑ adrenal insufficiency ↓ circadian HPA hormone secretion	↓ LH ↓ TESTO	↓ libido ↑ risk for ED ↑ mci	↓ GH ↑ Ins ↑ glucagon
Cocaine		↑ CRH ↑ ACTH ↑ Cort	↑ FSH ↑ LH	↑ sexual feelings ↑ mci ↑ risk for ED ↑ risk for priapism	↑ PRL ↑ AVP ↓ renin
Amphetamine		↑ CRH ↑ ACTH ↑ Cort		↑ sexual desire ↑ risk for ED ↑ ejaculation latency	↓ PRL
Benzodiazepines	↓ TSH	↓ ACTH ↓ Cort	↑ TESTO ↑ 11-hydrocorticoid	↑ sexual dysfunctions ↓ libido	↓ PRL ↓ GH

HPT axis hypothalamic-pituitary-thyroid axis, *HPA axis* hypothalamic-pituitary-adrenal axis, *HPG axis* hypothalamic-pituitary-gonadal axis, *TSH* thyroid-stimulating hormone, *TRH* thyrotropin-releasing hormone, *ACTH* adrenocorticotropin, *CRH* corticotropin-releasing hormone, *GnRH* gonadotropin-releasing hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *PRL* prolactin, *DXT* dexamethasone, *DHEAS* dehydroepiandrosterone sulfate, *GH* growth hormone, *AVP* arginine vasopressin, *ED* erectile dysfunction, *Ins* insulin, *Ins-R* insulin resistance, *Cort* cortisol, *Aldo* aldosterone, *Adr* adrenaline, *NAdr* noradrenaline, *TESTO* testosterone, *ESTRO* estrogen, *Andro* androstenedione, *mci* menstrual cycle irregularities

and erectile dysfunction has also been suggested. Smokers were 1.5 times more likely to suffer erectile dysfunction than non-smokers [61], and the significant association of smoking with erectile dysfunction was strengthened as the number of cigarettes smoked increased. Smoking results in alterations of the male sex hormones and is a key cause of and contributor to erectile dysfunction. Smoking may cause erectile dysfunction by several mechanisms, including adversely affecting intrapenile blood flow caused by endothelial dysfunction. A decrease in sperm quality and a reduced response to fertility treatments have also been reported in male smokers.

Opioids

Opiate users who inject heroin, or those on methadone maintenance treatment, may exhibit adrenal insufficiency and atypical circadian patterns of hypothalamic-pituitary-adrenal hormone secretion [64]. Opiate use increases corticosteroid-binding globulins, which can mask adrenal dysfunction. During chronic administration of opioids, the acute stimulatory effect on prolactin, growth hormone, and thyroid-stimulating hormone secretion is abolished, whereas adrenocorticotropin is inhibited and luteinizing hormone remains suppressed. The inhibition of

adrenocorticotropin release can be explained by the concomitant release of beta-endorphin. A lower, but substantial, percentage of individuals may develop hypocorticism. This condition should be properly diagnosed and treated to avoid Addisonian crises. Growth hormone deficiency may affect an equivalent number of individuals. Methadone dose showed a significant direct correlation with increased orgasm dysfunction, both before and after adjusting for duration of treatment [35]. Heroin addiction influences sexual function negatively. Although opiate addicts often equate the drug experience with sexual orgasm, diminished libido and impaired sexual performance such as erectile dysfunction are common sequelae of chronic use. Substitution therapy by sex steroids restored libido in most men and women and improved their quality of life. A clear and significant suppression of luteinizing hormone and testosterone in virtually all males and a similar decrease in luteinizing hormone secretion with a disrupted menstrual cycle in females were found in a recent study [56].

Cocaine

There is evidence from brain imaging studies that the pituitary gland is larger in men who abuse cocaine chronically than in controls [130]. Chronic cocaine abuse can be associated with hyperprolactinemia. Prolactin release is pulsatile. Hyperprolactinemic cocaine abusers have higher average prolactin peak heights than controls or normoprolactinemic cocaine abusers, and they have higher average prolactin levels between peaks than the other groups. Intravenous cocaine administration is usually followed by an increase in adrenocorticotropin and a subsequent increase in cortisol in human males [130]. When cocaine was administered intranasally, a change in adrenocorticotropin was not detected, but there was a significant increase in cortisol levels [87]. Peak plasma cocaine levels were coincident with the peak increase in plasma adrenocorticotropin levels; adrenocorticotropin peak amplitude and height increased significantly after intravenous cocaine administration, and pulse frequency remained unaltered. These data are consistent with the hypothesis that the reinforcing properties of cocaine may occur as a consequence of its effects on dopaminergic neural systems, which co-modulate corticotropin-releasing hormone release in the brain. Cocaine also reduces renin secretion and increases arginine vasopressin. Acute administration of cocaine intravenously or intranasally was followed by a significant increase in luteinizing hormone. Clinical effects include increases in sexual feelings and energy as well as intense euphoria. The adverse effects of cocaine on reproductive function include disorders of menstrual cycle duration and impairments in folliculogenesis, ovulation, and luteal phase adequacy. Compared with placebo, both luteinizing hormone and, to a lesser degree, follicle-stimulating hormone levels increased significantly after cocaine administration [87]. Chronic cocaine abuse is associated with erectile dysfunction, perhaps due to endothelial dysfunction [85]. Finally, several reports have associated priapism with intranasal, intraurethral, intracavernous, and topical recreational use of cocaine [135].

Amphetamine

Cocaine- and amphetamine-regulated transcript is suggested to be involved in the regulation of the hypothalamic-pituitary-thyroid axis. Co-secretion of cocaine- and amphetamine-regulated transcript with thyrotropin-releasing hormone into the portal pituitary circulation, therefore, may have an important modulatory influence on the effect of thyrotropin-releasing hormone on pituitary hormone secretion [66]. D-amphetamine resulted in poor prolactin suppression in normo- and hyperprolactinemic subjects. Methylenedioxymethamphetamine use can cause neurochemical, behavioral, and endocrine alterations, similar to those produced by exposure to acute stress, suggesting its

possible role as a "chemical stressor" [32]. In humans, acute methylenedioxymethamphetamine treatment results in a rise in cortisol plasma concentrations, supporting the hypothesis of methylenedioxymethamphetamine-induced release of corticotropin-releasing hormone from the median eminence of the hypothalamus and subsequent hypothalamic-pituitary-adrenal axis and sympathetic nervous system activation. A recent study showed that amphetamine or methylenedioxymethamphetamine abusers were prone to having increased sexual desire, erectile dysfunction, and increased ejaculation latency [31].

Benzodiazepines

While benzodiazepines produce inconsistent effects on basal hormone secretion, they have potent effects on the inhibition of adrenocorticotropin, cortisol, thyroid-stimulating hormone, and prolactin secretion in response to stressful and pharmacological stimuli [97]. However, it is still unclear whether benzodiazepines reduce thyroid hormones. Acute diazepam administration causes stimulation of growth hormone secretion, but individuals taking this medication regularly over periods of years have an impaired growth hormone response or no response at all (tolerance). Benzodiazepines may act on the gamma-aminobutyric acid-coupled benzodiazepine receptors at the hypothalamus or other brain regions to reinforce the effects of endogenous gamma-aminobutyric acid. Nevertheless, some neuroendocrine effects of benzodiazepines are mediated through actions on benzodiazepine receptors in the pituitary gland. Plasma testosterone and 11-hydrocorticoid levels are increased by benzodiazepine ligands in humans [74]. In males, testosterone modulates peripheral-type benzodiazepine receptor density in the genital tract. The peripheral-type benzodiazepine receptor density is increased in the human ovary proportional to greater cell maturation and differentiation. Finally, individuals with benzodiazepine abuse can present with significant sexual dysfunctions such as erectile dysfunction [68], including a complete loss of libido.

Nutrition and Body Composition

Alcohol

There is some controversy about the effect of ethanol on body weight and about the contribution of alcohol energy to body mass. In fact, several studies have shown a positive, a negative, or no relationship between alcohol consumption and body composition alterations. These discrepancies are at least partially related to the different sample of subjects evaluated (healthy social drinkers, alcohol abusers, or subjects affected by chronic alcoholism) (Table 8).

According to Cordain et al. [52], the intake of small quantities of alcohol by social drinkers seems to have no effect on body composition or metabolism. On the other hand, in a study carried out in Italy, the caloric intake from alcohol in males was related to a significant increase in body mass and in the waist-to-hip ratio value, indicating a greater body fat distribution in the intra-abdominal region [159], which is considered as "harmful fat" for hypertension. These differences could be related to several factors, including age, gender, and the kind of alcoholic beverage used. Consistently, Addolorato et al. [3] have recently reported no significant modifications of body weight, fat mass, fat-free mass, or total body water in healthy social drinkers. However, while fat-free mass and fat mass were unmodified in the control group, fat mass increased in subjects drinking beer and wine and decreased in subjects who drank liquor. Fat-free mass was stable in beer and wine drinkers and increased in subjects who drank liquor.

On the other hand, the intake of large amounts of alcohol is related to several nutritional disorders. According to Lieber [117], long-term consumption of up to 2,000 calories/day in the form of alcohol does not produce the expected

Table 8 Main nutritional and metabolic features in subjects with substance abuse or dependence

Substance	Nutritional features	Metabolic features
Alcohol	Reduced BMI, reduced FM, increased ECW	Increased REE, lower carbohydrate oxidation, higher lipid oxidation
Nicotine	Reduced BMI, increased WHR	Increased lipid oxidation and lipolysis, decreased lipoprotein lipase activity
Opioids	Reduced BMI, reduced FM	Normal REE
Cocaine	Reduced BMI, reduced FM	Normal REE
Amphetamines	Loss of appetite	Indirect fat-mobilizing action, through an endogenous catecholamine release, and exercise-promoting effects, increasing EE
Benzodiazepines	Hyperphagia, enhanced palatability	

BMI body mass index, *FM* fat mass, *ECW* extracellular water, *WHR* waist-to-hip ratio, *REE* resting energy expenditure, *EE* energy expenditure

gain in body weight. Chronic alcohol abuse deeply affects nutritional status, first due to the fact that ethanol may supply more than 50% of the dietary energy in alcoholics partly because of the high caloric content of ethanol (7.1 kcal/g), its appetite suppressant action, and its promotion of a satiety effect by inhibiting gastric motility. Moreover, chronic intake of heavy amounts of alcohol may cause malabsorption of intestinal origin, steatorrhea, and pancreatic disorders, together with impaired hepatic metabolism of nutrients [117]. In recent years, a set of studies performed in our laboratory were aimed at evaluating the effect of chronic alcohol abuse on energy metabolism and substrate oxidation in alcoholics without clinical or laboratory evidence of liver disease or malabsorption. Alcohol-dependent individuals seem to have a high resting energy expenditure, thus consuming, even at rest, more energy than social drinkers and producing heat instead of storing energy in response to food or liquid intake as happens in normal metabolic pathways [1]. The increased resting energy expenditure in these individuals is related in part to the induction of the microsomal ethanol oxidizing system caused by chronic alcohol abuse [3]. Ultrastructural abnormalities of mitochondria have also been shown in alcohol-dependent individuals, with formation of giant mitochondria and functional alterations characterized by increased thermogenesis with dissipation of heat [117]. A further loss of energy by thermogenesis may be related to increased catecholamine levels [166]. Chronic heavy amounts of ethanol exposure in individuals without malabsorption also produce a lower body weight with respect to control groups and induce a preferential utilization of lipids as energy substrate and a lower carbohydrate oxidation, as indicated by a significantly lower non-protein respiratory quotient measured by indirect calorimetry assessment [2, 3]. These alterations cause alcoholics to have a lower body mass index and fat mass and a similar fat-free mass value with respect to controls as measured by dual-energy X-ray absorptiometry [3, 4, 8]. The alterations in body composition and metabolism seem to be completely reversible, at least in alcohol-dependent individuals who do not have severe alcohol-related disease, after 3 months of complete alcohol abstinence without pharmacotherapy or nutritional supplementation [3, 6]. With regard to body fluid distribution, alcohol-dependent individuals show an increase in the extracellular water compartment, with a higher extracellular water/total body water ratio compared with controls [7]. The mechanism responsible for this increase remains unclear. It could be hypothesized that the increased extracellular water/total body water ratio in alcoholics is a result of an increased leak of vacuolar fluid into the interstitial space caused by endothelial damage that occurs due to ethanol-induced vasoconstriction [22] and/or a direct toxic effect of ethanol on the cellular membrane [4]. Finally, compared with non-cirrhotic subjects, alcoholics affected by liver cirrhosis, and especially those with ascites, show a more impaired nutritional

status, with not only increased resting energy expenditure, preferential lipid oxidation, and a reduction in fat mass, but also a reduction in fat-free mass [5, 82, 161]. This could be due to the low protein intake with the diet, aggravated by ascites gastric compression and consequent anorexia, and impaired enteric absorption due to portal hypertension [161].

Nicotine

Chronic nicotine administration and its withdrawal produce significant effects on body weight and food intake. Several studies have reported a significantly lower weight and body mass index in cigarette smokers than in non-smokers. However, the former had a significantly higher waist-to-hip ratio than the latter [179], indicating that cigarette smoking could have harmful effects on the pattern of distribution of body fat. According to Perkins et al. [149], an acute intake of nicotine significantly increases energy expenditure, slightly at rest and more significantly during physical exercise. On the other hand, chronic administration of nicotine seems to be not associated with increased resting energy expenditure [98]. However, changes in body weight could be related to enhanced fat oxidation [98] and increased lipolysis and, over time, decreased lipoprotein lipase activity [168], suggesting an alternative mechanism by which nicotine modifies body weight despite changes in food intake.

Opioids and Cocaine

Data available in the literature focus overall on the metabolic and nutritional alterations in subjects with opioid and/or cocaine abuse and dependence. According to Santolaria-Fernandez et al. [160], drug addicts, especially those with heavier consumption, are undernourished. Poor nutritional status is mainly related to female sex, intensity of drug addiction, anorexia, and disturbance of the social and familial networks. Consistently, in a small cohort of opioid-addicted subjects evaluated before and after 4 years in a methadone maintenance program, weight loss and decreased body mass index were observed in the women, whereas the men experienced an increase in body mass index [108]. Drug dependence, especially when parenteral, is frequently complicated by infections, which are particularly harmful when affecting a previously malnourished person. Repeated infections, such as the hepatitis B virus, staphylococcal phlebitis, endocarditis, sepsis, systemic yeast infections, etc., contribute through the enhancement of catabolism to the development of undernutrition [160]. Moreover, human immunodeficiency virus infection may be a main cause of malnutrition (wasting syndrome) in drug addicts. Among human immunodeficiency virus-infected individuals with a high prevalence of drug use, females have lower average weight, body mass index, and fat mass than non-users. In particular, women with "heavy drug use" have lower whole body fat in both absolute and percentage amounts and higher lean mass. In a recent study, Forrester et al. [67] reported a lower weight and body mass index in Hispanic men with and without human immunodeficiency virus infection who used cocaine alone or with opiates compared with men who used only opiates or men who were human immunodeficiency virus-positive but did not use drugs. The observed differences in body mass index are not attributed to differences in reported dietary energy intake, resting energy expenditure, malabsorption, or infection with human immunodeficiency virus or hepatitis. In sum, the only factor associated with reduced lean and fat mass is heavy illicit drug use among women, a pattern not seen in men, while other factors, such as human immunodeficiency virus or hepatitis C, seem not to be associated with body composition parameters [48].

Amphetamine

No data are available in the literature on the nutritional status and energy expenditure in

amphetamine abuse. However, several studies have shown a marked loss of appetite secondary to 3,4-methylenedioxymethamphetamine and methamphetamine exposure, which persists for a day or more after the drug is taken [184]. Moreover, amphetamines have an indirect fat-mobilizing action, dependent on endogenous catecholamine release [152], and exercise-promoting effects, which increase energy expenditure [53].

Benzodiazepines

Benzodiazepines have the property of enhancing palatability through their central brain action. The effects of this action include the promotion of food consumption [51]. However, further studies are necessary to establish whether benzodiazepine abuse is correlated to changes in nutritional status and metabolic features.

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Pain and Addiction

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Contents

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Introduction

The undertreatment of pain is considered a significant public health problem. Over the last two decades, clinicians have been encouraged to actively manage painful conditions, and the concept of using opioids for chronic, non-cancer pain has gained more widespread acceptance. The significant increase in opioid prescribing for analgesia has been mirrored by an increase in prescription opioid abuse, highlighting another pervasive, undertreated, and significant public health problem: substance abuse and addiction [39]. Concerns about initiating addiction and fear of penalties against clinicians who act in good faith threaten to reverse the gains made in pain management to the detriment of both of these patient populations. With proper education and resources, most patients can be treated effectively without undue risk to themselves and society.

Use of opioid analgesics to treat cancer and acute pain is not controversial, and data support its efficacy. Treatment of chronic non-cancer pain with opioids is controversial and will be discussed. The clinical role of cannabinoids as analgesics has not been established and is not discussed. This chapter is intended to provide an understanding of the chronic, neurobiologic diseases of pain and addiction, key clinical

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_57,

characteristics, and strategies for treating pain and addiction as comorbid diseases.

Definitions

Pain

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or perceived in terms of such damage". It has also been defined as "whatever the experiencing person says it is, existing whenever that person says it does" (Margo McCaffery, 1967). The latter definition has been amended by Fishman to state that pain "is whatever the patient states it is unless proven otherwise by poor adherence to an agreed upon medical regimen" [23]. Pain has also been conceived as primarily a motivational state that has a powerful influence on decision making.

Pain states have been further classified as: physiologic and pathologic; acute and chronic; inflammatory; neuropathic, and malignant bone pain. Physiologic pain exists as an innate protection. It is transient, well-localized, may have an inflammatory component, and exhibits a stimulus-response relationship. Pathologic pain, sometimes known as clinical pain, does not serve a protective function and is indicative of maladaptive changes in the peripheral and central nervous systems. Pathologic pain is either inflammatory, neuropathic, malignant bone pain or a combination of these. Acute pain exists in the presence of an injury or painful disease and resolves with resolution of the injury or disease event. Chronic pain exists in the absence of any injury or discernable tissue damage or in conjunction with chronic diseases that have ongoing inflammatory or neuropathic components. Inflammatory, neuropathic, and malignant bone pains have distinct neurochemical profiles and respond to pharmacologic and physiologic interventions in specific ways.

Addiction

The definitions of addiction, abuse, tolerance, and dependence have evolved over time. One major problem is the inclusion of pharmacological dependence and tolerance in the definition of drug addiction. Both conditions are an expected consequence of long-term opioid therapy, and neither indicates problematic drug use or addiction per se. Lack of consensus has led to confusion among clinicians, patients, regulators, and the general public, resulting in misconceptions regarding the medical use of opioids for analgesia or for addiction. This has caused unnecessary suffering, stigmatization of the disease of addiction, undue economic burdens to society, and inappropriate legal and regulatory actions against clinicians and patients.

In 2003, Savage et al. published "Definitions Related to the Medical Use of Opioids: Evolution Towards Universal Agreement" [63]. This document contains the recommendations of the Liaison Committee on Pain and Addiction, formed jointly by the American Pain Society, the American Academy for Pain Medicine, and the American Society for Addiction Medicine in 1999, to clarify the nomenclature used to define terms that are used to describe addiction and therapeutic opioid use. Its definitions are:

- Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving;
- Physical dependence is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist, and
- Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Additionally, an understanding of pseudoaddiction and chemical coping is relevant when considering pain and addiction. Pseudoaddiction is described as drug-seeking behavior in the setting of uncontrolled pain. It disappears when analgesic interventions, including increased doses of an opioid, become effective [78]. Frequently, this drug-seeking behavior is indistinguishable from that of an opioid addict, including the use of illicit opioids. However, unlike in drug addiction, the motivation to use opioids is to achieve analgesia and not for its psychological rewarding effects. When analgesia is achieved, aberrant drug use behaviors resolve.

Chemical coping is described as using medications in non-prescribed ways to cope with stress. It constitutes an avoidance-type coping strategy. Individuals who suffer from depression, anxiety, alexithymia, and somatization, as well as sensation seekers, are frequently identified as chemical copers [37]. It is often extremely difficult for this population to acknowledge and participate in non-pharmacological aspects of their treatment, including learning more adaptive coping skills, and to change from their coping medication of choice. All addicts are chemical copers but not all chemical copers are addicts.

Incidences of Pain and Addiction

Approximately 50–70 million people in the United States are inadequately treated or untreated for a chronic painful condition, resulting in an estimated cost of $61 billion in lost productivity [8].

The 2007 National Household Survey on Drug Use and Health reported that 9.2% of the population aged 12 years and older abuse substances or are substance dependent. The range varies from 3 to 16%. Over 15 million Americans have admitted to abusing prescription drugs, of whom 1.6 million are prescription opioid addicts. This is the second-largest type of illicit drug abuse after marijuana, and exceeds the total number of people abusing heroin (0.3 million), cocaine, hallucinogens, and inhalants. Opioids are the most commonly prescribed medications in the United States [35].

Based on these data, approximately 5–7 million people have addiction and a chronic pain condition. In one study of an addicted population on methadone maintenance treatment the incidence of chronic non-cancer pain was 61.3% [31]. When chronic pain and addiction exist together, they are mutually reinforcing conditions.

Neurobiology of Pain

Pain exists as a physiologic protection. It is innate, except in extremely rare people with anociceptive mutations. Nociceptive afferent pathways are present and functional from 24 weeks post-conceptual age. The development of central inhibitory pathways lags behind and is not mature until 4–6 months of age.

In the classic pain pathway unmyelinated C-fibers and myelinated A-δ fibers transduce noxious stimuli at the periphery and transmit them to laminae I–VI of the dorsal horn in the spinal cord, where they are modulated. Secondary and tertiary neurons in the central nervous system transmit impulses to higher centers where the sensation is perceived and acted upon. Persistent pain that no longer serves a protective role is pathologic and should be considered as a disease of the nervous system. Neuroplasticity in the central nervous system allows pain to become pathologic. Congenital anociception [1, 14] is a rare, fatal condition. Sufferers typically die of sepsis during childhood. In contrast, fibromyalgia appears to represent a constitutional hyperalgesic state [60].

There are two types of specialized peripheral primary sensory nociceptive neurons. Those activated by specific stimuli, e.g., chemical, thermal or mechanical, and those that are more adaptive called wide dynamic range neurons. Wide dynamic range neurons evidence weak activation by innocuous mechanical stimuli and more intense excitation by noxious mechanical or thermal stimuli. The presence of these distinct

receptor types indicates differences in coding of information from the periphery. Stimuli-specific neurons that synapse in laminae I and II provide the basis for differentiating noxious and non-noxious events. The large receptive fields of the wide dynamic range neurons that synapse in laminae V and VI set the responsiveness of higher centers. The axons of spinal neurons arising from dorsal horn laminae I, V, and VI terminate in the midbrain and thalamus. Activated peripheral nociceptive afferent fibers exhibit a notable propensity to increase their responsiveness to subsequent stimuli.

Tissue injury results in inflammation and changes in the extracellular milieu as intracellular contents issue from injured cells. The presence of protons, potassium ions, adenosine triphosphate, serotonin, bradykinin, prostaglandins, growth factors, and cytokines at nociceptive nerve endings sensitize them, and are partially responsible for increased pain (primary hyperalgesia) in injured tissue. Continued peripheral activation leads to central sensitization and "cross-talk" in the dorsal horn laminae. "Cross-talk" occurs when high-intensity firing from acute pain (inflammatory) or low-intensity firing from chronic pain (neuropathic) induces Aα and Aβ fibers to conduct "pain" signals. Inflammation also recruits silent nociceptors. Once activated, these previously silent nociceptors increase afferent transmission of mechanical stimuli, e.g., pain associated with inflammatory arthritides [58].

Persistent noxious stimuli are associated with increased synaptic activation of spinal neurons and up-regulation in the central nervous system, leading to evoked pain in uninjured tissues (secondary hyperalgesia). This phenomenon of "central sensitization" is the postulated mechanism for chronic and neuropathic pain. It is characterized by decreased thresholds for activation, shorter response latencies, spontaneous neural activity, and exaggerated responses to a given stimulus (hyperalgesia and allodynia). Central sensitization is primarily mediated by activation of *N*-methyl-*D*-aspartate glutamate receptors, which leads to the recruitment and increased activity of non-*N*-methyl-*D*-aspartate α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, kainate, and 1-aminocyclopentane-1,3-dicarboxylate spinal glutamate receptors. *N*-methyl-*D*-aspartate receptor activation, in particular, induces a persisting afferent facilitation, leading to the generation of long-term potentiation of synaptic effectiveness. Descending inhibition of spinal pain-related activity is produced by neurons utilizing different chemical mediators from those involved in activation of peripheral nociceptors and afferent secondary neurons. Chemical mediators of descending inhibition include serotonin, catecholamines, and endogenous opioids.

Chronic pain arises from changes in neural functioning leading to persistent nociceptive input. Long lasting aberrant central nervous system-generated activity that triggers the perception of pain also produces plastic alterations in behavior and nervous function. In addition to phenomena such as sensitization of peripheral nociceptors and central neurons, rearrangements of activity and neuronal connections occur through gene induction. Principal factors in clinical circumstances are the emotional and motivational concomitants of persisting pain symptoms.

Brain imaging confirms that the cerebral cortex plays an important role in pain processing. Noxious stimulation evokes prominent signs of localized metabolic increases in several distinct cerebral cortical areas, including the anterior insula, the anterior cingulate cortex, and somatosensory II regions. A robust correlation exists among stimulus intensity, activation of these cortical areas, and patient reports of pain [22]. The lateral thalamic nuclei contribute terminals to several nuclei of the ventral posterior thalamus, a main somatosensory zone with spatial and modality characteristics suggestive of a role in discrimination. In contrast, the medial thalamic ventrolateral projection targets neurons in nuclei usually associated with affective or motivational regions. Less consistent, more context-influenced or smaller activations occur in other cortical regions. The amygdala and hypothalamus participate in affective and homeostatic functions related to nociceptive

mechanisms in addition to other sensory inputs. Mental state, attention, and disposition modify the pattern and details of imaged cortical responses to noxious input distinguishing pain as special from other sensations [4, 29]. For example, the activity in the anterior cingulate cortex evoked by pain-causing stimuli is related to emotion and motivation. Nociceptive signals also reach higher brain centers via multi-synaptic routes by way of connections in subthalamic brainstem nuclei.

The combined evidence supports pain as a discriminative sense and as an emotion [15, 58]. As such, it consists of a sensation and a motivation for action. The affective-motivational component of pain includes perception of the negative hedonic quality of pain, emotional autonomic and motor reactions, a general activation or arousal, and the drive to terminate the stimulus that causes the pain [71]. It is thought to be mediated via the anterior cingulate cortex. The anterior cingulate cortex has a high density of opioid receptors and is one of the brain regions most consistently activated by painful stimuli in human imaging studies. The opioid receptor density in the posterior, motor part of the anterior cingulate cortex, the midcingulate cortex, is lower than in the anterior cingulate cortex proper in the perigenual region. Morphine binding has been shown to modulate affective aspects of pain via receptors in the anterior cingulate cortex proper and motivational aspects of pain via receptors in the midcingulate cortex. This would explain the finding that morphine has a more profound effect on the affective component of pain than the sensory component.

There are many hypotheses describing the neurobiology of pain, but none of them fit all the data available. It is known that the mechanisms of pain include specialized receptive organs, selective and convergent pathways, plasticity of responsiveness, and interactive modulation, and that three neurochemically distinct types of pain have been identified in the central nervous system: inflammatory, neuropathic, and malignant bone pain [12]. Although research into the role of glia in pain physiology and opioid efficacy is in its infancy, early data are promising. This knowledge could allow targeted therapies to correct underlying abnormalities in the central nervous system to relieve pain. For example, anti-inflammatory medications are most appropriately used to treat inflammatory pain. Unfortunately, there are many more ions, neurotransmitters, receptors, and cell types involved in pain and nociception than there are therapies to modulate them. This field is rich with ongoing research and the potential for development of new therapeutics.

Neurochemistry of Addiction

Physiologically, dopaminergic and opioid systems modulate a number of processes including: the regulation of reward and affective states; cardiovascular, immunological, and neuroendocrine functions, and the effects of substances of abuse and the development of addiction [65].

Addiction is a chronic neurobiological disease of the brain's reward and motivation centers. The reward centers exist to preserve the organism and propagate the species. Natural cues that stimulate these centers include eating, sex, social interactions, and unexpected novel stimuli. Opioids, as well as other drugs of abuse, stimulate these centers in a similar fashion to endogenous ligands, but their effects are more intense and prolonged. For drugs that use brain reward centers, craving assumes the strength and characteristics of a primary survival drive. Thus, addictive drugs activate and dysregulate endogenous reward centers. By utilizing these brain circuits, they take over behavior. This leads to progressive loss of control over drug use despite negative consequences to the user. Dopamine, gamma-aminobutyric acid, and glutamate are key to these reward circuits. Serotonin, norepinephrine, enkephalin, endorphin, and cholecystokinin are also functionally important [65]. Interestingly, the central nervous system areas involved in physiologic drug tolerance and dependence are separate from the reward centers, which confirms the clinical observation that physical dependence and

tolerance to drugs are not associated with addiction and craving, although the converse is true.

Addiction involves drug, host (trait variables), and context (state variables) (Fig. 1). Their interrelationship regulates the functional set point for hedonic tone. Manipulating the neural connections can alter drug-taking behavior.

The cortico-mesolimbic reward pathway is a specific limbic circuit generating feelings of pleasure [65]. It is also involved in traditional memory and in mediating addictive behavior. Emotional memories can be very powerful and may be relevant in the etiology and persistence of addiction, e.g., victims of childhood sexual abuse have an increased incidence of subsequent substance abuse and addiction. Notable structures of the cortico-mesolimbic reward pathway are the ventral tegmental area in the brainstem, the nucleus accumbens in the basal ganglia, and the medial prefrontal cortex.

Cortico-mesolimbic dopamine neurons arising from the ventral tegmental area project to the nucleus accumbens and terminate on medium-sized spiny cells that contain gamma-aminobutyric acid (GABA) and endogenous opioid peptides. These cells reportedly fire in anticipation of food and water [17]. Opioids produce their rewarding effects via activation of μ-opioid receptors located on GABAergic midbrain interneurons that negatively regulate dopamine cell firing. Activation of these inhibitory Gαi-coupled μ-opioid receptors reduces the GABAergic inhibition of midbrain dopamine neurons, thereby increasing their firing rate and the amount of dopamine released in the nucleus accumbens [28]. The nucleus accumbens has been termed the universal addiction site because it is a region where drugs as diverse as cocaine, amphetamine, alcohol, opioids, marijuana, and nicotine all increase dopamine levels. Opioid-containing neurons project from the nucleus accumbens to several reward centers, including the lateral hypothalamus (feeding and sex center), medial prefrontal cortex, and other limbic structures.

The ventral tegmental area is an important site of opioid control for goal-directed behaviors. Dynorphin is an endogenous peptide that is κ-opioid receptor selective. Dynorphin terminals synapse onto dopamine dendrites in the ventral tegmental area and inhibit dopamine neuron signaling by a direct post-synaptic action via activation of a G-protein-coupled inwardly rectifying potassium channel.

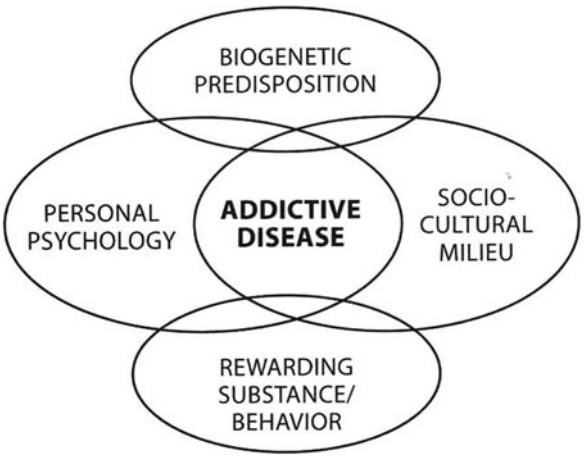

Fig. 1 The relationship between drug, host, and context variables in the etiology of addictive disease—biogenetic predisposition (altered neurochemistry); personal psychology (patients with comorbid bipolar disorder, attention-deficit hyperactivity disorder, schizophrenia, antisocial personality disorder, and psychopathic personality disorder are especially at risk); rewarding substance/behavior (exposure to the drug of choice), and socio-cultural milieu (environmental stressors, especially in those with the following psychological traits: extreme shyness, borderline personality, anxiety proneness, alexithymia, and poor stress coping). Reprinted from Jovey [32] with permission from the International Association for the Study of Pain

Kappa-opioid receptor agonists infused into the ventral tegmental area inhibit dopamine neurons that project to the medial prefrontal cortex but not to the nucleus accumbens. Thus, medial prefrontal cortex dopamine concentrations decrease, with attendant behavioral effects, while nucleus accumbens dopamine concentrations remain unchanged. Midbrain dynorphin levels increase after amphetamine administration. Prolonged administration of drugs of abuse, e.g., alcohol or cocaine, produces long-lasting down-regulation of κ-opioid receptor messenger ribonucleic acid levels in the ventral tegmental area. Alterations in dopamine release in the cortex may also contribute to the psychotomimetic effects of κ-opioid receptor activation in humans [44].

Initial drug use stimulates dopamine release in the reward centers. However, over time, dopamine stores and receptors become depleted, and higher concentrations are needed to overcome this. When dopamine release is maximal but stimulation continues, or increases, other brain areas are recruited, particularly the glutamate rich frontal cortex. Glutamate release enhances second messenger systems, activates nuclear transcription factors, and changes long-term gene expression. These glutamatergic pathways mediate drug "cues". Glutamate is proalgesic and is one of the excitatory amino acids associated with hypersensitivity to pain in the central nervous system manifested as hyperalgesia and allodynia. Reduced dopamine-mediated reward is associated with high rates of depression, irritability, anxiety, and suicide—characteristics common to patients in pain and with addiction.

The effects of excessive dopamine associated with addiction cause a decrease in dopamine type-2 receptor numbers over time. The reward circuitry becomes damped, a state maintained long after drug use stops since it takes a prolonged period for the dopamine type-2 receptor density to return to normal. On magnetic resonance imaging, recovering addicts demonstrate persistent reductions in metabolic activity in the prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex and reductions in the neuronal density of frontal lobe regions. These changes make these brain areas particularly sensitive to re-exposure to drugs of abuse. Deficits in impulse control and decision making that characterize addictive behavior are mediated by the orbitofrontal cortex and anterior cingulate cortex. Limbic impulses are also suppressed.

In primate studies stress increases vulnerability to cocaine self-administration [50], whilst a less stressful, more privileged environment attenuates the reinforcing effects of drugs and provides a degree of protection from addiction and relapse during recovery. A less stressful, more enriched lifestyle boosts the number of dopamine receptors in the brains of primates and makes them less vulnerable to the reinforcing effects of cocaine and less likely to relapse. The role of environmental enrichment in humans is unknown. However, human studies have suggested that the number of dopamine type-2 receptors an individual has might be related to his or her vulnerability to the rewarding effects of a drug. Relatively, people with subnormal levels of dopamine type-2 receptors might experience euphoria with stimulants while those with normal levels of dopamine type-2 receptors could perceive them as unpleasant. Nevertheless, although treatments that could increase the brain's dopamine type-2 receptors have been suggested as potential treatment for drug abuse [38], the results of clinical studies have been disappointing.

It has been theorized that opioid abusers may have a biologic predisposition to opiate dependence in much the same way that some individuals appear predisposed biologically to developing alcohol dependence. According to this proposal, exogenous opioids might be filling a neurochemical deficiency in the central nervous system, and opioid addicts may be self-medicating to correct the deficit. This proposal has not been proven but is supported by data from patients in opioid maintenance therapy who have a near normal, stable brain chemistry whilst in treatment.

The overlap of addiction and pain pathways in the brain, e.g., at the nucleus accumbens, anterior cingulate cortex, and hippocampus, might

explain, at least partially, the close association between pain states and addiction. Pain circuits and addiction pathways both utilize endogenous opioids. Also, both conditions involve sensitization and synaptic plasticity, which alter the responsiveness of the central nervous system to sensory input.

Neurochemistry of Opioids

Opioid analgesics do not simply inhibit pain transmission pathways. They mimic the actions of endogenous opioids released in response to specific conflict situations. Agonists at each receptor modulate neurons in a circuit that selectively controls nociceptive transmission. Opioid actions contribute to, and are determined by, the state of the circuit. The circuit can operate in both pain-inhibiting and pain-facilitating states. Thus, opioids can produce either analgesia or pain, depending upon the circumstances [20].

Opioid receptors (μ, κ, δ, and opioid receptor-like) belong to a large superfamily of G-protein-coupled receptors. Endogenous opioid peptides are released in the central nervous system in response to stressful stimuli. Mu-opioid receptors couple preferentially to the pertussis toxin-sensitive G proteins, Gi and Go, and inhibit the adenylyl cyclase/cyclic adenosine monophosphate pathway. Mu-opioid analgesia is attributed to the $G_{\beta\gamma}$ dimer (released from Gi/o proteins) that activates G-protein-activated, inwardly rectifying potassium channels and inhibits voltage-dependent calcium channels, thereby suppressing cellular activities through hyperpolarization. In particular, it inhibits signaling between primary afferent terminals and second-order dopamine neurons. The anatomic distribution of δ-, κ-, and opioid receptor-like opioid receptors parallels those of the μ-opioid receptors present in the component nuclei of the pain modulating circuit. Ligands selective for each opioid receptor regulate various motivated behaviors including feeding, alcohol and psychostimulant consumption, and pain [74].

Opioids control the pain-transmission pathway directly through actions in the superficial layers (laminae I, II, and IV–VI) of the dorsal horn. Both primary afferent terminals and second-order dorsal horn neurons bear μ-opioid and δ-opioid receptors [22]. Mu-opioid agonists are powerful analgesics and produce profound appetitive motivational actions. The contribution of δ- and κ-opioid receptors to motivational states is less clear.

In addition to their direct action on the spinal cord, μ-agonists also activate supraspinal structures that project down and control pain transmission at the level of the spinal cord. This "top–down" pain modulatory circuit includes the frontal lobe cortical regions, hypothalamus, and amygdala that project to the para-aqueductal gray, which in turn projects via the rostral ventral medulla and dorsolateral pontine tegmentum to the superficial layers of the dorsal horn. This anatomic arrangement enables the descending system to control nociceptive transmission at the first central synapse where the nociceptive primary afferents terminate. The component nuclei of this pain-modulation pathway contain μ-opioid receptors and a relatively high concentration of the endogenous opioid peptides leucine- and methionine-enkephalin. Activation of the rostral sites leads to release of endogenous opioids in downstream regions. Lesions to, and antagonists applied at, these sites block the analgesic effects of systemic μ-opioid agonists.

There are three distinct types of component neuron in the descending modulating pathway: OFF cells activated by μ-opioid agonists that inhibit responses to noxious stimuli; ON cells that are activated by noxious stimuli, are inhibited by μ-opioid agonists, and facilitate responses to noxious stimuli; and NEUTRAL cells that do not change their activity [48]. ON and OFF cells are found in the para-aqueductal gray, the dorsolateral pontine tegmentum, and the rostral ventral medulla. The rostral ventral medulla ON and OFF cells project directly to the dorsal horn, where they modulate pain transmission. Increased OFF cell activity contributes to the anti-nociceptive effect of μ-opioid receptor

ligands while analgesic doses of μ-opioid receptor agonists silence ON cells. Very simply, OFF cells "switch off" pain whereas ON cells "switch on" pain. OFF cells are activated by decisions to ignore pain, μ- and δ-opioid receptor agonists, cannabinoid agonists, and gamma-aminobutyric acid-A antagonists. ON cells are activated by decisions to respond to pain and conditions associated with hyperalgesia, e.g., tonic noxious stimuli, acute opioid abstinence. The rostral ventral medulla neurons contain primary and secondary cells. Primary cells respond to κ-opioid receptor agonists and represent physiologically characterized ON cells. Secondary cells respond to μ-opioid receptor agonists and represent OFF cells.

Endogenous μ-opioid receptor agonists increase OFF cell activity by pre-synaptic inhibition of GABAergic inputs and directly hyperpolarizing ON cells. These actions tip the balance in favor of OFF cell activity and, hence, analgesia. Activation of OFF cells, rather than the inhibition of ON cells, is critical for the suppression of noxious stimuli.

Kappa-opioid receptor agonists alter OFF and ON cell function via glutamate release. Kappa-opioid receptor agonists attenuate μ-opioid receptor agonist-mediated analgesia by hyperpolarization of OFF cells, a direct post-synaptic inhibition, and by pre-synaptic inhibition of glutamate release. They also inhibit glutamatergic transmission at ON cells, reducing ON cell stimulation. Glutamate antagonists applied directly to the rostral ventral medulla have the same effect, i.e., OFF cell activation and anti-nociception by systemic μ-opioid receptor agonists (e.g., morphine) are prevented. The selective inhibition of OFF cells explains the anti-analgesic effect of κ-opioid receptor agonists while the selective inhibition of ON cell firing explains their anti-hyperalgesic effects. These effects are demonstrated in studies where κ-opioid receptor agonists applied directly to the rostral ventral medulla reduce the analgesic behaviors observed in response to systemic μ-opioid agonists but also produce analgesia themselves. It also predicts that other conditions that result from activation of rostral ventral medulla pain-facilitating neurons (presumably ON cells) such as hypersensitivity produced by nerve injury will also be relieved by κ-opioid receptor agonists. Endogenous κ-opioid agonist actions in the rostral ventral medulla regulate behavioral responses to noxious stimuli in a state-dependent manner [48].

Pain has been conceptualized as primarily a motivational state that has a powerful influence on decision making. Stress-induced analgesia represents a "do not respond to pain" decision as occurs with OFF cell activation in the endogenous opioid-mediated, pain-modulatory descending pathway described above. It can be blocked by lesions of the central nucleus of the amygdala and by opioid antagonists (e.g., naloxone). A "do not respond" decision occurs under conditions of threat and anticipated reward. The specific brain circuitry of the analgesic effect of reward expectancy is not known. It is hypothesized to involve the mesostriatal dopamine neurons implicated in drug and food reward. Mu-opioid agonists placed directly on the nucleus accumbens promote analgesia and increased food consumption. Opioids directly affect the decision process through an action in the mesostriatal dopamine pathway, where they concomitantly promote reward seeking and raise the threshold for responding to noxious stimulation.

In the rostral ventral medulla, δ-opioid receptors are present on axon terminals. Selective antagonists block analgesia produced by para-aqueductal gray activation. Delta-opioid receptor agonists produce changes in rostral ventral medulla ON and OFF cells that are similar to, but weaker than, those produced by μ-opioid receptor agonists and produce weak-to-moderate analgesia. Prolonged inflammation is associated with an enhanced anti-nociceptive effect for deltorphin (a δ-opioid receptor selective ligand) in the rostral ventral medulla. Delta-opioid receptor function might be more robust if the receptor is studied under appropriate conditions.

Nociceptin, a ligand selective for the opioid receptor-like opioid receptor, strongly hyperpolarizes all classes of neurons in the rostral ventral medulla and para-aqueductal gray through

activation of an inwardly rectifying potassium channel. Nociceptin inhibits gamma-aminobutyric acid release by a pre-synaptic action. In vivo, the opioid receptor-like ligand acts post- synaptically to strongly inhibit all ON and OFF cells in the rostral ventral medulla. The behavioral effect of an opioid depends on whether the circuit is in the ON cell or OFF cell state. When morphine is given, ON cells become silent and OFF cells fire continuously. In the OFF cell-activated state, dorsal horn neurons and withdrawal reflexes are inhibited. Serotonergic neurons in the rostral ventral medulla that project to the dorsal horn provide a third, state-dependent element that controls nociceptive transmission.

Placebo and nocebo (development of adverse effects or worsening of a condition after administration of a placebo) effects are mediated via central dopamine and opioid systems [65]. Placebo analgesia is mediated through activation of μ-opioid receptors in the midcingulate cortex, insular cortex, and nucleus accumbens. It is thought to represent a form of reward expectation processing; a process mediated by cortico-mesolimbic dopamine neurons. Molecular imaging studies have examined the response of nucleus accumbens dopamine transmission in the presence of a placebo with expected analgesic properties, and the relationship between nucleus accumbens dopamine and endogenous opioid systems. Placebo analgesia is most strongly predicted by activation of dopamine neurotransmission in the nucleus accumbens (25% variance). Dopamine activation in this region is correlated with μ-opioid activation in the rostral and subgenual anterior cingulate cortex, orbitofrontal cortex, anterior and posterior insulae, medial thalamus, nucleus accumbens, amygdala, and para-aqueductal gray. The magnitude of the placebo response correlates directly with the degree of neurotransmitter activation. Conditioned analgesia is blocked by application of μ-opioid receptor antagonists into the basolateral amygdala, para-aqueductal gray, and rostral ventral medulla, but not by δ- or κ-opioid receptor selective antagonists. The analgesia that accompanies conditioned fear is inhibited by κ-opioid receptor agonists in the rostral ventral medulla.

Opioid-mediated pain modulatory circuits can be engaged during appetitive as well as aversive motivational states. The rostral ventral medulla ON cell burst and OFF cell pause are reduced during food and water consumption. In animal studies, eating and food cues activate an opioid-mediated pain modulatory circuit, increasing the probability that the food will be consumed despite conflicting drives. Mu- and δ-opioid receptor agonists in the nucleus accumbens (the region of the basal ganglia crucial for linking motivation to action) induce both anti-nociception and consumption of sweet and rich food and ethanol. Instinctive as well as learned motivational states with either appetitive or aversive valence are associated with activation of opioid-mediate anti-nociceptive mechanisms. Dopaminergic activity in the nucleus accumbens is activated during both rewarding and aversive environmental events. It increases with anticipation of a positive outcome and reduces when the desired outcome becomes less likely. In rodents, a robust morphine locomotor response is dependent upon, and specific to, dopamine release. Dopamine-deficient mice display morphine analgesia, but the dose-response curve is shifted rightwards, suggesting that dopamine may mediate some of the analgesic effects of morphine. Data support the hypothesis that dopamine projections to the spinal cord provide tonic pain suppression mediated through dopamine-type 2 receptors.

Role of Glia in Analgesia, Pain, and Nociception

The role of glia in maintaining pain syndromes and in the efficacy and adverse effects of opioid drugs has only recently been identified and studied. It may be the key to understanding chronic pain and analgesia. Glia are microglia, astrocytes, and oligodendrocytes. They were originally considered to have a passive, supportive role in the central nervous system. Now it is known that they actively participate in

brain functioning and information processing [2]. Microglia are part of the immune system and enter the brain from the bloodstream during development. Microglia have primarily a surveillance role, rapidly extending and retracting processes to sample constantly the extracellular environment. The remaining glial cells arise from the neuroectoderm. Astrocytes are primarily involved in providing energy sources and neurotransmitter precursors to neurons, cleaning up debris, regulating extracellular levels of ions and neurotransmitters, and actively modulating synaptic transmission [76]. Under basal conditions, glia are not important regulators of pain transmission. However, when activated by damage to peripheral tissues, peripheral nerves, spinal nerves, or the spinal cord, microglia and then astrocytes in the spinal cord become activated. Activated glia release numerous neuroexcitatory substances including pro-inflammatory cytokines and chemokines, nitric oxide, reactive oxygen species, adenosine triphosphate, prostaglandins, and excitatory amino acids, all of which are pro-algesic and contribute to the maintenance of pain syndromes. Microglia and astrocytes also produce D-serine, an endogenous ligand for the glycine modulatory site on *N*-methyl-*D*-aspartate receptors, that enhances C-fiber-mediated excitation of pain-responsive neurons. Glia also decrease reuptake of glutamate in the spinal cord, thereby increasing synaptic glutamate and potentiating nociceptive signaling.

Astrocytes communicate with each other in a bidirectional manner through waves of calcium ions, propagating information over large distances. They possess many of the same neurotransmitter receptors as neurons, and neurotransmitter release by neurons activates calcium-based signaling cascades in astrocytes. Astrocytes then release neuroactive substances, signaling back to neurons in a feedback loop. Different types of molecules secreted by astrocytes can either inhibit or enhance overall levels of neuronal activity, and this is implicated in the etiology and maintenance of pathological pain, specifically neuropathic pain. These effects occur throughout the pain pathways including peripheral nerves, dorsal root ganglia, and spinal cord. Additionally, activated glial cells are known to reduce the analgesic effects of opioid drugs and may have a role in the evolution of opioid tolerance, physical dependence, and withdrawal [76].

Neuropathic pain arises from trauma, inflammation, and/or infection of peripheral nerves. It is characterized by allodynia, hyperalgesia, paresthesias, dysesthesias, and spontaneous pain. Damaged nerves alter their axon receptor expression to become increasingly responsive to substances that cause pain and to substances that normally do not. Neurons that do not normally signal pain can alter their gene expression and produce "pain" neurotransmitters (e.g., substance P, adenosine triphosphate, excitatory amino acids). Immune cells in and around peripheral nerves, and immune-like glial cells in the spinal cord, are key to both the creation and maintenance of pathological pain states. These same glial cells compromise the efficacy of opioids for pain control.

Peripheral nerve injury is associated with the local release of chemokines, bradykinin, serotonin, prostaglandin E2, histamine, substance P, and calcium gene reactive peptide. This "inflammatory soup" leads to enhanced afferent excitability that is exacerbated by neutrophils, macrophages, and pro-inflammatory cytokines, along with nitric oxide and reactive oxygen species, activated to kill invading microorganisms. Unfortunately, these substances also directly increase nerve excitability, damage myelin, disrupt the blood-nerve barrier, and expose the nerve to immune cells, thus creating a vicious cycle of nerve damage. Nerve damage is further exacerbated by the release of calpain, a calcium-activated protease in Schwann cells and associated myelin that destroys myelin. Destruction of myelin releases pro-inflammatory cytokines (primarily tissue necrosis factor, interleukin-1, and interleukin-6) and chemokines. In animal models, thalidomide and clonidine (an α-2 adrenoceptor agonist) both prevent neuropathic pain [76]—the former by concomitantly decreasing tissue necrosis factor while increasing the anti-inflammatory

cytokine interleukin-10, and the latter by reducing tissue necrosis factor and interleukin-1 while increasing the anti-inflammatory cytokine trophic growth factor β1. Tumor necrosis factor is thought to increase excitability in spared sensory neurons as a result of nearby neuroinflammation by stimulating retrograde transport leading to changes in gene expression and exerting autocrine and paracrine actions within the dorsal root ganglion. Additionally, tissue necrosis factor can trimerize and insert itself into lipid membranes, forming cation-permeable pores and cause demyelination of peripheral nerves. This increases membrane conductance by altering sodium and calcium channel functioning and leads to nerve damage with consequent insertion of ectopic sodium channels in the exposed membrane. This is associated with ectopic nerve firing and neuropathic pain. Tumor necrosis factor also increases the conductivity of glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors (pronociceptive), and stimulates the overproduction and release of glutamate from microglia by upregulation of microglial glutaminase. Similar changes occur in the dorsal root ganglion, where satellite glial cells, along with resident and recruited immune cells, are well-positioned to alter the excitability of both damaged and healthy dorsal root ganglion neurons [76].

Activation of spinal cord glia amplifies peripheral and dorsal root ganglion-associated pain states. Release of substance P, adenosine triphosphate, and excitatory amino acids in response to afferent nociception leads to activation of microglia and then astrocytes with the consequent release of neuroexcitatory substances, including prostaglandins, interleukin-1, interleukin-6, and nitric oxide. Microglia are exquisitely responsive to extracellular adenosine triphosphate [76]. They release plasminogen, a protein that enhances *N*-methyl-*D*-aspartate receptor function and brain-derived neurotrophic factor. Both cause neuroexcitation by decreasing GABAergic and glycinergic inhibition.

The effects of glial products, such as pro-inflammatory cytokines, on spinal cord dorsal horn neurons depend on the presence or absence of ongoing neuropathic pain [76]. Glial activation in one central nervous system region can lead to glial activation in projection regions. Glia in the brain regulate many important functions, including responses to opioids such as morphine. The mechanisms underlying neuropathic pain and morphine tolerance are surprisingly similar.

Glial activation dysregulates the action of opioids at both spinal and supraspinal sites [76]. Recent data show that chronic morphine dosing activates microglial p38 mitogen-activated protein kinase and stimulates the production of spinal pro-inflammatory cytokines, both of which are associated with morphine tolerance. Blocking the pro-inflammatory cytokines reverses morphine tolerance. Morphine tolerance is associated with down-regulation of glial GLAST (excitatory amino acid transporter (1)) and GLT-1 (glial glutamate transporter-1, also known as excitatory amino acid transporter (2)) glutamate transporters (major transporters responsible for regulating extracellular levels of excitatory amino acids) in spinal cord dorsal horn which concomitantly leads to an increase in extracellular excitatory amino acids. Tolerance may occur through an opposing increase in neuronal excitability due to glial-induced elevations in glutamate and pro-inflammatory cytokines. Spinal inhibition of pro-inflammatory cytokines abolishes morphine resistance in neuropathic animals [76].

Glia may also play a role in opioid withdrawal symptoms. Rodents given a glia inhibitor during morphine administration did not manifest withdrawal when given a μ-opioid antagonist. Glia may also contribute to morphine reward. Injection of activated astrocyte cultures onto the nucleus accumbens or anterior cingulate cortex increased morphine conditioned place preference. Glia, in addition to regulating pathological pain, opioid analgesia, and opioid tolerance, should be considered as contributing to the phenomena of morphine reward and morphine dependence/withdrawal.

Endogenous μ-opioids (met- and leu-enkephalin) stimulate the release of interleukin-1 from microglial cultures. Spinal pro-inflammatory cytokine blockade increases the

magnitude and duration of action of acute analgesia to morphine and methadone. Different receptors mediate the pain-suppressive effects of morphine than its pain enhancing effects. Hence, it should be possible to separate the neuronally mediated, pain-suppressive effects of opioids from their glial-activating, pain-enhancing effects, either by structurally modifying opioids to prevent their binding to the glial non-stereotactic opioid receptor or by co-administration of a [+]-opioid antagonist that would block glial activation while allowing opioid action on neurons to remain unaltered, e.g., [+]-naloxone (inactive at neuronal opioid receptors).

Although pro-inflammatory substances may cause chronic neuropathic pain, anti-inflammatories, e.g., prostaglandin inhibitors and steroids, are not effective in its treatment. This may be explained by differences in chemical effects at different sites. What is anti-inflammatory in the periphery is not so in the central nervous system. Prostaglandin E2 (inflammatory and damaging in the periphery) is anti-inflammatory and neuroprotective in the central nervous system. Intrathecal steroids may decrease the expression of glial glutamate transporters and increase spinal neuronal expression of *N*-methyl-*D*-aspartate receptors, effects predicted to increase the excitability of neurons. Adrenal steroids increase microglial activation, including the induction of pro-inflammatory cytokines, and exert multiple pro-inflammatory effects in the central nervous system.

Lastly, clinical depression is associated with a profound loss of oligodendrocytes and myelin. The myelin loss that accompanies glial activation in the presence of persistent neuronal excitation may explain the strong association between depression and chronic pain.

Opioid Receptors: Pharmacologic Tolerance and Hyperalgesia

During chronic opioid exposure, opioid receptors desensitize via phosphorylation by G-protein-coupled kinases. Subsequent binding by the regulatory protein β-arrestin in turn reduces the efficiency of intrinsic Gi/o protein coupling leading to uncoupling of μ-opioid receptors and endocytosis or "internalization" [47, 74]. This receptor decrease and subdued Gi/o coupling contributes to opioid analgesic tolerance.

Other mechanisms of opioid analgesic tolerance include increased cyclic adenosine monophosphate production through activation of adenylyl cyclase by $G_{\beta\gamma}$. The $G_{\beta\gamma}$ dimer that signals to adenylyl cyclase after chronic morphine administration originates from the Gs heterotrimer and not the Gi/o proteins that have reduced their coupling to μ-opioid receptors. The excitatory effect on the cell that occurs during opioid tolerance appears to be additive or synergistic reflecting loss of adenylyl cyclase inhibition by Gi/o proteins and stimulation of adenylyl cyclase by both Gs proteins and their associated $G_{\beta\gamma}$ dimers [74]. The increase in cyclic adenosine monophosphate mediates an increase in cation conductance, causing increased excitability in the para-aqueductal gray and dorsal raphe areas with increases in glutamate and gamma-aminobutyric acid transmission. Dependence and withdrawal occur primarily due to this opioid receptor counter-adaptation [47]. Alternatively, continued signaling and recycling of opioid receptors and G proteins during prolonged μ-opioid exposure may result in regrouping of μ-opioid receptors, G proteins, effectors, and regulatory molecules that facilitate novel interactions merely by variations in proximities among these membrane constituents [74]. Prior subanalgesic doses of morphine reduce subsequent analgesia produced by an analgesic dose of morphine. This phenomenon is mediated by glial activation and p38 mitogen-activated protein kinase.

The presence of an ongoing painful neuropathic condition does not prevent the rapid and profound development of opioid tolerance. However, the central actions of morphine are modified in the presence of inflammatory pain, compared with when it is used in the absence of pain. Animal models of inflammatory pain have shown that the presence of inflammation inhibits the development of anti-nociceptive tolerance to morphine and suppression of morphine-induced

rewarding effects [69]. These effects are mediated via the activation of endogenous κ-opioid receptors in response to inflammatory nociception, which in turn blocks morphine activation of the mesolimbic dopamine system—a process that is reversed by administration of a κ-receptor antagonist.

Opioid-induced hypersensitivity [43, 66] is an opioid-activated, pro-nociceptive mechanism resulting in heightened pain sensitivity. This phenomenon is distinct from opioid tolerance and is mediated through distinct cellular mechanisms involving glia [76], increased endogenous dynorphin (a pro-algesic κ-receptor agonist), nitric oxide, glutamatergic *N*-methyl-*D*-aspartate receptors, and descending facilitation (ON cell activation). The cellular mechanisms of opioid-induced hyperalgesia have commonalities with those in neuropathic pain and opioid tolerance and include a diverse array of structures and peptides including substance P, glial cells, *N*-methyl-*D*-aspartate, cyclic adenosine monophosphate, alpha-calcitonin gene-related peptide, orphanin FQ/nociceptin, serotonin, cholecystokinin, and others. *N*-methyl-*D*-aspartate receptor antagonists, e.g., ketamine, can reverse the glutamatergic component of pain sensitivity. Opioid-induced hypersensitivity should be considered when previous opioid dose escalation has failed to achieve the expected analgesic effect, if pain diminishes as opioid doses are decreased, and if there is an otherwise inexplicable exacerbation in pain after an initial period of effective opioid analgesia. Opioid-induced hypersensitivity-induced pain is generalized and not confined to specific dermatomes.

Opioid-induced hyperalgesia is thought to be the cause of increased pain sensitivity noted in opioid addicts and patients on methadone maintenance treatment. In a study of 53 patients with chronic painful diseases, also diagnosed with prescription opioid dependence as determined by *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [3] criteria, admitted to an inpatient psychiatric unit for voluntary detoxification from opioid analgesics, the most significant finding was that self-reported pain scores improved during the detoxification period in hospital [49]. An analysis of variance of all assessed variables revealed that only the admission prescription opioid medications per day predicted a decrease in pain scores from admission to discharge, confirming that opioid medications can worsen pain syndromes.

Different opioids have varying abilities to induce hyperalgesia. Morphine is more likely to produce opioid-induced hyperalgesia than methadone. If opioid-induced hyperalgesia is suspected, treatment includes tapering the opioid dose, adding an *N*-methyl-*D*-aspartate receptor antagonist to the existing regimen, opioid rotation to a less "inducing" drug, and use of adjunctive, non-opioid analgesics.

The risks of unwarranted chronic opioid treatment include unnecessary invasive procedures and tests (for increased pain sensitivity), accident proneness, adverse health consequences, impaired judgment and cognitive function, a decline in occupational and social functioning, and strained family relationships. The adverse health consequences of long-term opioid use include pharmacologic tolerance, physical dependence, addiction, abnormal pain sensitivity, hormonal changes (primarily androgen deficiency and osteoporosis), and immune modulation [30].

The excitatory effects of chronic exposure to μ-opioid agonists are prevented by ultra-low-dose opioid antagonists [76]. Ultra-low-dose naloxone suppresses Gs coupling while enhancing Gi/o coupling, maintaining analgesia by continued inhibition of adenylyl cyclase or by the interaction of Gi/o-associated $G_{\beta\gamma}$ with ion channels. Naloxone's attenuation of the μ-opioid receptor-Gs coupling, concurrent with a restoration of μ-opioid receptor-Gi/o coupling, may explain its attenuation of both tolerance and dependence. A phase III trial of oxycodone with ultra-low-dose naltrexone showed significantly greater pain relief than the same doses of oxycodone given alone. Equivalent analgesia with less oxycodone was achieved in the combination preparation. Additionally, there was less

physical dependence, and the aversive effects of opioid withdrawal and the acute rewarding (euphoric) effects of opioids were reduced [76].

Physical Dependence and Withdrawal

Physical dependence occurs within days to weeks of opioid administration. It is a neuropharmacological phenomenon resulting from neuroadaptation and neuroplasticity [27]. Physiologic changes associated with physical dependence include increased respiratory rate, blood pressure, temperature, basal metabolic rate, glucose, inorganic phosphate, blood lactic acid, and erythrocyte sedimentation rate. Body weight, caloric intake, and sleep quality decrease. After discontinuation of opioids, blood levels of glucose, lactic acid, and inorganic phosphate return to baseline within a month. Body temperature, caloric intake, sleep quality, and respiratory rate regain their normal values within 2–3 months. Physiological equilibrium returns within 4–6 months.

Symptoms of opioid withdrawal include dysphoria, depression, nausea, vomiting, diarrhea, abdominal cramping, deep bone pain, joint pain, back pain, muscle aches, rhinorrhea, piloerection, lacrimation, diaphoresis, mydriasis, anxiety, irritability, fatigue, yawning, fever, insomnia, and an intense drive or desire to use more drugs. Acute withdrawal symptoms last 2–3 days and reach maximal intensity within 2 days. Conversely, intoxication includes euphoria followed by apathy, dysphoria, depressed mood and affect, impaired social and occupational functioning, drowsiness, impaired attention and concentration, faulty memory, and poor insight and judgment. Physiologic responses include papillary constriction, hypotension, constipation, slurred speech, psychomotor agitation or retardation, anxiety, depression, respiratory depression, and cardiovascular collapse. Drug tolerance is often insufficient to overcome the intoxicating effects of larger doses of opioid medications.

Individuals with chronic pain who use frequent doses of short-acting opioids on a regular basis become physically dependent and develop intermittent withdrawal phenomena including arousal, increased muscular tension, and receptor "hunger" between medication doses. This results in a low-grade protracted abstinence syndrome characterized by general discomfort, anhedonia, and drug craving, which serves to increase pain by mechanisms discussed previously. Withdrawal pain can be confused with breakthrough pain. It is usually severe and often indistinguishable from the original pain symptom. As opioids themselves, in larger doses, can produce pain, this situation is best remedied by reducing or ceasing opioid dosage, or by using long-acting rather than short-acting opioid drugs and formulations.

Opioid withdrawal is largely mediated by excessive norepinephrine release in the locus coeruleus, a mechanism separate from the dopaminergic pathways and limbic sites associated with reward. Alpha-2 agonists, e.g., clonidine, ameliorate withdrawal symptoms by suppressing pre-synaptic release of norepinephrine by inducing inhibition at the α-receptor on the pre-synaptic norepinephrine neurons. Diazepam may act similarly at the benzodiazepine site on the gamma-aminobutyric acid chloride channel by diffusely reducing sympathetic nervous system discharge of catecholamines in general by acting to suppress central nervous system excitability during opioid withdrawal. In addition, general anesthesia has been used to treat withdrawal since it activates gamma-aminobutyric acid receptors and will inhibit glutamate release.

Psychiatric Disorders and Opioid Use

Prospective studies of primary care populations suggest that chronic pain promotes depression and vice versa, equally strongly [67]. This is supported by research on glial function showing that biologic mechanisms important in the etiologies of depression and chronic pain are

linked [76]. Pain has also been shown to induce an anxiogenic effect in animals 4 weeks after induction of an inflammatory or neuropathic pain state [52]. Anxiety decreases pain thresholds and pain tolerance, and increases endorsement of medical symptoms and catastrophizing misinterpretations of arousal associated with pain [25]. Attitudes toward pain and fear of harm in humans significantly alter clinical functioning [73].

Chronic pain, depression, and anxiety are linked through changes in opioidergic function in the amygdala. The amygdala is rich in endogenous opioid peptides and plays a key role in fear and anxiety. Dysfunction of μ- and δ-receptors and possible enhancement of κ-opioid receptor function in the amygdala mediate the mood-altering effects of chronic pain. Sustained pain, via regionally selective release of endogenous opioids, induces a reduction in μ-opioid receptor availability in the amygdala as measured by positron emission tomography. Mu-opioid receptors are internalized and recycled.

Inflammatory, but not nerve injury, pain models cause marked activation of the endogenous κ-opioidergic system in the amygdala and nucleus accumbens. Kappa agonism produces a dysphoria similar to that seen in depression and chronic stress. Concomitantly the central stimulatory effects of selective μ- and δ-opioid receptor agonists are diminished. Delta-opioid receptor activation is associated with anxiety and depression. Delta-opioid receptor knockout mice exhibit less anxiety behavior than wild type mice [52]. Neuropathic pain-like states are associated with a reduction in μ-opioid receptor function in the ventral tegmental area. Together these data confirm that the mechanisms of neuropathic and inflammatory pain-like states are distinct, and that physiologic changes in supraspinal opioid transmission can alter mood and analgesic efficacy. Specifically, μ-opioid receptors are less responsive to endogenous opioids in pain-free patients with a high negative affective state (e.g., anxiety and depression). Thus, if chronic pain and negative affect both diminish the analgesic effects of endogenous opioids in the central nervous system, it is not surprising that patients with severe mood disorder have greater pain intensity and experience less analgesia from opioid therapy than patients with low psychiatric morbidity. In one study, opioid analgesic efficacy was reduced by 40% in patients with high psychiatric morbidity [75].

Approximately 50% of patients with chronic pain have clinical depression. These individuals also are at higher risk for opioid abuse. Treating a comorbid affective disorder can decrease current substance-abuse behaviors or the risk of relapse. Patients with high psychiatric morbidity have higher self-reported symptoms of anxiety, depression, history of sexual or physical abuse, and history of psychologic adjustment. Patients with a mood disorder and aberrant drug behaviors show a reduction in risky behavior when their mood disorder is treated, indicating that chemical coping rather than addiction is motivating their behavior.

Although chronic pain and negative emotions including anxiety and depression share certain neurophysiological pathways, and while negative emotions can be increased by chronic pain, chronic pain is rarely suppressed by treatment with anxiolytic medications. However, pain intensity and pain interference are improved when depression is treated.

Clinical Correlates of Opioids, Pain, and Mood

Much of the attention in managing chronic, non-cancer pain has focused on the minority of patients who engage in drug misuse and addiction. Consequently, many studies seek to characterize patient factors and opioid-use patterns in an attempt to identify and avoid prescription opioid therapy in patients lacking a clear indication and who do not evidence a subsequent reduction in pain intensity or improvement in functional abilities.

Population-based observation surveys have identified that the prescription of opioid drugs is as closely related to mental health as it is to

pain states [67, 68]. Endogenous opioids modulate basal emotional state. Opioids are frequently used to treat poorly differentiated states of mental and physical pain—a situation that has persisted for centuries. Exogenous opioids elevate mood at least temporarily. Opioid analgesics are much more likely to be prescribed to individuals with psychological distress arising from depression, anxiety, and other psychiatric disorders than to those with comparable physical discomfort without mental health disorders. Pain arising from chronic medical disorders is perceived by patients as more severe in the presence of major depression.

Illustrative of this is a longitudinal study of 6,439 patients in a primary care setting from 1998 to 2001 [68]. Respondents with a mental health disorder in 1998 were twice as likely to use prescribed opioids in 2001 compared with patients without mental health or substance use disorders. Patients with a mental health disorder who were not using opioids in 1998 were more likely to initiate prescription opioid use during the 3-year study period. Patients with problem drug use in 1998 were 3 times more likely to use prescription opioids in 2001. However, as a proportion of patients surveyed, the number of patients with common mental health disorders (major depression, dysthymia, generalized anxiety disorder, and panic disorder) far exceeded the number with problem drug use. Individuals receiving long-term opioids reported a greater perceived need for mental health care, but not substance abuse care, compared with non-opioid-prescribed patients (30% vs. 10%) [67, 68]. While respondents with problem alcohol use only were only somewhat more likely to receive opioid therapy than non-problem drinkers, antidepressant use was significantly related to opioid use [67]. The more psychological distress patients manifested, the more likely they were to be prescribed opioids. When one or two mental health disorders were present, there was a 5 times higher likelihood, and with three or four disorders, a 9 times higher likelihood of prescription of opioids.

In another population sample of 9,279 patients surveyed for regular prescribed opioid use, substance use problems, mental health disorders, physical health, pain, and sociodemographics, those individuals prescribed opioids for chronic non-cancer pain had higher rates of substance misuse compared with non-users of prescribed opioids (14.5% vs. 3%) [19]. Patients using prescribed opioids had higher rates of non-opioid illicit drug use, non-opioid problem drug use, and problem alcohol use compared with non-users of prescribed opioids. However, these data appear to be partially mediated by depressive and anxiety disorders, indicating that mental health disorders strongly contribute to substance abuse among prescription opioid users, rather than prescription opioids themselves prompting abuse.

It is not known whether improved recognition and treatment of mental health disorders will decrease the need for chronic opioid therapy [67]. However, it is clear that the unmet need for mental health care is associated with higher rates of substance use [19, 67, 68] and that depressive and anxiety disorders are significantly undertreated in patients receiving opioids [51]. Of the common mental health and addictive disorders, comorbid depression is the strongest indicator for drug misuse [19]. This poses a significant clinical problem given the high prevalence of depression in the general population, one that overshadows drug misuse by patients with an existing drug abuse history.

Pain beliefs play an important role in patients' adjustment to their illness and influence their physical as well as psychosocial functioning. Beliefs about medications are central to patients' adherence to medication regimens. Patients also appear to engage in a cost-benefit analysis prior to taking medications.

In a study of 288 opioid-prescribed patients with chronic non-cancer pain, the role of opioid medication beliefs was compared with therapeutic response [64]. Patients without a history of substance abuse, or with a history of alcohol abuse alone, did not believe they needed higher prescription drug doses and had similar low levels of medication misuse behaviors. In contrast, patients with a history of substance abuse believed they required significantly higher doses

of prescribed opioid analgesics. They reported higher symptoms of anxiety and that pain more frequently stopped them from completing activities. They were also more likely to endorse beliefs that narcotics are effective for pain control, that medication use will improve mood, that they would be more able to function with free access to medications, and that they need higher amounts of narcotics to experience pain relief than other patients. They also had a greater belief in the addiction potential of narcotic medications. These attitudes were magnified in patients with a dual diagnosis of a psychiatric disorder and substance abuse. Overall, the belief in a better quality of life associated with freer medication access and higher doses exceeded the belief in the potential for addiction, and this may lead to medication abuse in patients with psychiatric morbidity.

A history of substance abuse was related to higher rates of mediation misuse behaviors unrelated to medication effectiveness or the amount of medication prescribed. A prior psychiatric disorder was also associated with increased medication misuse regardless of substance abuse status. Rates of medication use increased the most in patients with both a psychiatric diagnosis and previous substance abuse. There were no significant differences in the overall amount of narcotic prescribed to patients with and without a substance abuse history; nor did pain relief, medication effectiveness, or level of disability differ between patients based upon their pain beliefs.

Anxiety was the only mood variable independently related to medication abuse behaviors and was a significant, although partial, mediator of the relationship between substance abuse history and medication beliefs. State anxiety accounted for 30% of the effect of addiction history on beliefs. The effects of addiction history on the prescription drug use questionnaire (see Section "Screening Tools") results were completely mediated by medication beliefs and state anxiety. After accounting for beliefs and state anxiety, addiction history had no direct influence on prescription drug use questionnaire scores.

Misattribution of anxiety-related physical symptoms leads patients to control these symptoms with pain medications and to alter beliefs about their medication needs. Clinicians have to identify not only physical sources of pain but also psychological contributors. These must be addressed as part of the regular treatment plan. Specific cognitive-behavior interventions may help patients differentiate and cope with symptoms associated with anxiety versus symptoms associated with chronic pain.

Diagnosis of Addiction

Addiction is a disease of the brain that is diagnosed by assessing the patient's behavior and ability to function in society and within a therapeutic framework. The typical profile of an addicted patient who has chronic pain is remarkably similar to that of a non-addicted patient with severe untreated pain and has the following characteristics: chaotic social situation, concurrent mental health problems that exacerbate their pain experience, limited coping mechanisms with a bias toward chemical coping, and resistance to utilizing non-pharmacological analgesic treatments.

Seemingly non-addicted patients who present for pain management and go on to abuse opioid medications tend to be younger (18–30 years old), have a greater severity of lifetime psychiatric disorders, are more likely to have a positive toxicology screen (usually cocaine or marijuana), and demonstrate four or more aberrant drug use behaviors [25]. This mirrors the epidemiologic profile of extramedical analgesic users in the general population who, in addition, tend to be female, have less than a college education, and have lower incomes [18]. Twenty percent of non-addicted patients with pain engage in drug-seeking behavior [64].

The commonest cause of "iatrogenic" opioid addiction is a previous history of substance abuse. Thus, a psychological assessment and attention to existing psychiatric disorders are essential in treatment planning and risk stratification in patients with chronic pain. In patients who are opioid naïve, with no previous substance

abuse, therapeutic prescription of opioids very rarely induces addiction, and the rate of opioid abuse is approximately 2% in such individuals [21]. Should abuse behavior occur, the challenge is to determine whether it represents recreational use, addiction, intentional criminal diversion, or an attempt to treat depression or anxiety associated with undertreated pain. Risk factors for addictive disease include a genetic predisposition, a risk-taking personal psychological profile, and the socio-cultural context in which the drug exposure occurred. The differential diagnosis for dependence and addiction includes "therapeutic dependence" (chronic pain patients receiving adequate doses of opioids but who hoard opioid medications to ensure an adequate reserve), pseudoaddiction, chemical coping, and recurrent subtle withdrawal [30].

Prerequisites in Providing Pain Management

One of the root causes of undertreated pain is the apparent belief on the part of clinicians that the treatment of pain should be based upon a different set of principles and practices than any other type of patient care. Pain complaints in the setting of cancer, or acute illness or injury, are accepted and treated, while people suffering from chronic, non-cancer pain are met with skepticism and do not receive the same therapeutic approach to care. There is also a failure on the part of health care professionals to acquire and maintain up-to-date knowledge and skills, thus preventing their ability to provide adequate, appropriate care and counseling, resulting in the persistence of so much myth and misinformation [61]. Patients with addictive disorders can suffer the same fate. One of the biggest obstacles to caring for patients with chronic pain, addiction or both is ignorance in the medical community and general population. In one survey, only 39.6% of physicians noted receiving any training in diagnosing medication abuse and addiction [42]. A revised, comprehensive educational input into health care teaching programs is essential if the next generation of clinicians is to diagnose and manage these diseases effectively.

Approaches to Treatment

"Ethically, what is worse? To give 16 people medications they do not need or to withhold from 84 people medications they do need?" [59]. These questions address the fact that the majority of patients with painful medical conditions treated with opioid analgesics do not develop substance misuse. De novo addiction is very rare when opioids are used for acute pain relief [49]. However, if every sixth patient with chronic pain can be expected to misuse prescribed opioid therapy in some way, and at some time, are opioids worth the risk? Some clinicians consider a 3.8% rate of opioid addiction [25] a small risk compared with the alternative of continuous pain and suffering. Yet, are opioid analgesics necessary in the treatment of chronic pain? Drugs acting at the μ-opioid receptor are the most powerful analgesics available that permit a reasonable level of function. They are the first line in the treatment of acute severe pain. However, in the treatment of chronic non-cancer pain, efficacy has not been demonstrated beyond the first 3 months of therapy [21]. Consequently, opioids should not be first-line treatment for non-cancer pain expected to last longer than 1 month.

Chronic pain, like other long-term diseases, is multifaceted and complicated by substantial psychological and functional impairment, including depression, disability, and loss of livelihood. The traditional treatment model of diagnosis and acute management of medical problems in a single provider-patient relationship does not serve this patient population well. The strong interaction between pain and psychiatric morbidity, especially depression and substance misuse, mandates that pain management encompass more than pharmacological management directed at pain scores and include a variety of behavioral and psychosocial therapies. To this end, psychological and rehabilitation

programs emphasizing patient self-management skills were endorsed to improve function, mood, and pain relief, and the biopsychosocial or "disease management" model of pain became the preferred therapeutic model. It integrates the physical, psychological, emotional, social, and spiritual elements of pain and suffering and attends to aspects of quality of life and life meaning that foster enrichment and relevance of the individual. It forms the basis of the multidisciplinary, multimodal approach to pain management. The focus of a multimodal, multidisciplinary treatment strategy is to free the patient of dependence on the medical community by lifestyle adaptation, rational use of medications including opioids, and treatment of pain symptoms with various therapies [57].

The goal of any pain treatment is to maximize the efficacy of alleviating discomfort and limit unwanted side effects. Multidisciplinary models for chronic pain management include a structured psychological investigation and psychological therapy. This approach identifies those with a mental health or substance abuse history earlier, thereby permitting appropriate changes in psychiatric and analgesic management [57]. Mental health professionals play a significant role in facilitating care, especially during initial patient assessment, ongoing assessments for substance use and mental health, and psychological treatments such as developing effective coping strategies for managing chronic pain (e.g., cognitive behavioral therapy, relaxation techniques, biofeedback) and better resource utilization, including medications [51].

The impact of a multidisciplinary team providing integrated care and utilizing evidence-based algorithms, interval visits to monitor responses to therapy, and information systems that permit tracking of outcomes and adjustment of therapy was evaluated in an academic general medical practice over a 3-month period [8]. In that study, the multidisciplinary team comprised the patient's primary care physician, a clinical pharmacist, a program assistant with training in health behavior, a psychiatrist with subspecialization in pain management, and a study nurse.

The management principles algorithm utilized: longer-acting opioids when short-acting preparations were only partially effective; short-acting opioids for breakthrough pain; longer-acting opioids were titrated at interval visits; less costly, generic medications were favored, and tricyclic antidepressants, gabapentin, and other non-opioid medications were used adjunctively, especially for neuropathic pain. All patients underwent a psychiatric evaluation and urine drug screen and signed medication contracts. Substance misuse was monitored through clinical history, review of medications, communication with pharmacies and providers, and urine drug screening. Serious drug misuse violations meant termination of opioid therapy (but not discharge from the clinic per se) and referral for substance abuse treatment.

Long-acting opioids were favored because continuous occupation of the endogenous ligand μ-opioid receptor system allows interacting physiological and behavior systems to return to normal. Their use avoids rapid increases in opioid concentrations in the brain, reducing euphoria and addictive potential [30]. Around-the-clock dosing reduces pain, increases function, minimizes the development of tolerance, abolishes anticipation of the medication produced by frequent medication peaks and troughs throughout the day, and provides a better quality of life [27, 51]. In cases where short-acting opioids are warranted, e.g., incident pain, they should be given on a time-contingent basis and throughout around-the-clock dosing. The maximal daily dosage should also be clearly established with the patient [51].

Overall, this multidisciplinary pain management approach improved pain, depression, and disability scores in opioid-treated patients with chronic non-malignant pain and improved their quality of life. These results were attributed to the combined effects of systematizing pain management and treating depression. Clinical improvements were independent of opioid dose. Intensifying pain management may have a beneficial effect on depression by enhancing antidepressant efficacy. Severe pain impairs the response to antidepressant therapy. The

prevalence of substance misuse was 32%. Opioid therapy was to be reconsidered after 6 months if the patient continued in recovery. Substance-abusing patients who did not complete the study tended to be non-white, have a history of illicit drug or alcohol use, worse depression, and higher pain scores at baseline. Meticulous documentation in an electronic medical record and centralized monitoring for opioids and other controlled substances allowed patient tracking within the program and prevented migration within their practice. Despite the inclusion of mental health professionals in the team, difficulty accessing mental health and substance abuse treatment services remained. Not surprisingly, higher rates of aberrant drug use have been reported in multidisciplinary pain management programs [49]. These programs screen for mental health and addictive disorders, and "challenging" patients are referred to them.

Chronic back pain is one of the most common long-term non-cancer pain syndromes. The prevalence of opioid treatment, its efficacy, and the prevalence of substance use disorders among patients receiving opioid medications for chronic back pain was assessed by meta-analysis and systematic review [45]. Opioids are commonly prescribed for chronic back pain, and short-term efficacy (less than 16 weeks of treatment) was confirmed. Opioid analgesic efficacy lasting longer than 16 weeks is unclear as no longer-term studies were evaluated. Substance use disorders were common with a prevalence of aberrant medication-taking behaviors of up to 24%. Opioid prescribing for chronic back pain varied by treatment setting (range, 3–66%) and was more common in patients with impaired functional status. Pain relief was not significantly different in patients managed with opioids compared with those taking non-opioid analgesics or placebo. These data suffer from a paucity of high-quality studies of opioid analgesia and chronic back pain. The studies reviewed were very heterogeneous, with small sample sizes and too short an evaluation period, and used various diagnostic criteria and functional conditions. However, patients who fail to respond to opioid analgesia should be weaned and other classes of analgesics and additional non-pharmacological treatments utilized. The American Pain Society has endorsed guidelines for the management of chronic back pain [9, 11].

Multidisciplinary, multimodal pain management approaches are especially useful in patients with psychiatric illness, substance misuse, or both. Patients with primary opioid dependence report high levels of chronic pain and have lower pain thresholds to experimental pain than controls [49]. This pattern of lower thresholds and shorter tolerance to pain than non-addicts continues into recovery. Thus, active and recovering opioid addicts have increased opioid requirements, reflecting inherent differences in underlying neurophysiology, perception, and experience of pain compared with non-addicts [25]. Additionally, the long-term administration of opioids modifies pain perception [41, 76].

The initial assessment of all chronic pain patients should include a mental health and opioid abuse risk assessment and triage into one of three risk categories [36] (Table 1). Attempts should be made to identify patients who seek opioid drugs in the absence of pain. The diagnosis and treatment of psychiatric disorders are important steps when considering patients for opioid therapy. Opioid abuse risk is highest in patients who have binge use, use opioids for their psychoactive effects, obtain opioids from other sources, and experience withdrawal symptoms and other features of dependence. Inquiry should be made as to mood, occupational and family functioning, sleep disorders, and physical functioning. Urine should be tested for drugs (licit and illicit) and records from previous

Table 1 Opioid abuse risk stratification

Category 1	No standard risk factors for abuse or diversion
Category 2	Family history of substance abuse or other evidence of increased risk of opioid abuse, e.g., previous substance abuse, history of physical or sexual abuse, history of or current psychiatric disorder
Category 3	Active drug abusers

care providers obtained. Spouses and significant others should be interviewed to obtain information regarding early signs of dependence and aberrant drug use behaviors [34].

Assumptions by clinicians that a positive drug screen (e.g., cocaine or marijuana) or aberrant drug use behaviors automatically mean opioid use disorder have veracity. When 801 patients with chronic non-cancer pain, treated in a primary care setting, were studied for all types of chemical substance abuse over a 30-day period, 24% had positive toxicology tests for illicit drugs, significant underreporting of drug use, and a strong association between illicit drug use and substance use disorders. Forty-six percent of patients with a positive toxicology screen denied illicit drug use even when anonymity was guaranteed [25]. The presence of other mental illness was not specifically examined.

This patient sample was assessed for 12 aberrant drug behaviors [54] (Table 2) and the Addiction Severity Index [46] (see Section "Screening Tools"). Four specific aberrant behaviors were identified with substance abuse and opioid addiction: sedating oneself, using opioids for non-pain reasons, increasing dose without authorization, and having felt intoxicated when using opioids [25]. The causes of aberrant drug behaviors were considered to be pseudoaddiction, untreated psychiatric syndromes, organic mental syndromes, chemical coping, situational stressors, and criminal intent. Co-occurring medical disorders, higher lifetime rates of substance use disorders, and younger age were associated with, and increased the frequency of, three aberrant behaviors: lost or stolen medication, documented use of multiple physicians, and requests for two or more early refills. Patients with a family or personal history of substance abuse were more likely to exhibit aberrant behaviors. In that study [25], opioid use disorders were 4 times higher in the chronic non-malignant pain population than in general population samples (3.9% vs. 0.9%, or 1 in 25 patients on opioid therapy).

Table 2 Aberrant drug behaviors

1.	Purposely oversedating oneself
2.	Frequency of drug intoxication
3.	Involvement in motor vehicle accidents
4.	Requesting early renewals
5.	Self-directed changes in dosing
6.	Lost or stolen prescriptions
7.	Obtaining opioids from more than one doctor
8.	Non-pain-related use of medication
9.	Using alcohol for analgesia
10.	Success in obtaining additional medication
11.	Missed doctor's appointment
12.	Hoarding of medication

Opioid misuse is associated with untreated, or inadequately treated, psychiatric disorders, most notably depression, anxiety, panic disorder, post-traumatic stress disorder, borderline personality disorder, somatization, and other dissociative disorders [68]. These conditions must be diagnosed and treated adequately before initiating opioid analgesic therapy. Close follow-up is essential to prevent negative outcomes such as declining functional status or opioid misuse. Clinicians treating patients with chronic pain should be proficient in treating common psychiatric disorders or refer to a mental health specialist. A high index of suspicion for mental health disorders should be maintained in patients prescribed opioids.

Addiction patients can have pain treated effectively with opioids if they are properly monitored and supervised. They should be referred to a center that can provide the necessary analgesic therapy while simultaneously managing the comorbid substance abuse. Unfortunately, the number of centers nationally that can provide this type of care is extremely limited.

When chronic pain exists in an opioid-dependent patient, or in one with significant risk factors for substance misuse, it is even more important to attend to confounding psychiatric morbidity and to ensure the therapeutic efficacy of pharmacotherapy and behavioral interventions. The treatment model for opioid-dependent pain patients includes education as to why chronic opioids are likely to maintain pain, to correct chemical coping, detoxification, treatment of pain with non-opioid analgesics, psychological support, coordination of care, and

promotion of healthful behaviors. Prescription of opioids with a high addiction potential (e.g., oxycodone, hydromorphone) should be avoided. Psychological and physical needs must be treated simultaneously.

Many non-controlled drugs or their metabolites have central effects that can interact with opioids to increase their harmful adverse effects, e.g., sedation and respiratory depression. Examples include muscle relaxants, antiemetics, and sleep aids. Tramadol, an analgesic that works primarily by inhibition of norepinephrine and serotonin reuptake and is not classified as an opioid analgesic, does have weak μ-opioid agonist effects. It has been identified in addiction relapse and in de novo addiction in susceptible individuals. In addition, over-the-counter and herbal (natural) remedies should be monitored to prevent unfavorable drug interactions and relapse.

Individuals in recovery should be asked about cravings. A positive response provides an early warning sign of relapse and allows renewed efforts to maintain recovery [51]. Family involvement with the rehabilitative process is essential and may include the family in therapy, e.g., family cognitive behavioral therapy. Relapse is more likely during stressful life events, including exacerbation of pain. The psychosocial state of patients should be re-evaluated at regular intervals in addition to pain intensity and function and whenever changes in compliance patterns occur. Several of the non-opioid treatments for chronic pain overlap with those used to treat substance abuse, e.g., family involvement, group support, and "contingency contracting". Cognitive behavioral therapy is particularly useful in treating cravings. Addiction as a disease leaves memory traces laid down in circuits in the brain. These circuits become overlearned during addiction. As no single treatment works for everyone, therapists must be flexible and tailor treatment to the individual.

Case reports of patients with chronic non-cancer pain and concurrent opioid abuse can be helpful in illustrating the treatment models recommended [16, 66].

The Role of Opioids in Pain Medicine

Although it is beyond the scope of this chapter, it is essential that clinicians are knowledgeable about drug pharmacology, especially the medications they prescribe. Key factors in the selection of drugs include their physicochemical properties, absorption and transportation characteristics, metabolism, excretion, and drug interactions. Pharmacogenetics is extremely important in determining whether a patient will experience analgesia from an opioid prodrug, e.g., codeine and hydrocodone. Morphine has analgesic and sedative metabolites that are renally excreted. Thus, morphine is relatively contraindicated in the presence of renal failure. Methadone is a racemate of l- and d-methadone. L-methadone is a μ-agonist similar to morphine. D-methadone is an *N*-methyl-*D*-aspartate receptor antagonist. Thus, methadone is unique in being composed of two analgesic racemates. This combination may explain its utility in neuropathic pain. Selection of analgesics in general is also determined by efficacy, adverse effects, and cost. Of the non-opioid analgesics used to treat neuropathic pain, tricyclic antidepressants are more efficacious than serotonin-norepinephrine reuptake inhibitors, which are more efficacious than selective serotonin reuptake inhibitors. However, the tricyclic antidepressants have a higher incidence of treatment limiting adverse effects. Although all anticonvulsants have efficacy in relieving neuropathic pain, currently gabapentin and pregabalin are most commonly used because of unwanted effects with other drugs in this class.

Opioids are analgesic in that they reduce the sensitivity of the central nervous system to noxious stimuli, i.e., raise the pain threshold. However, they do not treat the biologic etiology of pain. Inflammatory, neuropathic, and bone cancer pain have distinct neurochemical profiles in the central nervous system [12]. Treating pain by addressing its etiology with pharmaceuticals targeted to correct the unique neurochemical changes associated with pain makes more sense. Additionally, the neurochemical changes associated with the affective components of pain

can be relieved by non-pharmacological therapies such as distraction, e.g., virtual reality analgesia [29]. Thus, the mainstay of chronic pain treatment should include psychological, physical, social, emotional, and pharmacologic therapies—the latter focusing on disease modification, and anti-inflammatory, anticonvulsant, and antidepressant analgesia with opioid analgesics as adjuncts (Table 3).

Table 3 Analgesic therapies used in multimodal pain management

Pharmacological	Acetaminophen
	Non-steroidal anti-inflammatory drugs
	Cyclo-oxygenase type 2 inhibitors
	Opioids
	Pro-drugs
	Mu-receptor agonists
	Partial agonists
	Agonist/antagonists
	Tricyclic antidepressants
	Serotonin-norepinephrine reuptake inhibitors
	Selective serotonin reuptake inhibitors
	Anticonvulsants
	Steroids
	Muscle relaxants
	Antispasmodics
	N-methyl-D-aspartate receptor antagonists
	Alpha-2 adrenoceptor agonists
	Local anesthetics
Physical	Hot/cold
	Massage
	Transcutaneous electrical nerve stimulation
	Exercise
	Physical therapy/occupational therapy
	Relaxation
	Yoga/tai chi
	Therapeutic touch
	Splinting painful joints
	Comfortable mattress
	Surgical stabilization of fractures
	Grafting of burns
Psychological	Music
	Guided imagery
	Virtual reality
	Art therapy
	Journaling
	Hypnosis
	Biofeedback
	Cognitive behavioral therapy
	Treatment of mood disorders
Emotional	Social support
	Good communication
	Sleep hygiene
Spiritual	Prayer
	Meditation
	Acceptance of disease
Disease modifying	Chemotherapy
	Radiation therapy
	Radioisotopes
	Bisphosphonates
	Immunotherapy
	Hormone therapies

Any opioid is effective for relieving any type of pain in the short term, but the efficacy of long-term opioid analgesia for chronic non-cancer pain remains unproven. Data suggest that only 30–40% of patients with chronic non-cancer pain accrue sustained benefit (i.e., stable function without significant tolerance or side effects worth reporting) from long-term opioid therapy over months and years [35]. Equally, 30–40% of patients do not report an analgesic response to opioid therapy either initially or with increased doses [81]. When an initial response is not seen, management strategies include up-titration of the opioid dose, addition of another analgesic, introduction of a non-pharmacological therapy, e.g., physical therapy, obtaining a psychological consult, or trying a different opioid or route of administration. If these measures fail, non-opioid analgesics and non-pharmacological therapies including rehabilitation therapies, physical modalities (e.g., ice or heat), psychological therapies (e.g., cognitive behavioral therapy), and complementary alternative medicine should form the basis of the pain management plan. Opioids should be weaned whenever their efficacy is in question or other therapies have become effective. In the context of chronic non-cancer pain, opioids for analgesia have been likened to a "bridging therapy", used to achieve analgesia in the face

of severe pain but not to be considered the primary analgesic therapy. Their use for 1 to 3 months is intended to provide sufficient comfort and function to allow other analgesic therapies to work. When these other long-term therapies are in place the opioids are withdrawn in a controlled fashion. The use of etiology-specific analgesic therapies (e.g., anti-inflammatory medications to treat inflammatory pain) in the context of multimodal therapy offers better analgesia with fewer adverse effects. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain are available [10, 72].

Medication tapering is indicated if the opioid dose is well above 300 mg/day of morphine or its equivalent [34]. Tapering can improve patients' mood and pain because the cycle of intoxication and withdrawal is less extreme once they have been stabilized at a lower dose. It also reduces the incidence of drug tolerance, physical dependence, withdrawal hyperalgesia, and opioid-induced hyperalgesia. The endpoint of successful tapering is either abstinence or a moderate scheduled dose that provides effective analgesia with minimal withdrawal symptoms.

Screening Tools

Fears of being sued for both the undertreatment of pain and iatrogenic opioid addiction have created huge dilemmas for many practitioners. Attempts to predict who is at risk for medication misuse and addiction have led to the creation of risk assessment tools [33]. These vary between those intended for use prior to the initiation of opioid therapy and others designed to assess patterns of opioid use during therapy. Self-report measures dominate, but physician-rated observation scales are available. Screening for risk of addiction should be performed before initiating long-term opioid treatment in chronic non-cancer pain patients and at intervals throughout their therapy. The most comprehensive review of assessment tools to date is provided by Passik et al. [56]. Examples of several scales follow.

The Chemical Coping Index Tool Evaluation [37] is intended to identify chemical copers a priori. This tool evaluates 38 items over 6 categories: self-treatment, overly drug focused, not making progress, alexithymia/somatization, sensation seeking, and tendency toward accidental overmedication. Psychotherapy and rehabilitative approaches are particularly important in these patients as symptom and functional improvement are unlikely to occur until their coping abilities improve.

The Screener and Opioid Assessment for Patients with Pain [6] includes 24 patient administered items over several domains including substance abuse history, doctor-patient relationships, and psychosocial problems. It is intended to predict aberrant drug-taking behavior prior to the initiation of opioid therapy. The score generated is based on the sum of 14 of the 24 items. A score of 8 or above suggests a high risk for problematic opioid use. The most predictive items for high-risk patients are a positive urine drug screen and the need for a cigarette within the first hour of the day. Although this tool has the best psychometrics of all the screening tools, it utilizes few medical and demographic data and may lack sensitivity in some patient subpopulations.

The Opioid Risk Tool [77] is one of the briefest measures available, utilizing 5 yes-or-no self-report items to predict the probability of a patient displaying aberrant behavior when prescribed opioids for chronic pain. It has excellent discriminatory ability in both men and women. It has been validated in pain patients and is specifically designed to predict problematic behavior in patients prescribed opioids for pain. Its brevity and ease of scoring make it very useful clinically. It suffers from being susceptible to deception. A score of 3 or more out of 5 indicates opioid abuse.

The Addiction Severity Index [46, 62] is intended for use by primary care physicians. It utilizes information regarding medical illnesses, legal events, employment status, family/social problems, psychiatric treatment and severity, and current and lifetime substance use problems and treatment. Collateral information from family,

friends, and previous providers is very helpful, especially in patients who are in denial or unwilling to disclose sensitive clinical information. By focusing on problems and their previous treatments, the Addiction Severity Index can assist in formulating a more comprehensive pain treatment plan. It particularly addresses the impact of the high rate of psychiatric disorders in chronic pain patients, their tendency to misuse alcohol and other substances, and their higher risk for suicide.

The Drug Abuse Screening Test [80] is a 28-item yes-or-no self-report questionnaire. A cutoff score of 6 indicates drug abuse or dependence. The Drug Abuse Screening Test has face validity, high test-retest reliability, and good sensitivity and specificity. It is susceptible to deception and has yet to undergo a validation trial in pain patients. It predicts substance abuse but not the risk of aberrant drug behaviors during treatment.

The Diagnosis, Intractability, Risk, Efficacy score [5] is designed to predict which chronic, non-malignant pain-suffering patients will experience effective analgesia and be able to comply with long-term opioid maintenance therapy. It shows high sensitivity and specificity for predicting both compliance and efficacy. To be effective, the clinician needs to obtain a thorough history and maintain a good relationship with the patient as this tool works best when used over time, rather than as an initial screening instrument. It can be useful in identifying deception by patients and has the advantages of ease of use and rapid administration.

The Addiction Behaviors Checklist [79] utilizes a 20-item longitudinal tool to track behaviors characteristic of opioid addiction in chronic pain patients. The majority of items are scored on observed behavior or objective information. The minority are self-reported. A cut-off score of 3 correlates well with clinical decisions to terminate opioid therapy for problematic drug use. It also has good correlation with the Prescription Drug Use Questionnaire. The Addiction Behaviors Checklist score bears no relationship to the pain intensity score.

The Prescription Drug Use Questionnaire [13], for use in opioid-treated chronic pain patients, consists of 39 items over 5 domains: the characteristics of the pain condition, opioid use patterns, social/family factors, familial/personal history of substance abuse/addiction, and psychiatric history. Scores > 15 correlate with substance use disorder. The 3 items most predictive of addictive disease are: patient believes he or she is addicted, increases analgesic dose/frequency, and has preference for a specific drug or route of administration. This tool assesses risk at a single time point. It can be used to complement other risk tools.

The Chronic Opioid Misuse Measure [7] is designed for use in patients already receiving chronic opioid therapy. Seventeen of the original 40 items in the alpha version were found to measure aberrant behavior adequately. This tool continues to undergo study to refine it and assure its validity.

Most prescription controlled drugs abused by young adults (18–25 years old) are obtained from friends and relatives with and without their permission (67.4%) [34, 53], stolen from pharmacies, or obtained from one physician. Thus, in addition to screening for high-risk patients, high-risk families and social situations should also be identified.

The most studied predictor of opiate misuse in chronic non-malignant pain is a history of substance abuse. The presence of two or more risk factors is positively associated with clinical evidence of opiate misuse. Risk factors included patients' report of substance abuse history, family history of substance abuse, and a history of legal problems related to substance abuse. Behaviors most closely associated with risk variables are a urine drug screen positive for illegal substances or non-prescribed opioid drugs, a high dose of opioid medication, and the need for a cigarette within the first hour of the day. Recent polysubstance abusers and oxycodone abusers are poor candidates for opioid therapy [64]. Alcoholics in recovery with no other psychiatric morbidity are generally good candidates for opioid therapy.

Universal Precautions in Pain Medicine

A strategy of "Universal Precautions" has been advocated when treating patients with chronic opioid therapy. Just as one takes precautions not to contract and spread communicable diseases by performing the "Universal Precautions" of hand washing, wearing gloves, etc. when handling body fluids because it is not always apparent who has an infection, so it is not possible to tell immediately which patient is at risk for substance abuse or addiction. This forms the basis of the "Universal Precautions" recommended by Gourlay et al. [26]. They propose adopting ten steps that constitute best medical practice to reduce abuse risk while optimizing therapeutic outcome:

1. *Make a diagnosis with an appropriate differential*: The pain experience is multifaceted. Treatment should be directed at the cause of the pain whenever possible rather than to the symptom alone. Comorbid conditions, e.g., depression and other psychiatric disorders, must be treated.
2. *Psychological assessment including risk of addictive disorders*: Risk factors for addictive disorders, including a history of personal and family drug misuse, past and present, should be sought. This should be done non-judgmentally and with a reassurance that the pain will be treated seriously regardless of risk. Urine drug testing should be considered in high-risk patients regardless of treatment regimen and periodically in all patients on chronic opioid therapy. A finding of illicit or non-prescribed licit drug use should lead to further assessment and treatment for substance use disorders. Patients who refuse treatment, or whose psychiatrist considers the risk of opioid therapy too great, are not suitable candidates for treatment with controlled substances. Absence of the prescribed substance warrants re-evaluation of the patient [51].
3. *Informed consent*: The treating physician must explain and discuss the treatment plan with the patient, including the anticipated benefits and potential risks. When opioid therapy is prescribed, the issues of addiction, abuse, physical dependence, withdrawal, tolerance, and lack of efficacy should be explained.
4. *Treatment agreement*: This can be written or verbal. The expectations and obligations of the patient and the clinician should be stated explicitly and understood. Clearly defined boundaries help in identifying aberrant drug behavior. The treatment agreement with informed consent forms the basis for a treatment trial. Sample treatment agreements can be found at www.oqp.med.va.gov under "Opioid Therapy for Chronic Pain" and www.guidelines.gov [51].
5. *Pre- and post-intervention assessment of pain level and function*: This is essential before embarking on a therapeutic trial. Continuing a particular treatment modality relies upon evidence that the therapy is effective in meeting the stated clinical goals. Failure to meet the treatment goals requires reassessment of the diagnosis and treatment plan.
6. *Appropriate trial of opioid therapy with or without adjunctive medication*: Opioids are analgesic but non-specific in regard to targeting the etiology of painful conditions. Thus, they should be used as part of a multimodal treatment plan in doses appropriate to the individual patient and be weaned when benefit no longer accrues.
7. *Reassessment of pain score and functional level*: This is essential to establish ongoing efficacy. It may be helpful to have the patient's reports of comfort and function corroborated by a relative or close friend.
8. *Regularly assess the "Four A's" for pain medicine*: Assessment of analgesia, activity, adverse effects, and aberrant behavior helps direct therapy and provides appropriate documentation for justification of therapeutic interventions or withdrawal. The Pain Assessment and Documentation Tool

originally proposed documenting outcomes using these domains [55]. "Affect" is often added as the fifth "A".

9. *Periodically review the pain diagnosis and comorbid conditions including addictive disorders*: Underlying disorders change over time. Pain and psychiatric morbidity may change in dominance, dictating that the focus of treatment should change over time. Untreated psychiatric disorders will likely prevent successful pain management.
10. *Documentation*: Thorough documentation of all patient contacts is necessary for appropriate treatment tracking and management planning in addition to being a medicolegal requirement. This combined with a positive doctor-patient relationship improves the quality of the treatment regimen and protects against regulatory sanction.

These recommendations complement the United States Federation of State Medical Boards' Guidelines that call for a patient evaluation, treatment plan, informed consent, periodic review, consultation, that medical records be maintained accurately and completely and ready for review, and be in regulatory compliance [36].

How well do these precautions work? One multi-disciplinary, comprehensive, interventional pain management center found that adherence monitoring reduced controlled substance abuse in their patient population by 50% [42]. Their strategy included a controlled substance agreement, periodic monitoring, pill counts, periodic drug testing, and education to reduce abuse.

Systems that support safer prescribing are being advocated [36, 40]. Tamper-proof prescription pads and use of state prescription-monitoring data for each patient are recommended [24] in addition to urinalysis and addiction screening in all patients on long-term opioid therapy. However, very few prescription-monitoring programs have been adequately evaluated to determine their impact on the availability of controlled substances for legitimate medical purposes or the subsequent incidence of drug abuse and diversion. It is known that when physicians are faced with barriers to prescribing a certain type of medication, they will often prescribe around that barrier by selecting medications that are perceived as less scrutinized even if they are less efficacious and/or potentially more harmful, e.g., hydrocodone instead of morphine. Barriers to benzodiazepine prescribing in New York led to an increase in alcohol use by patients to compensate. The maximum value from electronic prescription-monitoring programs will be realized in states that design them as health care programs with significant law enforcement benefits. The combination of an electronic data transmission system that monitors prescribing practices with a forgery-resistant security paper prescription program for all prescription medication schedules appears able to balance the frequently disparate needs of physicians and law enforcement officials.

In the meantime, all controlled medications should be prescribed by one physician and all prescriptions filled at one pharmacy [81]. Initially, weekly prescriptions without refills will help to demonstrate the patient's ability to adhere to the treatment program. No deviation from the prescribing plan is allowed, e.g., no telephoned prescriptions or early refills. Short-acting opioids, should they be required for break through pain treatment, should be held by a participating friend or relative who understands how they are meant to be taken to reduce the possibility of misuse. Patient-controlled analgesia is generally not recommended in persons recovering from addictive disorders.

The creation of opioids with less abuse potential is being sought. Specifically, opioids that are naturally long-acting with 100% bioavailability are much less susceptible to abuse than short-acting opioids formulated as long-acting preparations. The addition of ultra-low-dose opioid antagonists to a μ-opioid agonist has also been shown to enhance analgesic efficacy while decreasing tolerance and physical dependence [74].

Non-opioid pharmacological treatments (e.g., non-steroidal anti-inflammatory drugs, anticonvulsants, antidepressants), physical therapies,

and psychosocial, emotional, and spiritual support should form the mainstay of chronic pain treatment, especially in addicted persons, whenever possible. More intensive social and emotional support will be needed at times of increased environmental and physiologic stress to guard against relapse and aberrant drug behaviors.

Substance Use Disorders and Pain: Clinical Considerations

Programs that treat psychiatric disorders and substance use disorders simultaneously produce better substance use treatment outcomes. The need for pain treatment in substance use programs has been generally overlooked. Pain is associated with a unique and more severe pattern of substance use, and should be an essential part of the treatment of addictive disorders.

Co-occurring pain in patients with substance abuse disorders complicates their substance abuse treatment in several ways. Pain drives drug-seeking behavior in animals and humans. Patients with substance use disorders and chronic pain have increased drug-seeking behavior and craving. Pain may increase the drive to use substances that produce euphoria. Therefore, effective pain treatment would be expected to improve outcomes in substance abusers. Further, pain is often associated with mental health problems that worsen substance abuse outcomes. This is especially true after traumatic injuries, where the occurrence of post-traumatic stress disorder is associated with greater drug abuse severity and worse treatment outcomes. The functional and social disabilities associated with pain make it more difficult for substance-abusing patients to remain in substance abuse treatment programs, as does the requirement to be "drug free" when benefit is accruing from opioid therapy. Thus, this patient group has unique treatment requirements that differ from patients with substance abuse without pain and those with pseudoaddiction [70].

Particular differences between substance abusers with chronic pain and those without pain include more relief-seeking behaviors (e.g., illicitly obtained analgesics, increased health care visits to primary care and substance treatment providers), pain avoidance behaviors (e.g., depression and anxiety), and reduced physical and social functioning. Attempts made to minimize their pain frequently exacerbate their substance abuse, which exaggerates their emotional, physical, and functional impairments. All of these behaviors and conditions worsen with increasing pain intensity, indicating that pain is responsible for these behaviors. The ability to improve the pain experience in these patients, even without complete pain relief, has been shown to improve incrementally patients' well-being.

The pattern of substance abuse engaged in by abusers with chronic pain shows a greater use of non-prescribed analgesics, the selective administration of substances known to provide pain relief, and higher doses of alcohol. Patients in chronic pain drink more in one sitting than abusers without pain [70]. This increases the toxicity of opioid therapy by augmenting its central depressant effects. Opioid abstinence syndromes, and opioid therapy in some individuals, are associated with hyperalgesia, which further complicates pain management [21].

One other consideration is the use of buprenorphine rather than methadone for opioid substitution therapy. Buprenorphine is a partial μ-agonist with an analgesic ceiling. When it is added to therapy utilizing a full agonist it can precipitate withdrawal. Thus, patients maintained on buprenorphine for addiction may need to change to methadone maintenance therapy in order to benefit from acute opioid analgesic therapy.

Analgesic Management of Opioid Substitution Patients: Acute Pain

All too frequently, patients on chronic opioid therapy for pain and/or addiction treatment fail to receive their baseline drug doses upon admission to the hospital for acute care and undergo drug withdrawal [47]. This is especially

problematic in the surgical population where increased pain postoperatively is inevitable. Clearly, at the very least, patients should continue to receive their pre-admission drugs in their pre-admission doses with additional analgesia as needed. The fear of relapsing into drug abuse behaviors drives some recovering addicts, and those in opioid substitution programs, to refuse analgesia in the belief that exposure to another opioid will cause craving, etc. Physicians' fears that opioid analgesia will make an addict worse lead to failure to provide analgesia and undertreatment. In actuality, the cellular and molecular changes that accompany long-term opioid use make the endogenous opioid system less responsive. This manifests itself in higher pain scores and lower pain tolerance. Cross-tolerance to morphine and other opioids requires higher doses than in opioid-naïve subjects to obtain pain relief. In the author's experience, in methadone maintenance patients, greater analgesia is experienced when the daily maintenance dose is divided into thirds and given at 8 hourly intervals. The problem of buprenorphine in μ-opioid agonist therapy is problematic as described previously.

Fortunately, opioid analgesia is not the only effective therapy available for acute pain management. In the majority of patients, local anesthetic-mediated techniques (e.g., epidurals, peripheral nerve blocks, intravenous lidocaine), non-opioid analgesics (e.g., non-steroidal anti-inflammatory drugs, cyclo-oxygenase type 2 antagonists, anticonvulsants, antidepressants), low-dose ketamine and dextrometorphan (*N*-methyl-*D*-aspartate receptor antagonists, which enhance opioid analgesia), and physical therapies (e.g., thermal modalities, massage, exercise, transcutaneous electrical nerve stimulation) are extremely effective and will suffice in combination or singly, with or without supportive psychotherapy.

Conclusions

Pain and addiction are complex, chronic neurobiologic disorders that are poorly understood, inadequately treated, and underresourced in health care settings and society. Physical and affective components of these diseases should be treated simultaneously in multimodal, multidisciplinary disease management programs for best outcomes.

Expansion of health care resources and collaboration between pain medicine and addiction medicine specialists to allow patients with comorbid conditions to be treated effectively are necessary. Pain physicians need support and resources to effectively implement care programs and "Universal Precautions". Addiction physicians need support and resources to effectively provide rehabilitation programs with the flexibility for patients requiring therapeutic opioids for pain, i.e., non-drug free.

Opioid prescribing is, directly or indirectly, a major driver of prescription opioid abuse. Depression, generalized anxiety disorder, panic disorder, and somatization associated with painful conditions may be a large and heterogeneous patient group mistreated with opioid analgesics. Education is paramount in achieving the balance and cooperation needed to provide dual care to addicted individuals who also require opioid analgesia and for pain patients at risk of developing abusive or addictive disease. Health care providers, law enforcement agencies, and the general population alike should be educated in the nature of these diseases if they are to be diagnosed, assessed, and treated appropriately. Law enforcement should complement the efforts of clinicians in providing needed medical care while clinicians fastidiously assess, treat, and document therapies.

New areas of research, such as glial function in nociception and mood disorder, have the potential to provide unique therapeutics with strong analgesic potential, and possible antidepressant effects, without the risk of addiction and other serious adverse effects associated with current analgesic medications.

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The Triple Threat: Mental Illness, Substance Abuse, and the Human Immunodeficiency Virus

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Contents

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Introduction

Concurrent substance abuse and psychiatric disorders in individuals who are infected with the human immunodeficiency virus (HIV) are common. Prevalence rates vary significantly across reported studies and range from 10% to nearly 70% depending on the study [64, 67]. In a large cross-sectional study, as many as half of the clients in an HIV clinic had at least one psychiatric disorder, with nearly 40% abusing drugs (other than marijuana) and up to 12% with drug dependence during the previous 12 months. There are high rates of bipolar II disorder and cyclothymic and hyperthymic temperaments that have been linked with up to 70% of the HIV population [64]. All have been associated with higher rates of increased impulsivity along with greater novelty-seeking and risk-taking behavior in this population. Thus, we can infer that unsafe sexual practices and needle-sharing are very common.

Similarly, psychiatrically ill individuals often go on to develop substance abuse disorders. Independently, substance abuse disorders may contribute to psychopathology and the emergence of psychiatric illness. Both will impair judgment and contribute to high-risk behaviors such as sharing needles and injection paraphernalia or trading sex for money.

Given the high comorbidity between the dually diagnosed (mentally ill and substance abuse) and HIV, the purpose of this review is to examine recent data regarding the interactions

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_58,

between dual diagnosis and HIV as well as associated comorbidities—especially hepatitis C infection.

Scope of the Problem

The highest rates of HIV infection are in individuals with dual diagnosis of severe mental illness and substance use disorder. In one study of HIV-positive participants with comorbid substance use and psychiatric problems ($n = 1{,}848$), HIV prevalence was 4.7% in those having a diagnosis of both substance abuse and mental illness, whereas HIV prevalence was only 2.4% in those diagnosed with a substance abuse disorder alone. Psychiatric illness appeared to almost double the risk of HIV—especially in those with concurrent poor psychosocial support [10]. These findings were confirmed by a cross-sectional survey of 3,806 adults living with HIV across four major metropolitan areas in the United States, which showed that 72% of respondents reported at least occasional use of various drugs, and 40% of respondents reported frequent use of various drugs—only 28% declared abstinence from all drugs [50]. In the group reporting frequent use of drugs, more were likely to be identified as heterosexual, had public health insurance, and endorsed increased symptoms of depression [10, 50], which illustrates the complexities of the relationship between the triple diagnoses of mental health-substance abuse and HIV infection.

Drug Abuse Disorders

Alcohol use alone has been linked to multiple risk factors associated with HIV including sexually transmitted disease histories, condom non-use, multiple sex partners, and lower HIV-related knowledge. These risks appear to increase substantially with increasing amounts of alcohol use and those demonstrating abstinence from alcohol appear to have the lowest risk profile. The impact of alcohol upon these risk factors remains present even in the absence of other drug abuse [61].

Intravenous drug use has long been associated with an increased prevalence of comorbid psychiatric diagnosis—especially dysthymia and depression [1]. Depressive syndromes in intravenous drug use populations have also been repeatedly linked to increased willingness to share needles, syringes, and other paraphernalia, which further increases the risk of HIV transmission [1, 12, 75]. Stein and colleagues examined the association of depression severity and drug injection HIV risk behavior among injection drug users. Even after controlling for multiple confounding variables, including age, race, gender, number of days on which injection drugs were used, and the average number of injections per injection day, a diagnosis of depression was significantly associated with injection risk behavior [75].

Similarly, other data illustrate that depressed individuals are more likely to engage in sex with intravenous drug use populations, heightening an already substantial risk of transmission [38]. This same population also demonstrates increased rates of sexual abuse. This again predicts depressive features, increased suicidality, and increased non-adherence to antiviral therapy, making the risk of disease progress and viral resistance greater in this group [11, 51, 65]. Poorer outcomes in HIV-infected intravenous drug users have been related to a variety of factors, including increased rates of hepatitis C, delayed access to treatment, diminished adherence to highly active antiretroviral therapy regimens, depression, psychosocial stressors, and death [49].

Among individuals who inject drugs, studies have shown that up to one-third are at risk for severe depression with women appearing to experience increased depressive symptoms as compared with men. Correlates of depression in both men and women include perceived functional limitation, greater negative feelings regarding condom use, lower social support, and a lower sense of empowerment/external locus of control. Similarly, being physically abused

as an adult and Latino race also appeared to be significant predictors of depression among HIV-seropositive intravenous drug users of both genders [79].

Methamphetamine-dependent men who have sex with men also demonstrate high lifetime rates of psychiatric disorders including major depression and anxiety disorders. Generalized anxiety disorder, specific phobia, bipolar disorder, and major depressive disorder have all been linked to higher rates of sexually transmitted infections including gonorrhea and HIV [72]. Crystal methamphetamine use has evolved to be a major risk factor for the development of depression and other mental illness as well as increased transmission rates of HIV. Naturalistic interview studies have demonstrated the wide prevalence of a cycle of severe depression and anxiety in the context of methamphetamine use as well as persistent anhedonia. Almost all respondents in such studies reported that crystal methamphetamine was severely damaging to social relationships with a resultant increase in self-isolation. In addition, methamphetamine use has been closely tied to random sexual encounters and increased numbers of sexual partners with a decreased likelihood of condom use [59]. A better understanding of these patterns and risks are essential in developing effective prevention strategies.

Psychiatric Disorders

Common mental disorders among individuals with HIV and substance abuse include adjustment disorders, sleep disorders, depressive disorders, mania, dementia, delirium, psychosis, and personality disorders [8]. A careful psychiatric assessment is necessary in order to engage in differential diagnostic considerations and differential therapeutics. There are three categories of mental disorders of concern in HIV-infected substance abusers: substance-induced mental disorders, HIV-related mental disorders, and medication-related mental disorders [8].

Psychiatric Disorders in Human Immunodeficiency Virus Infection

Mania and Bipolar Disease

Bipolar disease in the context of HIV is especially problematic in that it involves cyclical moods that not only predispose its sufferers to the risk factors of depression, but also heightened risks of contracting HIV due to features of mania that include impulsivity, hypersexuality, and increased goal-directed behavior. Individuals with comorbid hepatitis C/HIV are more likely to have comorbid psychiatric disorders including bipolar type [5]. Bipolar illness frequently co-occurs with substance abuse and has been linked to heightened risk taking and impulsivity. One study examining the link between mania and HIV risk found that most study participants had been sexually active in the past 6 months (75%), and they reported high rates of sexual risk behaviors such as unprotected intercourse (69%), multiple partners (39%), sex with prostitutes (24%, men only), and sex trading (10%). Severity of bipolar illness was also associated with HIV risk profile [58].

Schizophrenia

Individuals with serious and persistent mental illness (schizophrenia, bipolar, major depressive disorder) have been noted to have approximately twice the incidence of HIV as compared with those without serious and persistent mental illness, and there is also a greater incidence of infection with hepatitis C [22]. However, the source of this increased risk has been debated, and some data suggest that in the absence of comorbid substance abuse, these individuals do not share an elevated risk for acquiring HIV compared with other non-serious and persistent mental illness populations [36]. Poor HIV knowledge and increased risk-taking behavior is also significant in this cohort [46, 47].

Identification of comorbid serious and persistent mental illness is important in this population in that comorbidity incurs a worse prognosis for both the schizophrenia and the HIV due to factors such as psychosocial instability and adherence [22].

Depression

Depression is a common co-occurring condition with HIV and is the most common mood disorder found in people living with HIV. While depression may decline in non-HIV-seropositive populations with advancing age, this does not appear true of HIV-seropositive individuals, which places them at continued risk of depression even during older age [69]. Depression has also been closely linked to apathy in HIV-seropositive populations, and both apathy and depression are linked to highly active antiretroviral therapy non-adherence [68]. Similarly, fatigue has also been linked to depressed mood and a diagnosis of major depressive disorder [29]. Depression severity has also been linked to a greater frequency of injection drug risk behavior among depressed injection drug users [75].

Women have been reported to be a special risk group in regard to depression and intravenous drug use. Depression rates and severity appear to be more present in women who are both infected with HIV and injection drug users [60]. Women also report the poorest quality of life scores in the context of HIV infection, in spite of showing some protection against cognitive decline with respect to male counterparts [84]. Drug use, violence, and depression have been deemed a "tripartite HIV risk" among African-American women and are underexplored areas of research. Women with a history of sexually transmitted diseases have been noted to be more likely to experience violence and depression—both alone and comorbidly. This described tripartite risk group is also reflective of those women having two or more sexual partners in the last 30 days as well as those having an early onset of alcohol abuse [42]. Similarly, antiviral adherence has been noted to be worse in drug-abusing women as compared with men. However, mental health care has been shown to be significantly associated with adherence in this population as opposed to men [77]—again highlighting the need for effective psychiatric services in this at-risk group.

Psychosocial Issues

Childhood sexual experiences have been linked as a strong predictor to psychological distress as well as risk of substance abuse and HIV transmission risk [3, 43]. Among men who have sex with men, those with a history of childhood sexual abuse were more likely to engage in high-risk sexual behavior including unprotected receptive anal intercourse, to engage in trading sex for money or drugs, to report being HIV seropositive, and to experience non-sexual relationship violence [43]. Additionally, when confronting this group of at-risk individuals, it is useful in distinguishing forced childhood sexual abuse versus consensual childhood sexual experiences. Individuals who experienced forced sexual contact have the highest risk of these three factors as compared with the consensual group who only demonstrated increased rates of substance abuse and HIV transmission risk as compared with a no-exposure group [3]. Thus, an assessment of these groups should include a discussion of patterns of risk exposure and childhood sexual exposure to better tailor interventions to the specific individual.

The role of past trauma in placing individuals at risk of HIV has also been found in large populations of HIV-seropositive women [39, 62]. Hutton identified that among women prisoners, HIV risk behaviors in the 5 years preceding incarcerations included unprotected sex (56%), injection drug use (42%), sexual intercourse with a partner who injected drugs (42%), prostitution (30%), needle sharing (30%), receptive anal sex (19%), and having more than 100 sex partners (7%). After adjusted for age, education, race, HIV status, and addictive disorders, post-traumatic stress disorder was associated

with the practice of receptive anal sex and prostitution and appeared to contribute to these high-risk activities.

In addition, Myers identified that greater drug dependence has been associated with increasing rates of HIV, depression, and higher chronic disease burden among women. Similarly, alcohol dependence and trauma have been associated with increased depression and social instability in this group as well [62, 74]. Importantly, both childhood trauma and depression severity appear to predispose to ineffective and avoidant coping strategies, which may predispose this group to additional burdens of depression and disease throughout life [74]. Likewise, among non-adherent women prescribed highly active antiretroviral therapy, the use of cocaine and heroin and a history of abuse decreased the likelihood of acceptable adherence to highly active antiretroviral therapy [18]. These items taken alone or together illustrate not only the need for substance abuse programs but also the important role of sexual abuse prevention efforts and abuse treatment strategies in at-risk groups.

Other data support a high prevalence of depression and substance abuse among HIV-seropositive individuals enrolled in methadone maintenance treatment programs or needle exchange. Depression is extremely common in these programs, and one study has estimated rates as high as 54%. Women, persons with a comorbid alcohol abuse diagnosis, and those with diminished social support were more likely to be depressed even after controlling for age, race, education, and HIV status. Those enrolled in methadone programs showed significantly less depression than similar participants in a needle exchange program [13].

Comorbid Medical Disorders

Hepatitis C

Another complicating factor that commonly exists in dually diagnosed individuals with HIV disease is the concurrent diagnosis of hepatitis C infection. Large observational retrospective cohort studies in high-risk populations have demonstrated that over one-third of people living with HIV are also hepatitis C seropositive, and the group with combined infectivity is characterized by being older minority men who were more likely to acquire HIV by intravenous drug use. In addition, individuals with both HIV and hepatitis C were more likely to have a diagnosis of mental health illness, depression, alcohol abuse, substance abuse, and hard drug abuse compared with those infected with HIV alone. Individuals with both HIV and hepatitis C were also less likely to have received highly active antiretroviral therapy during the previous year [4].

Cognitive Disorders and Dementia

One of the common complications of HIV infection is neurocognitive impairment. This alteration of brain-behavior functioning may range from a subjective sense that one has slowing of thinking and difficulty with memory retrieval to a severe dementia with confusion, mutism, and gross neurologic signs. Numerous studies indicate the percentage of HIV-infected individuals having any cognitive impairment during the course of their illness to be 38.8–54.4% overall and meeting the full criteria for dementia to be 10.4–25.2% [23, 63, 78], despite more and more effective antiretroviral therapy [63]. With this percentage of people with potential cognitive loss, it follows that clinicians working with HIV-infected individuals must be sensitive to any signs that cognition is declining, be prepared to refer for a formal neurocognitive evaluation to fully delineate the problems, and, if results show that there are deficits, have a treatment plan available to improve functioning [28, 37]. There may also be cognitive complications from substance-induced psychiatric disorders including effects from both illicit and prescribed drugs as well as antiretroviral and cancer-related chemotherapy [16, 35, 48].

Individuals with both HIV and hepatitis C may also experience significant impairment in the realm of cognitive functioning given that both HIV and concurrent disease such as hepatitis C impact central nervous system processes. In addition, hepatitis C has been linked to fatigue, increased depression rates, and impairments in health-related quality of life that are independent of the severity of the liver disease [30]. Multiple explanations for these symptoms have been offered, but central nervous system effects of substance abuse, personality types, and hepatitis C viral load have all been prominent reasons to explain these effects. In particular, the central nervous system impact of hepatitis C has been noted most in the domains of attention, concentration, and processing speed [17]—all of which can mimic deficits secondary to HIV illness as well as major depression [81, 84].

The impact of major depression upon cognitive performance in HIV-seropositive populations cannot be neglected, and data support the link with depression as a risk factor for neuropsychological disturbances in seropositive drug abusers. Cognitive performances across multiple domains appeared impaired secondary to depression in an HIV-positive, drug-abusing population including attention, cognitive flexibility, and motor speed [80].

Similarly, previous alcohol abuse has been demonstrated to be linked with additive levels of cognitive dysfunction in HIV-seropositive populations. Significant and synergistic interactions in the realms of verbal reasoning, auditory processing, and reaction time have been noted in HIV-seropositive populations with a history of alcohol abuse. These interactions did not exist in a HIV-seronegative control group with a history of alcohol abuse [34]. This illustrates the potential synergistic and combined cognitive effects that triply diagnosed individuals may experience, along with the need for a high level of clinical suspicion for cognitive disorders in this group. This is especially important in that cognitive disorders in HIV are also important predictors of highly active antiretroviral therapy nonadherence. Addressing hepatitis C and cognitive deficits will continue to be of high importance in a dually diagnosed population with concurrent HIV disease.

Role of Mental Illness and Substances of Abuse in the Treatment with and Adherence to Highly Active Antiretroviral Therapy

Previous studies examining the relationship between depression and HIV transmission have shown mixed results, but the role of depression upon adherence to highly active antiretroviral therapy has been confirmed in multiple studies on the subject. A recent longitudinal study on adherence rates from 2001 to 2004 of HIV-seropositive individuals with concurrent mental illness and substance abuse demonstrated several concerning patterns. Almost 73% of participants met criteria for major depressive disorder and depression was linked to non-adherence [9]. Importantly, this group was reflective of the growing HIV epidemic in that 75% were people of color, 66% described their sexual orientation as heterosexual, and most were unemployed [9].

Given that mental health diagnosis and substance abuse problems are common among individuals infected with HIV, a great deal of attention has been devoted to the study of these factors and their impact upon adherence. Large cross-sectional studies demonstrated that mental health diagnoses including depression, generalized anxiety disorder, or panic disorder were more likely to be non-adherent to highly active antiretroviral therapy over the previous week than non-psychiatrically ill counterparts. Non-adherence was also associated with cocaine, amphetamines, or sedative use in the previous month, but cocaine demonstrated the strongest predictor of non-adherence in the drug abuse group, while generalized anxiety disorder demonstrated the largest odds of non-adherence among the mental health diagnoses. However, frequent heavy alcohol abuse showed the largest odds ratio of non-adherence among all diagnoses combined, illustrating the need for effective interventions among this population [76].

The role of mental illness and substance abuse upon HIV populations is significant in that multiple studies have linked diminished adherence rates to these risk factors. Even active cigarette smoking is an independent predictor of non-adherence in HIV-infected individuals receiving highly active antiretroviral therapy, and, importantly, this risk of non-adherence diminishes with cessation of smoking [73]. Based upon available data, a history of substance abuse without current abuse does not predict non-adherence, which again illustrates the importance of active interventions designed to curb substance abuse and dependence.

Further, the presence of depression has also been linked as an independent risk factor in not only non-adherence but also HIV disease progression, viral load, and CD8 activation [27]. This pattern has most recently been documented in a study of highly active antiretroviral therapy-treated HIV-infected drug users of which intravenous drug users comprised 17% of the study group. Depression was encountered in 46% of the study group during the follow-up period, and non-adherence reached 31%. Clinical predictors of disease progression included both non-adherence to highly active antiretroviral therapy as well as a higher score of depressive symptoms following highly active antiretroviral therapy initiation, which remained significant even after controlling for non-adherence behavior [11]. Similar studies focusing upon HIV-seropositive women also found that chronic depression was a predictor of AIDS-related deaths with symptoms being more severe among women in the terminal phase of their illness [21]. Interestingly, mental health care has been associated with reduced mortality [21]. Other affective syndromes including bereavement and chronic grief have also been linked to disease progression in HIV-infected populations [32].

However, encouragingly, depressed individuals living with HIV who receive psychiatric treatment with antidepressants are more likely than untreated individuals to receive appropriate care for their HIV disease and increase adherence to HIV interventions. Antidepressant therapy for treatment of depression in this population has also been demonstrated to be associated with a lower monthly cost of medical care services based upon at least one study examining merged Medicaid and surveillance data. Encouragingly, women and drug users engaged in treatment were most likely to receive an antidepressant response, and those receiving antidepressants achieved a 24% reduction in monthly total health care costs as compared with a depressed but untreated cohort [71].

Risk-Taking Behavior

Previous cross-sectional data has illustrated a close relationship between substance abuse, depression, and at-risk behavior, but limitations of cross-sectional data include the idea that it difficult to infer causal relationships, whereas longitudinal data can better support causal associations. One longitudinal study examining the relationship between depression and sexual risk behaviors in a community sample of 332 inner-city drug abusers found that increasing severity of depression predicted sexual encounters with multiple partners as well as sexual encounters with known injection drug users [83]. Similarly, depression has been linked to greater frequency of injection risk behavior among depressed intravenous drug users [75].

Other studies have confirmed a link between mental health and risk-taking behavior, even when controlling for substance abuse patterns, across a variety of populations. One study examining a subset analysis of clinic clients with sexually transmitted diseases who met the criteria for major depressive disorder [38] found that depressed individuals were more likely to have sex for money or drugs, a greater number of lifetime sexual partners, and a higher likelihood of abusing alcohol or other substances. The HIV risk behaviors associated with depression persisted even when controlled for substance abuse, which again illustrates the importance of depression screening in at-risk populations.

Similarly, another longitudinal study examining the HIV risk behaviors and drug use among 557 Latino heroin and cocaine injectors not in treatment demonstrated a close association between both mental health and substance abuse variables [53]. Intravenous drug users in this study reported high rates of both depression (52%) and severe anxiety (37%), with concurrent alcohol intoxication in the last 30 days by 18% of participants. Those showing polysubstance abuse (alcohol and injecting behavior) were more likely to inject three or greater times daily, share needles, and share cotton. Polysubstance abusers were also more likely to engage in casual sex or prostitution as well as unprotected sex [53]. These studies illustrate that prevention efforts designed to reduce HIV risk behaviors cannot neglect addressing both mental illness and substance abuse in this triply diagnosed population.

Another impact of the presence of comorbid mental health disorders and substance abuse has been its role in promoting increased sexual risk-taking behavior in young age populations. One study examining a cohort of newly homeless youth who were followed longitudinally for up to 24 months demonstrated that drug use was a significant predictor of having multiple sexual partners as well as decreased condom use. Similarly, living in a non-family setting also was a significant predictor of sexual risk-taking behavior and condom use [66].

However, the impact of depression and substance abuse upon adherence and HIV transmission is heightened by consideration that available data do not only support a link between decreased adherence to highly active antiretroviral therapy and dually diagnosed individuals, but also support a link that dual diagnosis increases the risk of unsafe sexual encounters among those with a known resistant virus. Data from the Study of the Consequences of the Protease Inhibitor Era [15] showed that among participants taking highly active antiretroviral therapy, 60% had genotypic resistance to at least one drug. In those with documented drug resistance, 27% of men who have sex with men and 11% of heterosexual men and women reported at least one episode of unprotected penile-anal or penile-vaginal intercourse in the previous 4 months. Importantly, up to 17% of men who have sex with men reported unprotected intercourse with an HIV-uninfected or status-unknown partner. Significant predictors of these behaviors included younger age, depression, and the use of sildenafil and alcohol. As with other studies of this population, these risk factors were identifiable and allow a targeted intervention with limited resources [15].

As noted previously, the role of psychostimulant abuse—especially cocaine and methamphetamine—is a major risk factor in HIV behavior, and rates of methamphetamine abuse appear to be increasing in at-risk populations (e.g., men who have sex with men). Medical complications from methamphetamine abuse are myriad and include hypertension, hyperthermia, rhabdomyolysis, and stroke [15]. In addition, comorbid methamphetamine abuse and HIV infection has been linked to increased likelihood of severe cognitive and movement disorders [45].

A large analysis of 736 enrolled participants in the EXPLORE study, who were men who have sex with men, described patterns of use with methamphetamines, poppers, and cocaine as well as sexual risk behavior. Younger participants were more likely to increase their use of drugs over time, and high-risk sexual behavior was more common during periods characterized by increased methamphetamine, popper, or sniffed cocaine use. Importantly, a within-person analysis found that both light drug use (less than weekly use) and heavy drug use periods were significantly associated with engaging in unprotected anal sex with HIV-seropositive or unknown status partners as compared with periods of no drug use [19]. Importantly, these data suggest that a risk-reduction model of addressing substance abuse in this population is likely to be ineffective in reducing HIV transmission, while engagement in an abstinence model appears safer and more effective. Similar data regarding the risk of moderate alcohol use upon non-adherence also support an abstinence model over a risk-reduction one [76].

Assessment of the Triply Diagnosed

The assessment of the triply diagnosed poses special difficulties, as they are more likely to manifest complex disease in all aspects of care, including increased numbers of viral mutations and resistance, complex psychiatric needs including treatment-resistant depression and post-traumatic stress disorder, as well as either ongoing substance abuse or being at high rates of relapse for substance abuse. Ideally, psychiatric consultation liaison services and substance abuse services are available within the infectious disease clinic, so the client can be approached and evaluated simultaneously by multiple practitioners to gain a more three-dimensional understanding of his or her needs and risk factors so as to allow optimization of the individual treatment plan.

The comprehensive assessment of these individuals should include an extensive and detailed psychosocial history designed in part to elicit sources of stress, sources of support, past psychiatric history, and any history of abuse, given that these all appear significant in predicting non-adherence and disease progression. Additionally, a detailed substance abuse history including types of substances, age at first use, frequency and route of use, triggers, and any available protective factors is an essential step toward providing support and guiding individuals toward appropriate treatment that will both allow and run concurrently with their HIV treatment [7, 25, 26].

Substance Use/Abuse Treatment of the Triply Diagnosed

Many factors contribute to the delayed entry of the triply diagnosed. These can include dropping out of care, living in unstable housing, lack of food, lack of transportation, the complexities of the healthcare system, health maintenance organization-required payment authorizations, and idiosyncratic referral practices of the medical team for either psychiatric care or drug abuse/dependence consultations, or both. Injection drug users are less likely to receive antiretroviral therapy than any other population. Factors associated with poor access to treatment include active drug use, younger age, female gender, sub-optimal health care, not being in a drug treatment program, recent incarceration and lack of health care provider expertise [31]. Yet these individuals should be considered and can be treated effectively. Department of Health and Human Services guidelines state that antiretroviral therapy can be successful in intravenous drug users [31]. Antiretroviral therapy requires that providers and clinical care sites become more supportive, having increased awareness of interactions with methadone as well as risk of side effects and toxicities, and use of simple tenchniques to enhance adherence can be successful. One study of triply diagnosed women lost to follow-up in an HIV clinic [2] received nursing outreach intervention over 3 months to assist in treatment entry. Follow-up included home visits to assist in making and keeping appointments, accompanying the women on their initial clinic visits, integration of care among HIV, substance abuse, and mental health providers—all were found to assist in access, adherence, and retention.

Longitudinal data demonstrate that both HIV-seropositive status and baseline depression independently predicted recurrent or persistent episodes of major depression in intravenous drug users. HIV-seropositive drug abusers with baseline major depression showed a 90% rate of at least one subsequent episode of major depression over a 3-year period and 47% experienced at least three subsequent episodes [41]. However, less than 40% of this population received psychiatric treatment during this time [41], making them at high risk for not only engaging in behavior that perpetuates HIV transmission but also being undertreated for risk factors contributing to this same behavior.

One study examining the effects of an intensive outpatient cocaine treatment program over 9 months found that risky behavior among participants was correlated with high intake

problem severity and psychological symptomatology. Over the course of treatment, the amount of risky behavior was found to decrease significantly among those participating actively in the treatment program. The decrease in risky behavior was linked to decreased substance abuse, but did not appear affected by demographic variables, type, or duration of treatment in this study [33].

Other potential data-driven intervention models include brief peer-delivered educational interventions. This model has been shown to be effective as compared with a standard National Institute on Drug Abuse HIV testing and counseling protocol for cocaine abusers [20]. Both models, however, have demonstrated effectiveness in reducing crack cocaine use, injection drug use, and the number of intravenous drug-using sex partners. Subjects diagnosed with an antisocial personality disorder demonstrate less improvement than non-antisocial controls. However, neither intervention model was shown to be effective in improving condom use [20], which illustrates the complex nature of these risk factors and the need to have multiple interventions to target at-risk behaviors.

Methadone maintenance treatment programs are also an essential part of the treatment of triply diagnosed individuals. Increased numbers of clients in methadone maintenance treatment show intravenous drug use abstinence [24]. Methadone maintenance treatment has been demonstrated to dramatically reduce illicit opiate use as well as criminal activity. More recent data support that methadone maintenance treatment also reduces incarceration rates, which would likely diminish the risk factor of sharing needles while incarcerated and lower exposure to high-risk practices [82]. In addition, opiate treatment-resistant dually diagnosed individuals show better long-term survivability in methadone maintenance treatment programs than their non-dually diagnosed counterparts [52].

Non-methadone maintenance treatment programs centering on group activity and support also demonstrate significant roles for the treatment of this complex population, and involvement in either methadone maintenance treatment or non-methadone maintenance treatment programs is associated with improved antiretroviral therapy adherence [44]. Buprenorphine programs are likewise associated with improved highly active antiretroviral therapy adherence [70], although they are widely underused in HIV-seropositive populations in the United States. France appears to have the most experience with buprenorphine programs in HIV-positive populations, and data support their effectiveness in this population [14] even though both methadone and buprenorphine have significant drug-drug interactions with highly active antiretroviral therapy medications.

Methadone is primarily metabolized via cytochrome P450 3A4, and this cytochrome also is responsible for the metabolism of multiple highly active antiretroviral therapy medications—most notably, the protease inhibitors. Consequently, drug-drug interactions and potential complications involving methadone/buprenorphine prescribed concurrently with highly active antiretroviral therapy include changes in pharmacokinetics as well other effects such as a prolonged QTc interval [6, 54]. Ritonavir produces strong 3A4 inhibition initially, but has also been documented to induce 3A4 when administered chronically. Therefore, it is clear that drug-drug interactions are difficult to predict over time and require careful monitoring. For instance, initiation of a ritonavir- or other protease-containing antiretroviral therapy regimen in an individual on stable methadone maintenance treatment may result in opiate toxicity and overdose due to early cytochrome inhibition [40]. Conversely, lopinavir is a potent inducer of methadone metabolism, with one study finding that the combined effects of lopinavir/ritonavir administered to methadone maintenance treatment recipients included significant reductions in the methadone area under the concentration-time curve and reductions in the maximum serum concentration in the setting of increased methadone oral clearance [57]. Consequently, the authors also noted increased rates of opiate withdrawal in this population, highlighting the need for careful monitoring of clients during either methadone

maintenance treatment initiation or highly active antiretroviral therapy initiation.

Buprenorphine is also metabolized by 3A4, and concurrent ritonavir acutely inhibits its metabolism, producing higher levels as with methadone [40]. However, conflicting data also demonstrate relative safety in using buprenorphine in the setting of protease inhibitors as well as non-nucleoside reverse transcriptase inhibitors [56]. However, one case series of three buprenorphine/naloxone-maintained participants did report increased sedation with buprenorphine when the atazanavir/ritonavir combination was initiated, which raises the possibility that atazanavir or atazanavir/ritonavir may increase buprenorphine concentrations that require a subsequent dose reduction [55].

Summary and Conclusions

In summary, the triply diagnosed individual presents with significant disadvantages with regard to health potential. The highest HIV rates are seen in individuals with dual diagnoses, and multiple factors contribute to delayed entry or premature cessation of antiviral treatment. All those who enter an HIV treatment program should also be assessed systematically for mental disorders and substance abuse. Individuals with dual diagnoses who are also diagnosed with HIV should be referred both to substance abuse treatment programs and to programs offering psychopharmacological interventions coupled with individual, group, or family therapy as appropriate. Drug interactions between antiretroviral therapies and street drugs or psychotropics can increase or decrease action of either drug, so special attention must be given to potential drug-drug interactions. Cognitive remediation strategies can be used to address cognitive impairment, while a harm reduction approach can minimize the impact from concurrent drug or alcohol use.

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Substance Use Stigma as a Barrier to Treatment and Recovery

Jason B. Luoma

Contents

Introduction

Stereotypes and judgments about people with substance misuse problems are extremely prevalent and negative [15, 18, 22, 73]. The content of these stereotypes varies, with examples including "people who use drugs are immoral," "alcoholics are unreliable," or "addicts are dangerous." These negative evaluations are held not only by those who abstain from substance use, but also by those who themselves use and abuse substances. As the criminalization of drug use has increased over recent decades in the United States, the level of negative attitudes toward drug use has also increased [10].

While the exact form of these stereotypes and judgments may vary across different substances and social groups, substance misuse appears to be at least as stigmatized as psychological disorders such as depression, schizophrenia, or borderline personality disorder, if not more so [15, 18, 22, 73]. While the data are quite clear about the prevalence and negativity of stigmatizing attitudes, research to date on the links between these attitudes and subsequent negative outcomes for those with substance addiction is relatively sparse. As the body of data on stigma toward the mentally ill is much broader and deeper, especially for psychotic disorders, this chapter depends somewhat on extrapolation from mental illness stigma, to substance abuse stigma.

A review of sociological and historical analyses of factors that have contributed to the stigma

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_59,

of substance abuse is beyond the scope of this chapter. Other authors (e.g., [105]) have provided excellent narratives on such topics as the history of legal policy toward substance use and how larger values systems such as Puritanism contribute to stigmatization. Instead, this chapter will focus on the nature of stigma and its impact on those with substance abuse problems through review of scientific research and theory. We also will discuss implications for interventions regarding stigma, particularly in the context of the substance abuse treatment system. The chapter begins with a short review on the nature of stigma in general, followed by a focus on stigma as directed toward those using or abusing substances.

What Is Stigma?

As with most other common language terms that have been adopted by the social sciences, the concept of stigma has been difficult to narrow to a single definition. As used conventionally, stigma refers to an attribute or characteristic of an individual that identifies him or her as different in some manner from a normative standard and marks that individual to be socially sanctioned and devalued. One of the most widely cited definitions of stigma comes from Goffman [38], who saw stigma as an "attribute that is deeply discrediting". This attribute impacts the perceiver's global evaluation of the person, reducing him or her "from a whole and usual person to a tainted, discounted one" (p. 3). Another influential definition comes from Jones et al. [56] who suggested that a stigmatized person is "marked" as having a condition considered deviant by a society. Through an attributional process, this mark is linked to undesirable characteristics that discredit the person in the minds of others. Perhaps one of the most comprehensive definitions of stigma comes from the work of Link and Phelan [72], who define stigma as occurring when the following processes converge: (1) people distinguish and label human differences; (2) dominant cultural beliefs link labeled persons to undesirable characteristics that form a stereotype; (3) labeled persons are seen as an outgroup, as "them" and not "us"; (4) labeled persons experience status loss and discrimination that lead to unequal outcomes; and (5) this process occurs in a context of unequal power distribution, where one group has access to resources that the other group desires.

Stigma Depends on Basic Verbal/Cognitive Processes

Stigma is always in the eye of the beholder. At a psychological level of analysis, all the above definitions hinge on the role of the cognitive and emotional responses of the perceiver in determining who is stigmatized. Stigma emerges from some of the most basic functions of language and cognition, such as categorical, evaluative, and attributive processes [41]. As verbally able humans, a common cognitive activity is evaluating and classifying the people in our social world. This is particularly common when a lack of extensive personal experience with someone leads us to rely on cues for assigning that person to a social category, whether accurately or inaccurately. Our ability to classify according to socially defined categories is universal among language-able humans and also unique to us as a species. Just try it out for yourself. Read the following sentences and fill in the blank:

Men are _____.
Women are _____.
Alcoholics are _____.
Gays are _____.
Addicts are _____.

Were you able to fill in those blanks? Even if doing so felt uncomfortable, most people are able to provide responses that *seem* to describe the group in question. Answers may readily appear even when they are unwanted or disagreeable. Anyone who participates in a cultural/verbal system learns common stereotypes for the groups that have been defined in that culture [26] whether they agree with them or not.

Throughout a typical day we classify people into groups based on some identifying characteristic or behavior, make judgments about what this means about them, and respond based on this judgment. Much of this process of stereotyping and responding occurs outside of our normal awareness and is harmless, even adaptive. For example, we identify the person at the checkout counter in the grocery store as a clerk and proceed to have them scan our groceries. Research has shown that stereotypes help to reduce the burden of problem solving in complex social environments (e.g., [80]). We are able to quickly develop evaluations and expectations of individuals based on their perceived membership in a group about which we have some social knowledge (i.e., stereotypes [40]). These stereotypes allow us to predict that person's behavior and act accordingly. Sometimes this is quite useful, such as when purchasing items in a grocery store. Sometimes it is less so, for example, when seeing a bumper sticker on a person's car endorsing a disliked political candidate, we may make unsavory assumptions about the driver and may be more inclined to engage in discourteous behavior on the road. Sometimes this process is clearly harmful, for example where culturally sanctioned stereotypes devalue certain individuals and this same process results in stigmatizing, rejecting, and even discriminatory interactions. Through this process of objectification and dehumanization, we fail to appreciate the complex, historical human being and respond to the person solely in terms of their participation in verbal categories [43, 77].

Stigmatizing Thoughts are Resistant to Change

Stigmatizing thoughts and attributions have been shown to be difficult to change through direct intervention [43]. One reason for this may be that judgment and stereotyping are massively useful for the individual in many social situations and thus are highly prevalent and automatic, often happening without awareness. Additionally, verbal/cognitive networks, once formed, tend to maintain themselves [43]. Stereotype disconfirming information that occurs during social interactions tends to be forgotten if the new material conflicts with older stereotypes [49]. People tend to infer stereotype-congruent behaviors to dispositional causes, while stereotype-incongruent behaviors are inferred to situational causes [46], thus further supporting their already existing stereotypes. Even people who exhibit low levels of prejudice know the common stereotypes of stigmatized groups, and once learned, these stereotypes do not go away [26]. If a person learns new ways of thinking, the old ways of thinking do not disappear, but rather are available to re-emerge if the new ways of thinking are frustrated or punished (e.g., [144]). Thus, if new stereotypes are learned about a group, these generally do not replace the old stereotypes; rather, the new learning is metaphorically "layered over" the old learning. The old stereotypes are still available to reemerge under situations in which the newer learning is put under strain.

Stigma Is Sustained Through Cultural Practices

While stigmatization is a universal human phenomenon, *what* is stigmatized has been shown to vary over time and across cultures [66]. This suggests that stigma results from cultural practices that exist on the basis of their past ability to facilitate the survival of that culture [5, 143], much in the same way that genes are selected based on their contribution to the survival of a species. Cultural practices which support categorization and stereotyping facilitate membership in and favoritism toward a perceived in-group (e.g., [47, 127]), as well as the resulting mistreatment of those in a perceived out-group [131]. These distinctions preserve and sustain a variety of cultural practices when they generate advantages for the in-group, even when the groups are based on arbitrary characteristics bearing no direct adaptive value. Though stigmatization is defined as the behavior of an individual, it is

always generated and sustained by cultural practices which reinforce and support stigmatizing attitudes, stereotypes, and actions. Thus, in order to change stigma, it is important to change both the behavior of individuals and the cultural practices which support stigma among individuals of that culture.

Types and Levels of Stigma Toward Substance Abuse

The above section was only a brief overview of the vast literatures on stigma, stereotyping, and prejudice. In contrast, the rest of this chapter focuses specifically on stigma toward addiction and begins with a review of types and levels of stigma in relation to substance abuse. Stigma can be subdivided into various types and levels. One distinction can be made between structural and individual stigma. Structural or institutional stigma refers to macroscopic patterns of discrimination toward those with substance misuse that cannot be explained at the individual psychological level alone. This kind of stigma can be either intentional or unintentional [16]. Intentional stigma refers to the rules, policies, and procedures of private and public organizations and structures with power that consciously and purposely restrict rights and opportunities of the stigmatized group. Intentional structural stigma toward addiction would include laws and tax codes that provide inadequate levels of funding for addictions treatment compared to other health conditions or harsher sentencing laws for crack cocaine versus powder cocaine. In contrast, unintentional stigma refers to instances where rules, policies, or procedures result in discrimination, seemingly without the conscious prejudicial efforts of a powerful few [48]. Examples of unintentional structural stigma might include the lower wages and poorer benefits paid to substance abuse treatment professionals compared to other health care or mental health care workers, thus potentially resulting in poorer quality care. Another potential example of unintentional structural stigma would be the exclusion of substance abuse treatment benefits from the Mental Health Parity Act of 1997, resulting in less accessibility of addiction treatment services. This exclusion continued until 2008, when the Mental Health Parity Act of 2008 included substance use disorders.

It is conceivable that prevalent negative attitudes toward substance abuse might contribute to institutional practices that typify structural stigma. For example, prevalent attitudes that people who are addicted to substances are blameworthy and not likely to recover from addiction might make it less likely that the public would be supportive of spending a portion of their tax dollars on treatment. This phenomenon has been witnessed in a German sample who reported that during periods of economic difficulty, they would be prefer to cut funding for mental illness and addiction treatment before cutting funding for physical problems [119].

At the individual level, stigma can be broken down into two types [21, 78], public stigma and self-stigma. The most obvious form of stigma is public stigma, which refers to the reaction the general public has toward the stigmatized group. This includes stereotypes and attitudes toward the stigmatized group, as well as acts of discrimination, termed enacted stigma. For example, rejection by a friend following discovery of a person's substance abuse history, denial of a job opportunity because an employer suspects an applicant is in recovery, or disparaging remarks about people with addictive disorders would all be examples of enacted stigma. People abusing substances and those in recovery frequently encounter enacted stigma [1, 78]. Enacted stigma has been clearly associated with a number of adverse outcomes in mentally ill populations [68, 94, 97, 98, 100]. Though data demonstrating direct links between encounters with enacted stigma and negative outcomes are less available in substance-misusing populations, data showing more negative social attitudes toward substance abusers than those diagnosed with schizophrenia [15, 18, 22, 73] suggest that enacted stigma is even more severe toward those abusing substances.

The second type of individual level stigma is that of self-stigma, which refers to difficult thoughts and feelings (e.g., shame, negative self-evaluative thoughts, fear of enacted stigma) that emerge from identification with a stigmatized group and their resulting behavioral impact [78]. For example, a person with substance abuse problems or a person in recovery might avoid treatment, not apply for jobs, or avoid intimate social relationships because, as a result of self-stigma, they no longer trust themselves to fulfill these roles or fear rejection based on their substance-using identity. Among populations with serious mental illness and dual diagnoses, self-stigma has been associated with delays in treatment seeking [64, 117, 129], diminished self-esteem and self-efficacy [20, 74, 145], and lower quality of life [112].

Perceived stigma is a component of self-stigma and refers to beliefs among members of a stigmatized group about the level of public stigma in society (cf. [68]). A result of perceived stigma may be that people may limit their actions (e.g., seeking treatment or acknowledging their own struggles with recovery) in an attempt to avoid stigmatization. Some data are available showing that perceived stigma may serve as a barrier to treatment adherence, at least in some groups [126]. At least one cross-sectional study of stigma in addiction [78] has generated empirical support for the conceptual distinctions between public, perceived, and self-stigma.

The Need to Study Stigma in Context

Despite the volume of available research on stereotyping, prejudice, discrimination, scapegoating, social categorization, and social deviance, the amount of stigma literature relating these processes specifically to substance abuse is quite sparse. Ahern [1] has suggested that this hole in the literature may result from the common perception that stigma and discrimination against drug users serves to deter drug use and that the possible negative effects of stigma are relatively minor compared to the deterrent value of stigmatization. A substantial body of literature from a law enforcement and criminal justice perspective views stigma as a positive form of social control which discourages illegal activity [11]. This literature largely ignores the potential negative effects of stigma. In contrast, most of the professional literature from mental health and recovery perspectives views stigma as negative and in need of reduction [111]. This literature seems largely to ignore the possibility that stigma might have beneficial effects in some contexts. Each of these perspectives seems to minimize the importance of context and neither seems to acknowledge the possibility that stigma may have both beneficial and harmful effects depending upon the context in which it is found.

A comprehensive scientific approach to stigma would involve examination of the phenomenon across the myriad of situations in which it occurs. Stigma is a complex phenomenon with many forms and widely varying impacts on the individual. Prior to initial drug use and throughout the developmental trajectory for addition and recovery, stigma may have various possible functions. For example, stigma may affect some who are currently not using drugs by dissuading them from initial use. On the other hand, those who identify with marginalized populations may actually be attracted to drug use because of its marginalized status. Once a person has bypassed barriers to initial drug use, stigma could serve to further reinforce and isolate drug-using subcultures, further supporting consumption. For many, stigma serves as a barrier to entering treatment because of fear of being labeled and stigmatized by others. For others, experiences of being stigmatized and judged by others once drug use is discovered or labeled as problematic might serve as a motivator for treatment entry. The effects of stigma might change again after a person enters treatment. Those experiencing more self-stigma or who are more fearful of enacted stigma may stay in treatment for longer periods of time, perhaps benefiting more from treatment. On the other hand,

the impact of self-stigma may impede recovery by reducing substance abusers' motivation and creating negative beliefs about their ability to recover, resulting in earlier relapse. Some people may be relatively unaffected by stigma, perhaps because of personal conditions which help guard against its impact (e.g., financial resources), or because they do not identify with a stigmatized group. Finally, ongoing experiences of stigma-related rejection may serve as a barrier to reengagement with healthy, non-drug-using social relationships, returning to work, or obtaining a reasonable living arrangement. This array of possibilities suggests that simple judgments about the goodness or badness of stigma may be insufficient in understanding the role of stigma in initial drug use, the development of addiction, and recovery from substance abuse. Given the potential complexities, we need a contextually situated approach to examining the effects of stigma on drug use and related outcomes in order to maximally benefit all involved.

Straying from the hypothetical scenarios described in the above paragraph, a study by Farrimond [32] nicely demonstrates the contextual nature of stigma's impact. Qualitative analyses of reports from tobacco smokers in the United Kingdom showed that smokers from lower socio-economic status groups were more likely to internalize smoking related stigma and feel badly about themselves for smoking, rather than change their behavior to avoid it. In contrast, smokers from higher socio-economic status groups were less likely to internalize smoking related stigma and were more likely to have the resources to change their behavior to avoid being stigmatized. The authors suggested that this finding was a partial explanation for the much higher rates of smoking found in lower socio-economic status groups. They hypothesized that broad-scale campaigns to stigmatize smokers might reduce smoking in higher socio-economic status brackets who would work to avoid it, whereas those in lower socio-economic status may not be responsive, and furthermore, that such campaigns may even impede efforts to stop smoking because of increased internalized stigma. They argued that intervention efforts promoting stigma could actually exacerbate disparities already present between higher and lower status groups.

Thus far, this chapter has outlined the nature of stigma in general, including its types and levels. It has outlined how stigma is a complex phenomenon, the effects of which vary by context. The remainder of this text is more focused specifically on what is known about the stigma of substance abuse specifically, describing its importance for those individuals with substance abuse problems, information about stigma in families and social networks of those with addiction, stigma in the treatment system, and interventions to change stigma.

The Impact of Stigma on Individuals with Substance Abuse Problems

Self-Stigma

The psychological impact of stigma on the individual can be described under the term self-stigma. Self-stigma can be defined as shame, evaluative thoughts, and fear of enacted stigma that results from an individual's identification with a stigmatized group and serves as a barrier to the pursuit of valued life goals [77]. The dominant stereotypes about stigmatized groups are widely known in a given culture. Self-stigma comes about when a person first sees himself or herself as a member of a stigmatized group; now the negative stereotypes and biases of society that used to be about someone else apply to the self. For example, at the point when the person who misuses substances identifies himself or herself with the category "addict," relevant stereotypes (e.g., "addicts are irresponsible") that once applied to another now apply to himself or herself. To the extent that people believe this stereotype, they are likely to impede their own chances for success, for example, by not applying to jobs that would require them to be responsible. As the dominant stereotypes of marginalized groups are largely negative and

devaluing, self-stigma may further increase the shame that often comes with addictive behavior that violates important societal and personal values and norms.

A second component of self-stigma is the fear of enacted stigma. Out of this fear of being the target of stigma a person might avoid treatment in the first place or might not get needed social support that could come from disclosing their concerns to trustworthy others. People with substance abuse widely report fear of stigma as a reason for avoiding treatment [23, 50, 62, 136, 137]. Less evidence is available for other effects of self-stigma in addiction, but self-stigma in mental illness has been associated with delays in treatment seeking [64, 117, 129], diminished self-esteem/self-efficacy [20, 75, 145], lower quality of life [112], early dropout from treatment [126], poorer social functioning over time [99], and increased depression at follow-up [109].

Coping and Self-Stigma

Much of the harm of self-stigma comes not only from the presence of shame, painful self-evaluations, or fear of stigmatization, but also from understandable yet costly attempts to cope with these difficult thoughts and feelings. For example, when people who identify with a stigmatized group enter situations where they perceive the potential for devaluation based on this identity [130], they often expend energy searching for and defending against this perceived threat. The effort is taxing and distracts the individual in ways which might hinder social or intellectual performance. In a recent test of this idea, Quinn et al. [104] found that individuals with a history of mental illness who revealed this history prior to taking an intelligence test had poorer performance compared to a control group who did not relate their history of mental illness. These results are in line with more general findings on stereotype threat, that is, that people perform more poorly in situations where a specific stereotype about the group of which they are a member applies [130]. Specifically in relation to substance abuse stigma, these findings suggest that when people with a history of substance abuse problems are in a situation in which addiction-related stereotypes might apply, they may perform more poorly than they would in situations unrelated to addiction-related stigma.

People also cope with stigma by withdrawing their efforts from or disengaging their self-esteem from domains in which one's in-group is negatively stereotyped or in which they fear being a target of discrimination. In an attempt to cope with the potential judgment, failure, or shame that might result from "confirming" a stereotype, a person may exert less effort in domains of living that relate to relevant stereotypes [81]. For example, a person who identifies with the stereotype that alcoholics are immoral might not engage with spiritual or religious groups out of fear that he or she might be judged by others for their "moral weakness." Unfortunately, when a domain is one that might be part of living well (e.g., a steady job) and is likely to elicit thoughts of common stereotypes (e.g., "they won't hire an addict"), then disengagement from that domain (e.g., not looking for work) is likely to interfere with recovery.

Whether a stigmatizing mark can be concealed is also a relevant variable to how people cope. For example, some stigmas may be relatively concealable, such as a past felony conviction or a history of depression, while others may be quite difficult to conceal, such as obesity or diseases with obvious physical characteristics. For many people with substance abuse problems, their condition is concealable, while for others it is less so. Another way to think about concealable stigma is the distinction between "discredited" versus "discreditable" individuals [38]. For individuals with a concealable stigma, a common occurrence is deciding with whom, where, and when to disclose the stigmatizing identity. Whether disclosing a stigmatizing identity is helpful or harmful is likely to be highly dependent on context [29]. In some cases, through disclosing a stigma a person may be able to obtain social support or direct assistance from treatment agencies or health care professionals. Revealing a secret to a trusted confidant has

also been shown to be related to a number of psychological benefits, including improved psychological and physical health [59, 110]. On the other hand, disclosure of a stigma could result in social rejection and isolation, the loss of a job, rejection by family members, judgment from treatment professionals, or disappointment that others were not more helpful. Research on secrecy as a method for coping with the stigma of addiction is relatively scarce and what exists is somewhat crude, typically examining secrecy as a generalized tendency in response to the fear of stigma, rather than examining the patterns of disclosure and how they might interact with social context. As a general rule, the use of secrecy and withdrawal from others as a coping mechanism has been associated with negative psychosocial outcomes [1, 71, 78, 114]. However, this general pattern should not be overgeneralized as a recent large study of mostly minority drug users [1] found that talking with friends and family about being stigmatized and judged was associated with poorer health outcomes. One difference between the Ahern study and other studies of stigma was that Ahern specifically focused on discussions of being stigmatized, whereas most other studies examined the tendency to keep substance use a secret. This suggests that the content of what is disclosed may also affect the likelihood of a positive outcome from disclosure.

All of the coping processes described above (i.e., searching for potential threats, withdrawing efforts from valued domains, and secrecy) could be seen as forms of a broader process termed experiential avoidance. Experiential avoidance refers to the attempt to avoid, control, or reduce the frequency of difficult or painful emotions, thoughts, memories, or other private experiences [44]. Experiential avoidance overlaps with several closely related concepts, including lack of distress tolerance [9], cognitive and emotional suppression [140], and emotion/avoidance-focused coping [12]. As a broader pattern, experiential avoidance has been shown to contribute to a wide range of psychological and behavioral problems, including substance abuse, depression, anxiety, psychosis, and burnout among others [44]. Since experiential avoidance has been shown to be modifiable through mindfulness and acceptance based interventions [35, 45, 138], this suggests that teaching mindfulness and acceptance may be helpful in coping with stigma.

Multiple Stigmatized Identities

For a person with substance abuse problems, the stigma of substance abuse is often only one of several stigmatized identities. Each stigmatized identity is layered on top of the other, creating a dense web of ideas about the self that must be managed and responded to depending upon the social and personal context. For example, substance abuse disorders are highly comorbid with other psychiatric disorders, meaning that the majority of people in treatment for drug abuse also have to contend with the stigma of mental illness [30, 60]. Many people in addiction treatment are also sexual or racial minorities. They may have a stigmatized medical condition such as hepatitis or HIV. They are frequently poor or homeless, both situations which carry their own stigma. Women who abuse substances are often assumed to be promiscuous [118]. Many people with substance abuse histories also have had problems with the legal system or have been incarcerated. In addition to the stigmatization that people may experience directly from the legal system, they now have the added stigma of a prior conviction. Each additional stigmatized identity increases the chance of stigmatization. Each layer of stigmatized identity carries its own challenges that make it even harder to cope with the stigma of drug addiction.

In addition to the problem of multiple stigmas, the impact of substance abuse stigma can also compound existing social inequalities. For example, the stigma of substance abuse has disproportionately impacted the African–American community in the United States, whose drug-related incarceration rate far outstrips their comparative prevalence as drug users [141]. As many in treatment for addiction are relatively poorer, the stigma of drug abuse that tends to fall on those in treatment will also tend to further reduce

the life chances available to those who are experiencing poverty [32]. Again, in addition to the direct effects of the stigma of addiction, stigma also tends to exacerbate the effects of already existing prejudice, marginalization, and disadvantage based on other identities.

Stigmatizing Attitudes and Behavior of Friends and Family

Supportive, cohesive, and non-critical social networks predict good outcomes in addictions treatment [31, 89, 93], while conflict with several members of a social support network, interpersonal conflict, and isolation predict poor treatment outcomes [89, 90]. People entering treatment for addictive disorders are often marginalized, with few connections to family, friends, or coworkers. Entering treatment may be a marker for having exhausted their "moral credit" with employers and families [111]. Stigma may contribute to poorer outcomes by further contributing to the disruption of social ties and increasing isolation beyond the problems created through the direct impact of addictive behavior. Some data are available that bear directly on this point. A recent study of primarily minority drug users [1] found that discrimination and stigmatizing interactions from family and friends was common and independently associated with poorer mental and physical health.

Stigma appears to degrade social networks over time. In one longitudinal study of people with mental illness, many of whom also abused substances [70], perceptions of stigma were associated with reduction in support from non-household relatives over time. Stigmatizing attitudes and behavior of friends and family may also reduce treatment adherence. A recent study of individuals taking antidepressants for depression [121] found that stigmatizing caregiver attitudes predicted premature discontinuation of treatment.

Family members of substance abusers may also suffer from "courtesy stigma." Courtesy stigma refers to the tendency to devalue and stigmatize people who maintain or enter relationships with those in the stigmatized group [38]. For example, in a study by Barton [3], parents of adolescents who abused drugs reported that neighborhood children were told to stay away from their child, resulting not only in isolation for the child but also feelings of shame for the parents. Parents of substance-abusing adolescents also experienced shaming interactions when dealing with institutions such as schools, police, and the legal system. Courtesy stigma may disrupt social cohesion through contributing to struggles inside families that have a member who abuses substances. Family members may attempt to distance themselves from a substance-abusing family member in order to distance themselves from courtesy stigma and the shame that can accompany it. It may be the case that much of the behavior described in the literature as "enabling" or "co-dependent" may result from the family's attempt to avoid the shame of stigma [34] and maintain its identity as a "normal" family.

Stigma in Treatment Settings

Stigma as a Barrier to Initial Treatment Engagement

The public health implications of untreated substance abuse and dependence are enormous. Despite the proven benefits of substance abuse treatment, only a small fraction of those who could benefit ever enter treatment. In 2005, only about 2.3 million of an estimated 23.2 million Americans with substance abuse problems received some form of treatment [115]. Barriers to treatment entry are structural (e.g., location of facilities, lack of qualified personnel, lack of funding), and social (e.g., fear of stigma among those with substance misuse). Stigma contributes to structural barriers when people resist having substance abuse treatment facilities placed in their neighborhoods [6], thus limiting access to treatment. This is important since a having to travel a longer distance to obtain addictions treatment has been associated with poorer

retention [4]. The public is less interested in funding substance abuse treatment compared to other health or mental health problems [119], contributing to long waiting lists and prohibitive cost for treatment. Stressful job conditions result in high rates of burnout and job turnover in addictions professionals [61], resulting in less experienced counselors and less integrated, cohesive treatment centers.

Among the social barriers to treatment entry for addiction, probably the most common barrier cited in the literature is stigma [2, 23, 50, 62, 118, 136]. Across numerous studies, substance-abusing individuals report fear of stigma as a reason for not seeking treatment [23, 50, 62, 136, 137]. For example, Cunningham et al. [23] examined reasons for delaying or not seeking treatment among people with alcohol abuse problems who either self-changed and were in sustained recovery, were still actively abusing, or were currently in treatment. They found that people who were either actively using or self-changed saw treatment as stigmatizing, wanted to avoid the stigma of the label "alcoholic," and reported that embarrassment and pride were barriers to seeking treatment. All three groups reported relatively similar reasons for avoiding treatment, leaving the authors to conclude that "current treatment is stigmatizing and that some alcohol abusers believe that seeking treatment would reflect negatively on them" (p. 352). A study of depressed individuals in Australia found it common to fear that others would think less of them for seeking help and that professionals would respond to them in a condescending manner [2].

Stigma and Treatment Retention and Outcome

For those who are able to overcome barriers and enter treatment, the most stable predictor of positive outcome is length of time in treatment, with studies commonly finding rates of dropout in the first month of outpatient and residential treatment exceeding 50% [53, 54, 124, 125]. Early treatment retention is critical, as data show that early dropouts have equivalent outcomes to those who are untreated [128], and that more time in treatment is related to better outcomes [24, 55, 123]. Unfortunately, stigma doesn't only serve as a barrier to treatment entry; stigma also appears to increase when individuals enter treatment, possibly contributing to poorer retention and thus poorer outcomes [53, 122, 128]. Link and colleagues' [70] modified labeling theory of stigma in mental illness holds that stigma begins to impact people once they have officially received a label from the treatment establishment. A relatively large body of data on seriously mentally ill and dually diagnosed populations supports the hypothesis that entering treatment for a stigmatized condition can result in a labeling process that negatively impacts people's engagement with treatment, psychosocial functioning, and self-concept [20, 74, 145].

The data on such a stigma-labeling process are less developed in the area of addiction, but some direct data are available to support this view. For example, Semple et al. [120] found that methamphetamine abusers who had previously been in treatment reported higher levels of stigma-related rejection than those who had never been in treatment. Another survey of people in treatment for substance abuse [78] found that people with higher levels of current stigma-related rejection had more previous episodes of treatment and that this relationship remained stable even after controlling for other explanatory variables, such as current severity of addiction, demographics, secrecy coping, and current mental health. While this evidence suggests that the impact of stigma and the rate of contact with stigmatizing experiences may increase with treatment entry, we know little about how this happens. For example, we know little about whether stigmatizing messages and rejecting experiences primarily come from non-family social relationships, close family, employers, media, or treatment staff. Moreover, we do not know if certain sources have greater impacts than others, or whether the impact is different for those new to treatment versus those returning to treatment.

Stigmatizing Attitudes and Behavior of Professional Staff

The therapeutic alliance early in counseling has been shown to be a predictor of engagement and retention in substance abuse treatment [88]. Other data show that negative therapeutic alliances predict deterioration in substance abuse treatment [43]. Thus, any actions on the part of substance abuse treatment practitioners that harm the therapeutic alliance are likely to negatively impact retention and treatment outcome among their clients. Health professionals, including addiction counselors, nurses, physicians, and support staff, have been exposed to the same cultural environment that instills stereotyped beliefs in other people. Thus, whether they are aware of it or not, providers likely have internalized many of the same stigmatizing beliefs about substance abuse as others in society. Research shows that health professionals often have moralistic, negative, and stigmatizing attitudes toward substance misuse and believe that substance-abusing individuals are unlikely to recover [86, 89, 108]. For example, one study of mental health support workers in the UK found that alcohol and drug addiction produced more negative responses to an attitude questionnaire than did other problems or mental illness and that those with alcohol and drug problems were mostly likely to be seen as unable to improve if treated [134].

To the extent that stigmatizing attitudes are expressed by providers, they could negatively impact the alliance, thereby reducing retention and creating poorer outcomes. Similarly, support and non-treatment staff could potentially create a hostile atmosphere for clients, further contributing to reduced retention. Because stigmatizing attitudes tend to have a greater impact in situations in which one group has power over another [72], stigmatizing beliefs among healthcare providers may be particularly likely to negatively affect the recovery of those they are trying to help [8]. Some evidence suggests that stigmatizing interactions with providers may be more frequent than expected: one study of methamphetamine abusers found clients' inability to get along with treatment staff was a major reason for dropout [120], while two surveys of consumers of mental health services found that 19% [27] and 25% [139] of consumers had experienced stigmatizing provider behavior. Data from a qualitative study of alcohol and drug abuse counselors found that counselors largely saw illicit drug use as a failing of the individual that needed to be "fixed" with drug treatment rather than seeing the larger context which includes such factors as stigma. In this study, while counselors were generally aware that stigma serves as a barrier to drug treatment, they "did not perceive they as individuals and as treatment workers could perpetuate the same barriers and prejudices" [135] (p. 378).

Interventions to Reduce Stigma

While a large literature on the nature of stigma exists, research on how to change stigma or how to help people with stigma is much more limited [11]. Interventions can target either public or self-stigma and can vary from large-scale interventions targeting the general public to focused interventions targeting high risk or identified target populations.

Reducing Public Stigma

A number of kinds of interventions for reducing stigma in the general public have been proposed and researched. Corrigan et al. [17] proposed three strategies derived from social psychology theory for changing public mental illness stigma that could also be applied to substance abuse stigma: education, contact, and protest. Each of these approaches is reviewed below.

Educational approaches aim to provide new information about a stigmatized group and dispel negative stereotypes. Nearly all the research on education as a stigma reduction method involves mental illness rather than substance abuse

stigma. Cross-sectional research has shown that those who are more knowledgeable about mental illness are less likely to exhibit stigmatizing attitudes [68, 69]. Whether this indicates that people who are less stigmatizing are more open to learning about mental illness, or whether education reduced stigma is unclear. A number of studies have shown short-term improvements in attitudes toward stigmatized groups as a result of educational interventions [17, 19, 58, 92, 96], though results are sometimes inconsistent [52], and studies have generally lacked follow-up assessments. One study that did have a follow-up showed that initial positive results were not maintained [19]. Haghighat [39] has suggested that these positive results might be a product of social desirability rather than true attitude changes. Other data suggest that education may serve to increase positive attitudes among those who already exhibit positive attitudes but may not impact those with negative attitudes or may even reinforce preexisting negative biases [7].

Recently, researchers have also begun to pay attention to the content of educational interventions for stigma reduction, especially the effects of characterizing psychiatric symptoms as caused by psychosocial events versus a disease of the brain with biological, genetic, or structural abnormalities. In general, data are not very supportive for the effectiveness of a biological/genetic message as a method for reducing stigma, and some data suggest that it may actually increase stigma. The one exception is that a biological/genetic message has sometimes been shown to reduce blame toward those with mental illness for causing their own problems, which was found in two studies [67, 87] but not in a third [102]. One of these same studies showed that while a disease explanation reduced blame, it actually provoked *harsher* behavior toward a person described as mentally ill versus a psychosocial explanation [87]. Another experimental study showed that a biological explanation resulted in a less hopeful expectation of improvement [67]. Extensive correlational research shows that genetic or biological explanations for mental illness and diagnostic labeling are related to greater perceptions of dangerousness, desire for distance, and prediction of poor prognosis [102, 106, 107]. For example, surveys in the United States from 1950 and 1996 showed both an increased likelihood to view mental illness as having a biological cause and also to believe that those with mental illness are dangerous [103]. In contrast, data are more reliably supportive of interventions presenting psychiatric symptoms as understandable reactions to life events (i.e., psychosocial explanations). Psychosocial explanations of mental illness have also been related to more positive attitudes toward mental illness in correlational studies [107]. Interventions promoting a psychosocial explanation have resulted in a reduction in fear of dangerousness, desire for social distance, and other negative attitudes [67, 82, 91, 92], though the impact has sometimes been found to vary by target group [67], and these results have not been assessed for their long-term effects. In sum, while a small sample of data suggests that a brain disease message may reduce blame, the preponderance of existing data supports the idea that describing mental illness as a brain disease is not likely to improve stigma on a broad scale and may even lead to increased stigma of some kinds. At the current time, promoting a brain disease message as a stigma reduction method could not be considered an evidence-based practice, while promoting psychosocial explanations for mental illness appears to be promising, at least in these preliminary studies.

While the data indicate that educational interventions based on efforts to characterize mental illness as a brain disease are not likely to reduce stigma, these results do not mean that more complex and nuanced approaches to stigma education that emphasize both biological and psychosocial causes, such as diathesis-stress models, might not be effective. In addition, it remains unknown whether current findings will reliably generalize to the stigma of addiction. It may also be the case that there has been an overemphasis on educational approaches predicated on the idea of information provision as a primary method for stigma reduction and that information provision is simply not a very effective way to change

entrenched attitudes. Other types of interventions based on models other than information provision may be more effective in reducing stigma. Some of these models are explored in more detail below.

The second category of interventions, protest, involves attempting to suppress negative attitudes and representations of a stigmatized group through disputing the morality of holding and expressing such views or through threatening a boycott of a company's products. Research on thought suppression suggests that attempting to suppress or avoid unwanted thoughts can result in paradoxical increases in those very thoughts [140]. People who are asked to suppress thoughts about stereotyped groups can actually become more sensitized to them, resulting in unwanted intrusions of thoughts about that group and more behavioral avoidance of the stigmatized group [79]. Creating conditions that demand correct behaviors (e.g., "do not stare at the physically disabled") can also increase the physical avoidance of stigmatized persons [65]. As suggested by this basic research, most studies of protest strategies targeting attitude and behavior change in individuals have shown it to be inert [17]. In contrast, some anecdotal reports of the use of protest strategies, such as letter writing campaigns or product boycotts to get companies to remove or correct stigmatizing portrayals of mentally ill individuals in the media, have reported some success [13]. In sum, systematic confrontation and protest targeting the stigmatizing behavior of individual persons seems to be largely ineffective and may even exacerbate stigma. On the other hand, the effects of targeting corporations or organizations with organized protest campaigns have not been systematically evaluated.

Finally, contact strategies attempt to change attitudes toward stigmatized groups by creating positive social contact between members of the stigmatized group and the public. Research has shown that people who have more contact with mentally ill individuals endorse less stigma [69, 95, 96], though it is unclear whether contact with mentally ill individuals decreases stigma or whether those with lower levels of stigma are more likely to seek contact. Contact as a strategy for reducing prejudice has long been known to be successful in research on racial prejudice [101]. Interventions based on contact have been the most consistently successful at reducing negative attitudes toward the mentally ill [17, 19], generating at least some maintenance of attitude change over time and impact on related overt behavior. The limits and exportability of this approach are still somewhat unknown as past research has shown that there are a number of situational constraints that can make this approach difficult to implement in real world settings [14]. Specifically, as this approach does not appear to have been tested in stigma reduction with those with substance abuse or in recovery, its putative efficacy in that area remains hypothetical.

The lack of research on stigma reduction strategies in addiction may have to do with conflicting societal views about the usefulness and moral correctness of stigma toward substance use and substance users. In contrast with mental illness where few would argue in support of stigma, there are vocal proponents of actively stigmatizing drug use and drug users [116]. Some large-scale drug prevention programs, such as the Montana Meth Project, which uses advertisements featuring dramatic and often violent depictions of problem drug use, appear actively designed to stigmatize drug users. The Montana program appears to be focused largely on preventing initial drug use and some evidence suggests that this program may be effective in that aim [57]. However, as is common in the criminal justice literature, the potential impact of this campaign on those who are currently using illicit drugs or attempting to recover appears unexamined. Thus, while these types of approaches may reduce initial drug use through increasing stigma, they may have the unintended effect of compounding stigma toward and among those who do become addicted, though further research is needed to examine this question. Thus, the overall public health impact of campaigns such as the Montana Meth Project may be negative, despite the possible reduction in rates of initial drug use that may result from these stigmatization-focused programs.

Reducing Stigma in the Health Care System

Since stigma appears to increase after the person has entered the treatment system and has been labeled as a substance abuser, then it would make sense that interventions targeting the health care system and the process of entry into treatment might be particularly important in reducing the impact of stigma on those attempting to recover from drug addiction. Thus, interventions targeting the prevalent stigmatizing attitudes and behaviors of health care providers and professional staff or focusing on changing organizational structures or admissions procedures might have promise in improving treatment engagement or retention. In targeting stigma in addictions specialty providers, programs designed to provide direct education about stigmatized groups or to promote contact with those in the stigmatized group do not seem very relevant since addictions professionals already know vastly more about these topics than do average persons and have also had a great deal of contact. As protest has not shown much promise, other interventions are needed.

One alternative intervention that has been studied is the use of mindfulness, acceptance, and values processes derived from Acceptance and Commitment Therapy [42]. Acceptance and Commitment Therapy as applied to stigma in addictions professionals focuses on promoting psychological acceptance of difficult thoughts and feelings that come with working with difficult clients (i.e., those most likely to be stigmatized), reducing the behavior regulating impact of the literal content of stigmatizing and evaluative thoughts (e.g., "This client is hopeless"), and helping clinicians to contact the values they bring to their work so that these values can better guide their behavior. In one pilot study of this approach [42], 90 licensed or certified alcohol and drug abuse counselors were randomly assigned to 1-day workshops based on Acceptance and Commitment Training ($N = 30$), Multicultural Training ($N = 30$), or a control lecture about methamphetamine and MDA interventions. Stigmatizing attitudes were reduced post-training in both active treatment groups, but only the Acceptance and Commitment Therapy condition generated lower stigmatizing attitudes at the 3-month follow-up. An additional benefit of the Acceptance and Commitment Therapy intervention is that it decreased burnout at the 3-month follow-up, suggesting that interventions targeting stigma in providers may also have the effect of reducing burnout.

Organizational interventions might also be useful in identifying and remediating stigmatizing policies and procedures. For example, an admission process walk-through [33] might be used to examine whether stigmatizing messages or behaviors occur during initial treatment engagement. These stigmatizing messages might range from the more overt (e.g., telling a client they are hopeless) to more subtle (e.g., therapists telling jokes about "addicts"). Admission walk-throughs could identify stigmatizing interactions that happen during potential client's first contacts with the treatment system and options for remediating these problematic interactions. The overall goal of a walk-through exercise is to identify problematic processes and improve service delivery by allowing providers and those in charge of the system of care to understand what it is like to enter the treatment system [33]. Other organizational and quality improvement interventions might also be adapted to target organizational change relating to stigma.

Empowering Those in Recovery

Another way to help participants in the addictions treatment system is to empower them to overcome the negative evaluative thoughts, shame, and fear of enacted stigma that are part of self-stigma. For substance abuse related stigma, an uncontrolled pilot study targeting self-stigma with Acceptance and Commitment Therapy [78] showed promising outcomes with medium to large effects across a number of variables at

post-treatment. However, the intervention was delivered along with concurrent treatment, making it difficult to rule out the possibility the observed effects were not simply the result of concurrent treatment. Other studies that have examined interventions for self-stigma in mental illness might provide some guidance for developing interventions for self-stigma in addiction.

One aspect of self-stigma is the way that fear of enacted stigma can impede recovery. One study tested an intervention that consisted of education about stigma, discussion of methods to combat and cope with stigma, and discussion about personal experiences of stigma that focused more on coping with enacted stigma than on other aspects of self-stigma. In this study, rehabilitation clubhouse members ($N = 88$) were randomly assigned to either 16 group sessions of the stigma intervention or no treatment. At a 6-month follow-up the intervention group was not significantly different from controls on any measure.

Knight et al. [63] compared a six-session group intervention based on cognitive behavioral therapy to a waitlist. The cognitive behavioral therapy intervention was developed primarily from existing manuals on the group treatment of auditory hallucinations and the group treatment of poor self-esteem. At post-treatment, effects were seen for measures of psychopathology and self-esteem, with these effects mostly maintained through follow-up. However, no effects were seen on stigma coping or empowerment measures, making it less clear whether the effects were more general therapeutic effects or had any specific impact on self-stigma.

Another group intervention for mental illness examined the impact of a 12-session group intervention (1.5 h per group) that focused on helping individuals with first-episode psychosis to maintain an identity distinct from mental illness, promote hopefulness, minimize the impact of stigma, and help them to embrace a healthy sense of self [84]. Results of this randomized trial, comparing treatment as usual to treatment as usual plus the stigma intervention, showed that at post-treatment, the group that received the experimental intervention had improved scores on a measure of self-stigma, hopefulness, and quality of life, but not on several other scales [85]. A previous pilot study of the same intervention also showed an impact on a measure of self-stigma that the investigators termed engulfment, which refers to the tendency to allow illness and its associated stigma to entirely define the self-concept [84].

In summary, there exist a number of promising interventions for self-stigma, with some mixed findings regarding the specificity of their effects. Now that some interventions have begun to show promising effects on stigma and related variables, future research needs to focus more on testing of specific models of change.

Stigma and the Emotion of Shame

Both of the definitions of stigma and most of the research on stigma ignore the emotional responses that are entailed in this phenomenon [76] such as guilt, disgust, anger, and, most prominently, shame. Recently, several prominent stigma researchers called for more research into the relationship between stigma and shame [113]. Much of what has been described as characteristic of the personal experience of being stigmatized has also been described in the literature on the emotion of shame. For example, shame has been defined as an experience of "self as flawed and undesirable in the eyes of others" [37, 133], which is similar to Goffman's [38], idea of stigma as an "attribute that is deeply discrediting" that reduces a person "from a whole and usual person to a tainted, discounted one" (p. 3). Shame is often elicited in social contexts and is associated with thoughts that one is seen as inferior or that others are condemning the self [37]. Similarly, in self-stigma people are fearful of being condemned, stigmatized, or judged by others because of their member in the stigmatized group. Shame is also associated with cultural values, meaning that what is shameful varies according to the standards and ideals of a particular culture [66] as is what is stigmatized varies across cultures.

Shame has been called a "moral emotion" [132], in that it is seen as relating to transgressions of the norms and values of a society. While most authors agree that shame is a highly socially based emotion, substantial disagreement exists as to the usefulness of shame in regulating human behavior. Some authors see shame as a largely maladaptive, negative emotion, with little useful function [133]. Following similar reasoning, some therapy developers have suggested that shame should be directly targeted using shame reduction strategies [25, 142]. Other authors have suggested that shame may serve a valuable function in regulating people's behavior through limiting deviations from accepted norms [28]. As shame can also arise when people violate their own standards and values, shame may have a role in alerting people to important deviations from their own values or self-standards [83] so that they can self-correct their behavior. Seen through this lens, attempts to directly reduce shame during treatment may actually feed the addictive cycle [77] by allowing people to continue deviant behavior or violate self-standards and values [36] without feeling the shame that would ordinarily attend those actions. At least one study [78] specifically targeted the experience of shame in addiction and showed that it could be reduced through treatment. However, in this study, while shame was reduced at post-treatment, the target of the intervention was not the reduction of shame, but rather increasing acceptance of the feeling of shame and mindfulness of stigmatizing thoughts and evaluations. Thus, it may not be as helpful to try to reduce shame directly, but rather to help people change their psychological relationship to shame, so that they are more mindful and accepting of the experience.

As discussed above in reference to stigma, the context in which shame is experienced is probably extremely important in understanding its function and usefulness. In some contexts, shame may be an adaptive, though painful, emotion that highlights deviations from important values or self-standards, whereas in other contexts, shame may simply be excessive and serve no useful function. The debate over whether shame is a maladaptive or adaptive emotion will likely be resolved when more attention is paid to the specific social and psychological contexts in which shame is experienced and how people cope with and respond to shame.

Conclusions

Stigma operates at many levels. Self-stigma works within the individual to impede recovery. Structural stigma operates through the formal and informal policies and procedures of the health care and legal systems. Enacted stigma is expressed in the negative attitudes and behavior of the public. Courtesy stigma extends the impact of stigma to families and to addictions treatment professionals who are paid more poorly than those in other health care fields [51]. Furthermore, the stigma of substance abuse falls disproportionately on those who already experience greater societal injustice, such as racial and sexual minorities and those living in poverty, and who, as a result, have been denied many life opportunities. Stigma is such a broad, pervasive process that it is difficult to characterize its full impact, with any one study only able to document a small portion of its effects. Only by taking an expansive view and appreciating the effects of stigma across many contexts can we begin to see the tremendous cost of this process to the people struggling with drug and alcohol addiction and to society in general.

A broad and pervasive problem like stigma merits a comprehensive and systematic solution. Currently, research and theorizing about the impact of stigma in addiction is in its infancy. We know even less about how to reduce the burden of stigma on those who are attempting to recover from a life damaged by addiction. Anyone who has ever worked with addiction has seen its devastating effects on the lives of individuals and the immense struggle involved in living even a single day clean and sober. People attempting to climb the mountain of recovery do not need the additional burden of stigma, as their road is hard enough.

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Religiousness, Spirituality, and Addiction: An Evidence-Based Review

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Contents

Introduction

The 12-step model to the treatment of addiction is the most popular therapeutic model in the United States, and most adherents of the 12-step approach consider spiritual growth singular with recovery. This chapter offers a critical review and discussion of spirituality and religiousness as it has been investigated in the empirical literature on addiction. Curiously, while the 12-step model has been reported to produce relatively equivalent outcomes as more research-based therapies, e.g., cognitive behavioral and motivational enhancement therapies [43, 51], and actually a superior outcome when the treatment goal is total abstinence, the underlying *stated* mechanism of this approach, spirituality, has only begun to be systematically investigated using rigorous methodologies including randomized clinical trials. It is important to acknowledge that non-12 step spiritual and religious approaches also intended to mobilize and sustain addictive behavior change have proliferated in the United States, *regardless* of the presence or absence of empirical support. A cursory Internet search using "alcoholism" and "spirituality" as key words, for example, yielded 944,000 hits. It seems the absence of empirical support for the efficacy of spirituality in reducing substance abuse has hardly impeded its application. Further, referral to Alcoholics Anonymous during and after treatment is the norm in the United States, also regardless of therapeutic orientation of the treatment provider. In this light, the practical issue is not if treatment seeking alcoholics ought to be introduced to spiritual models of recovery. Rather, it is vital that researchers and clinicians have a working knowledge of spiritual approaches to addiction in order to better understand the psychological and

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_60,

social forces and resources facing prospective clients.

This chapter is organized into three sections. Historical reticence to investigate spirituality and religiosity by addiction researchers stems, in part, from the constructs poorly understood dimensions [20]. The first section of this chapter will therefore offer several working definitions of religiosity and spirituality. These definitions are intimately tied to distinct conceptual models pertaining to the role of spirituality in addiction. These models will be presented and discussed and some attention will then be given to four psychometrically validated measures that are available to clinicians and researchers. The second section of the chapter will advance the orientation that spirituality can be viewed as an outcome, a catalyst or intervention, a moderator, and as a mediational variable; in fact, the construct has been treated in each of these capacities in the empirical literature. A keen awareness of these distinctions is paramount to grasping the implications and avoiding the many pitfalls surrounding the study of alcoholism and spirituality. Third, this chapter will focus on what is currently known about Alcoholics Anonymous-related benefit, the largest and most studied of spiritual interventions. Here, special attention will be given to what is known about the importance of prescribed Alcoholics Anonymous spiritual practices in accounting for reduced drinking. The chapter will conclude with a brief summary.

Several caveats need to be voiced at the beginning of this chapter**.** First, the accelerating nature of empirical research in this area necessarily will result in a somewhat incomplete review. Studies now underway may offer findings that elaborate upon, clarify, or even contradict positions and interpretations offered in this chapter. Related, studies reviewed in this chapter were purposively selected based upon their scientific rigor, not because of the claims and interpretations made by study investigators. In essence, cross-sectional studies purporting to investigate causal temporal relationships were rarely selected for review. Third, it is important to stress the plasticity of spiritual and religious practices and beliefs. An individual rarely is "spiritual" in all situations with all people, nor does evidence indicate that the nature and expression of spirituality remains fixed over time. While this plasticity is obvious and volumes have been written about it, there is a tendency nevertheless to reify spirituality as a trait construct. It is wise to remember that even prophets question, at one time or another, the depth and value of their spiritual and religious beliefs. It is also instructive to remember throughout this chapter that the measurement of this fluid and evolving construct occurred, in general, in research settings. The extent that this context influenced that measurement of spiritual beliefs and practices is unclear but certainly raises concern. Related, the very subjective nature of spiritual and religious beliefs and practices and experiences requires, at this juncture in time and technology, self-report. Legions of studies have investigated the unintended and undetected biases that arise in relation self-report on subjective states. Beyond the scope of this chapter, we recommend that readers consult one of several excellent discussions on the reliability and validity of self-report in the areas of spirituality and religiosity [20].

Section I

Definitions of Religiosity and Spirituality

> Now the whole earth had one language and a common speech. . .let us go down and confuse their language so they will not understand each other. . .That is why it was called Babel—because there the Lord confused the language of the whole world. Genesis 11

The struggle of defining spirituality and religiosity makes it clear how far we've come from a universally understood language. Researchers and practitioners posit opinions on how to define these constructs; the diversity in meanings clearly echoes the confusion, disagreement and lack of productivity described in the book

of Genesis. Zinnbauer and Pargament [64] have aptly called these terms the "definitional tower of Babel." As Zinnbauer and Pargament wrote regarding those in the field who study spirituality and religion, "[We] can agree on one thing: we have never agreed about anything" ([64], p. 4). There is little disagreement that spirituality and religion are constructs deserving of research and clinical attention, but since an important first step in researching a construct is how to operationalize and measure the construct, we begin in a tumultuous place.

Definitions of religion, and particularly spirituality, have changed and evolved over the years. Once representing a single construct, these constructs are now distinct [37] and some would say even incompatible. Spirituality is increasingly defined in contrast to religion rather than as interchangeable terms [64]. The definitions are marked by explicit and implicit philosophical and theological underpinnings, and thus remain vulnerable to claims that the definitions are either too broad or too narrow. Koenig [27] described religion as an expression that is institutional, formal, outward, doctrinal, authoritarian and inhibiting, and spirituality as an expression that is individual, subjective, emotional, inward, unsystematic and freeing. Pargament [46] reported that religion is moving "from a broadband construct—one that includes both the institutional and the individual, and the good and the bad—to a narrowband institutional construct that restricts and inhibits human potential." (p. 3). Apparent in the polarization of these two constructs is an underlying message is an exaltation of spirituality and a condemnation of religion.

It is common for scholars to begin manuscripts with caveats of the difficulty in defining these terms, discuss the divergent definitions, and then provide an entirely new definition all together. Other researchers approach the complexity by simply avoiding a definition; instead asking questions such as "do you consider yourself spiritual?" or "how important is religion in your life?" [35] While results from questions such as these contribute to our understanding of the perceived importance of religiosity and spirituality and other variables, this approach is limited in terms of not furthering our understanding of how these terms are uniquely understood and defined by participants.

It is evident that defining these constructs is difficult; however, research evidence supports the usefulness of this pursuit because of the clear connection between spirituality and religion and mental health [31]. In a recent review [30] of longitudinal studies, increased spirituality and religion seem to consistently promote a longer, happier life. For individuals suffering with mental or physical health problems, spirituality and religion enhance pain management, improve surgical outcomes, protect against depression, and provide coping resources, and reduce the risk of suicide. While religion and spirituality are relevant to many problems dealt with by practitioners and there is a consistent link between spirituality/religiousness and physical and psychological well-being, in few areas of mental health are these issues as central as addictive behaviors.

The Relationship Between Religiosity/Spirituality and Addiction

In some sense, addiction represents the antithesis of spirituality. For example, one of the four noble truths of Buddhism is "Suffering is caused by attachment," and a central focus for followers of this tradition is to relinquish craving and clinging to things. Yet the centrality of attachment is readily apparent in the diagnosis of substance use disorders—part of the criteria for a substance use diagnosis is that a great deal of time is spent in activities necessary to obtain the substance [2]. May describes the spiritual nature of addiction as "a deep-seated form of idolatry. The objects of our addictions become our false gods. These are what we worship, what we attend to, where we give our time and energy" [33]. Attachment to a substance is a futile attempt to impose direction in one's life, a direction that displaces one's prior values, meaning structures, and goals. Instead,

individuals become concerned with purposeful action toward their next drink or their next high. In Tillich's [54] terminology, the substance becomes the individual's ultimate concern.

Spirituality is also central to the most influential model of recovery in the United States. The recovery program of Alcoholics Anonymous views addiction as a fundamentally spiritual problem and has promoted spirituality and religion as a central factor to recovery since 1935 [59]. In the words of Bill W., the co-founder of Alcoholics Anonymous, those with substance abuse problems "have been not only mentally and physically ill, [they] have been spiritually sick" ([1], p. 34). The program of recovery is therefore based upon a model of prescribed spiritual practices.

In addition to the spiritual program of Alcoholics Anonymous and other 12-step programs, the literature is also quite clear that religious involvement is predictive of lower current and future rates of problem drinking. For instance, over 80% of the nearly 100 studies on alcohol and religion reviewed by Koenig et al. [27] reported a negative association between religiosity and problems with alcohol. It seems that those who are more active in a religion and for whom faith occupies a central place in their lives are less likely to develop dependence on a drug. Similarly, those entering treatment for alcohol/drug problems tend to have very low religious involvement, and are often quite alienated from organized religion.

Religiosity/Spirituality and Addiction Research: An Overview

In a review of the literature on spirituality and addiction, Cook [8] examined 265 publications in order to identify the definition of spirituality by different authors. Cook found that only 12% of the papers explicitly defined the term "spirituality", 32% offered a description of the concept of spirituality, 12% defined a related concept (such as "the spiritually healthy person"), and in 44% of the papers the term "spirituality" was left undefined. Breaking the conceptual content of the definitions into component parts, Cook classified the content of the various definitions into thirteen conceptual components. Cook found that the four components that were encountered most frequently and were most central to the definition of spirituality were transcendence, relatedness, core/force/soul, and meaning/purpose. On the basis of these components, Cook proposed the following definition:

> Spirituality is a distinctive, potentially creative and universal dimension of human experience arising both within the inner subjective awareness of individuals and within communities, social groups, and traditions. It may be experienced as relationship with that which is intimately 'inner', immanent and personal, within the self and others, and/or as relationship with that which is wholly 'other', transcendent and beyond the self. It is experienced as being of fundamental or ultimate importance and is thus concerned with matters of meaning and purpose in life, truth and values. ([8], pp. 548–549)

One particular conundrum, evident in Cook's [8] definition and many other definitions of spirituality, is that scholars have now begun to include aspects of mental health within the definition [26, 20]. If terms such as well-being and connectedness with others are considered part of the definition of spirituality, there is an inherent measurement problem when examining spirituality and religiousness in relation to positive mental health functioning. As Koenig [26] stated, "Defining spirituality in this way assures that those who are "spiritual" will be mentally healthy, and excludes those who are mentally ill from this desirable classification" (p. 351). In addition to this classification problem, there is also a concern in terms of measurement of treatment outcome. If a client shows improvement in mental health, we encounter the dilemma of whether this improvement is due to an increase in spirituality or religion or whether we are simply measuring improvement in quality of life.

Koenig's [26] concern is particularly relevant to how researchers understand addiction. Addiction involves a setting apart from one's self, others and the world—a direct opposition to spirituality's emphasis of oneness with all of humanity. There is therefore a clear confound as individuals with substance use problems begin

to succeed in recovery—they begin to reconnect with humanity and realign their values and goals. The use of substances offers a way to "avoid being present to oneself" ([33], p. 44). It is common for individuals with substance use problems to report that they feel disconnected from others, and as attachment to the substance increases there is a tendency to isolate from important relationships. In Alcoholics Anonymous, a common term is "terminal uniqueness," describing a feeling the feeling of the alcoholic who feels an extreme uniqueness and alienation from his or her peers. Conversely, during recovery from substances, there is a tendency for individuals to attach to a Higher Power and reaffirm important relationships.

Readers interested in further exploring the definitions and distinctions of spirituality/religiousness are encouraged to access Geppert et al. [16]. These authors have compiled a priceless annotated bibliography of 1,353 scholarly papers on spirituality/religiousness and addictions that are divided into 10 categories ranging from the measurement of spirituality with attitudes about spirituality and substance use.

Conceptual Models of Spirituality and Religiousness in Addiction Research and Four Religiosity/Spirituality Measures

While there are diverse definitions and applications of spirituality/religiousness topics in addiction research, two conceptual models serve as a framework for a majority of these endeavors. On one hand, the deficit model of spirituality/religiousness and addictions assumes that the process of deepening addiction involves the loss of spiritual/religious values, beliefs, and practices. Recovery, then, necessarily involves the acquisition or re-establishment of these values and beliefs. Here, the seeking of spiritual/religious values, practices and beliefs fills an existential void created by years of substance abuse. Tacit to this model is the assumption that the quest or search for spiritual/religious meaning is innate. The second model, the coping model of spirituality/religiousness and addiction, makes few, if any, assumptions about the etiology of substance abuse and dependency. Instead, this model focuses on the potentially buffering properties of spiritual/religious practices and beliefs in avoiding relapse. Specifically, spiritual/religious practices and beliefs are interpreted to severe the linkage between aroused negative emotional states and subsequent substance use and abuse. In this regard, the coping model has explicit connections to two popular cognitive behaviorally based strategies in the treatment of addiction, relapse prevention [32] and cognitive behavioral therapy [21]. Less obvious is the theoretical relationship between the coping and protective factor models in addiction research. One of the most consistent and enduring findings in spirituality/religiousness addiction research is the inverse relationship reported between spiritual/religious beliefs and practices and the *development* of substance abuse [16]. Essentially, spiritual/religious practices are interpreted to buffer or attenuate processes that promote substance abuse. Processes within the coping model operate in a similar fashion, but with the key difference that spiritual/religious practices now buffer against the re-establishment of addictive behaviors.

Knowledge of these two spirituality/religiousness models offers at least two benefits. First, understanding these two models provides a conceptual framework to judge, classify, and select from the plethora of spirituality/religiousness measures available to addiction researchers and clinicians. Too often, authors of spirituality/religiousness measures do not explicitly identify the conceptual basis of their respective tool. As such, spirituality/religiousness measures are frequently misused or they fail to provide a sensitive assessment of the process under investigation. Conceptual models offer clear predictions about causal relationships, and knowledge of the different predictions of these two models offers an important second benefit. Most striking, the deficit model ultimately predicts that the failure to enlarge upon spiritual/religious practices and beliefs will result, in the long run, in relapse to substances. Some of the most explicit examples of this model and its prediction on relapse

can be found in the core Alcoholics Anonymous literature [1]. The coping model of spirituality/religiousness and addictions does not lead to such a categorical prediction. Instead, failures to develop and apply spiritual/religious behaviors and beliefs may result in a continuum of adverse consequences given the absence of the presumed positive buffering effect, but alternative resources at multiple levels may offset the absence of spiritual/religious practices, e.g., social networks supportive of abstinence. With this background it is instructive to briefly review four spirituality/religiousness measures that have demonstrated psychometric properties and that are frequently encountered in the addiction literature.

Religious Beliefs and Behaviors [6] is a 13-item self-report measure with demonstrated psychometric properties. The tool yields two scales: Formal practices and God consciousness. Items in the God consciousness scale inquire about the frequency of prayer, meditation, and thoughts about God while items in the Formal practices scale inquire about attendance at worship service and reading of scriptures or holy writings. Strengths of the Religious Beliefs and Behaviors measure include fast administration, normative data are available based upon an alcohol treatment seeking sample ($N = 1{,}637$), and the Religious Beliefs and Behaviors measure has documented sensitivity to discriminate three groups of Alcoholics Anonymous-exposed adults over time in predictable directions, e.g., gains in God consciousness and Formal practices increased at a faster rate over time among adults with more Alcoholics Anonymous exposure. Religious Beliefs and Behaviors does, however, have limitations. Noted by Johnson and Robinson [20], one cannot determine from the Religious Beliefs and Behaviors measure if the behaviors of prayer and meditation occur independently of Formal practices, and findings are mixed about the ability of the Religious Beliefs and Behaviors scales to predict positive outcome [7, 24, 53]. The Religious Beliefs and Behaviors measure is not copyrighted and can be used free of charge.

The Brief Multidimensional Measure of Religiousness/Spirituality [12] is a 38-item self-report questionnaire that has 10 scales: Daily spiritual practices (6 items), Values/Beliefs (2 items), Forgiveness (3 items), Private Religious practices (5 items), Religious and Spiritual Coping (7 items), Religious Support (4 items), Religious/Spiritual History (3 items), Organizational Religiousness (2 items), Religious Preference (1 item), and Overall self-Ranking (2 items). The Brief Multidimensional Measure of Religiousness/Spirituality was a collaborative effort between the Fetzer Institute and the National Institutes of Health to construct a multifaceted measure of spirituality/religiousness that explicitly decoupled private and public spiritual/religious behaviors and practices. Widely recognized scholars developed spirituality/religiousness scales independently, often by reducing parent instruments into a brief scale. In addition to strong psychometric properties and partial normative data, the Brief Multidimensional Measure of Religiousness/Spirituality is especially useful because the manual provides the rationale, application, and psychometric citations for each scale. Based upon a treatment-seeking adult sample ($N = 123$), half of the scales showed significant increases over a 6-month period, and the Daily Experience scale was prognostic of reductions in heavy drinking even after controlling for a number of rival explanations, e.g., Alcoholics Anonymous involvement and gender [53].

The Spiritual Coping Questionnaire [47] is a 22-item questionnaire that measures perceived relationship to God, with the basic premise that different kinds of God relationships imply different coping mechanisms. Three relationship-coping scales have been empirically validated with Alcoholics Anonymous-exposed persons and are labeled: Cooperative ($\alpha = 0.93$), Deferring ($\alpha = 0.89$), and Self-directing ($\alpha = 0.91$) God relationships. Items pertaining to the cooperative God relationship stress mutual exchange between a deity and individual in making choices and decisions while the deferring style is characterized by items that endorse the release of all responsibility for decisions to a deity. Finally, the self-directed style characterizes individuals who

assume all responsibility for choices and who do not seek spiritual guidance. Spiritual Coping Questionnaire scales have been attractive to 12-step researchers because of the hypothesized developmental changes in spirituality that occur among Alcoholics Anonymous members as they work through the 12 steps. Specifically, steps 1-3 have been interpreted as reflecting a deferring relationship with a Higher Power, while later steps encourage a cooperative deity relationship, e.g., steps 11 and 12. To date, temporal changes in coping styles have been documented among 12-step members [53], but the nature and pattern of these changes appear to be more complex than originally thought. In particular, longevity and participation in Alcoholics Anonymous appear to be related with shifting preferences in spiritual coping style, but actual step work was not 19].

Purpose in Life [9] is a 20-item self-report questionnaire that uses a 7-point Likert scale (anchors: Never and Constantly). Used in a number of alcohol studies [4, 50, 51], the Purpose in Life is used to assess the extent that one experiences life meaning. Lower scores on the Purpose in Life reflect a relative lack of current life meaning. Little support has been found for this construct predicting later substance use among outpatient and aftercare adult alcoholics [57], and the item content measuring life meaning itself has been criticized [20]. Specifically, the Purpose in Life along with other measures of life meaning are correlated with measures of well-being and, equally important, it is problematic to determine whether experienced life meaning is the result of spiritual/religious behaviors or practices or not.

Section II

Empirical Religiosity/Spirituality Questions in Addiction Research

There are four types of research questions that can be asked about spirituality using prospective longitudinal studies. Heuristically, these questions are: (1) what *direct* effect does spirituality, or changes in spirituality, have on drinking? (Intervention question), (2) what *changes* in spirituality occur as a result of trying to mobilize and sustain addictive behavior change? (Dependent measure question), (3) How may spiritual/religious practices and beliefs *attenuate* or enhance receptivity to treatment, aftercare, or Alcoholics Anonymous (moderation question), and, most complex, (4) how may spirituality, or changes in spirituality, statistically *explain* the direct relationship between a cause (e.g., prayer) and a desired effect (e.g., abstinence) (mediation question). This latter question, first formally described by Baron and Kenny [3], entails four subquestions that focus on the temporal and causal relationships between, at a minimum, three measured variables. Figure 1 highlights, with a hypothetical example pertaining to spirituality and addiction, both the ideal temporal relationship between measures and the nature of questions that must be affirmed to declare that a measure, here spirituality, explains or accounts for, an observed and desired effect. For the interested reader, a detailed collection of papers specific to mediation and alcoholism can be found in Huebner and Tonigan [19].

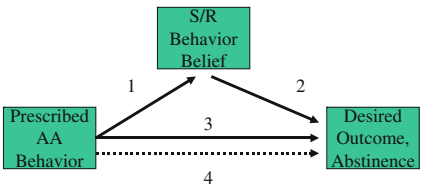

Fig. 1 Four conditions to establish statistical mediation in identifying spiritual or religious actions. AA = Alcoholics Anonymous; S/R = spiritual/religious. Condition 1: Active ingredient, prescribed AA behavior, mobilizes S/R practice or belief; Condition 2: S/R practice effects desired outcome, increased abstinence; Condition 3: Active ingredient, prescribed AA behavior, effects desired outcome; Condition 4: Strength of pathway from prescribed AA behavior and desired outcome is significantly reduced (eliminated) when statistically controlling for S/R practice or belief

Spirituality as an Intervention and Outcome

Investigations of spirituality/religiousness have used both cross-sectional and prospective longitudinal designs to address these empirical questions, with cross-sectional investigators frequently making the case that study findings offer insight into casual relationships. Although one-shot studies do offer some important perspectives on the correlational structure of domains of interest, a number of factors limit their value in understanding causality, not the least of which is the self-selected (and often) biased samples upon which study findings are based. As an example, Poage et al. [49] conducted a cross-sectional study of 53 Alcoholics Anonymous-exposed adults. From this volunteer convenience sample, the investigators asked if length of sobriety, spirituality, and general life contentment were associated. Consistent with predictions, Alcoholics Anonymous members with more years of sobriety reported significantly higher spirituality than Alcoholics Anonymous members with fewer years of sobriety, and spirituality and contentment were significantly and positively associated. Interestingly, years of sobriety and contentment were not associated. Pointed out by the authors, however, causal linkages between these three constructs remain unclear, at best. Did spiritual growth predict the sustaining of sobriety (or vice versa)? Alternatively, years sober and age were positively related ($r = 54$) in this sample. Did the enhanced spirituality of Alcoholics Anonymous members with more sobriety, then, simply reflect the well-documented phenomenon that as we age we become more open to religious and spiritual explanations for the human experience? While studies such as this certainly have value and should be conducted, they are generally avoided in this review because of the number of rival explanations for study findings.

With the exception of studies specifically focused on Alcoholics Anonymous (reviewed in Section III), there have been surprisingly few longitudinal studies that have investigated how, if at all, spirituality/religiousness-based interventions influence subsequent substance use. For clarity, the studies reviewed in this section are arranged according to the intensity of the spiritual/religious intervention, beginning with the studies that involved minimal or modest intervention efforts. Walker and colleagues [61], for example, sought to determine whether intercessory prayer impacted the drinking of 40 treatment seeking alcoholics. Consenting participants were randomized into treatment as usual, which consisted of individual and group counseling in an outpatient setting, and the other half of the sample was assigned to the intercessory prayer condition. Here, in addition to treatment as usual, volunteers prayed for the well-being and abstinence of individuals in the intercessory prayer group. No mean differences on key measure of drinking were observed between the two groups at the 3- and 6-month follow-ups. Findings suggested that prayer by the substance abuser did predict subsequent reductions in drinking in both groups, but this finding did not consider that prayer is a prescribed Alcoholics Anonymous-related behavior and, as such, this benefit may have reflected the social benefit of Alcoholics Anonymous as much as that of prayer. Counter to investigator predictions, alcoholics who reported that family members or close friends were praying for their welfare and treatment success tended to drink more frequently at follow-up relative to those alcoholics who did not report such prayer efforts by loved ones.

Extending this line of research, Miller et al. [36] tested the efficacy of a trained and monitored spiritual guide on later substance use. Here, the spiritual intervention intentionally went beyond Judeo-Christian beliefs and practices and included such Eastern practices as meditation. In the first of two companion studies, the investigators recruited 60 inpatients from a 30-day program to receive treatment as usual or treatment as usual plus 12 sessions with a spiritual guide. The spiritual intervention consisted of 13 modules that included such topics as prayer and meditation, gratitude, guidance, acceptance, fasting, service to others, and worship. While both intervention groups reported large pre-post gains

in abstinence, no between-group differences in substance use were observed between the treatment as usual and treatment as usual + spiritual guide groups at follow-up. Also contrary to prediction, the group receiving spiritual guidance did not report higher scores on three a priori selected measures of spiritual functioning: daily spiritual experiences (Brief Multidimensional Measure of Religiousness/Spirituality), meaning in life (Purpose in Life questionnaire), and private religious practices (Religious Beliefs and Behaviors). Not addressed in this study was whether the emphasis on 12-step attendance in treatment as usual adversely impacted the discriminability of the two interventions.

A second study at the same facility was done to increase exposure to the spiritual guide intervention. Here, facility counselors delivered the spiritual guide intervention and it was embedded into the treatment as usual program [15]. Employing a cohort design, 40 participants received treatment as usual and the following 40 received a spiritual guide in addition to the treatment as usual. In general, findings paralleled the earlier study: no group differences in substance use at 3- and 6-month follow-ups were found although both groups reported significant reductions across a variety of illicit drug use measures. Unlike the first study, modest between-group differences in daily spiritual experiences were found favoring the spiritual guide group at 4- and 6-month follow-ups, but this differential change in spirituality did not statistically mediate or explain increased abstinence for the spiritual guide group.

Bowen and colleagues [5] have provided tentative support for the effectiveness of Vipassana meditation in reducing substance use among incarcerated adults. While replication via a randomized clinical trial design is highly desirable, this work represents some of the more rigorous study of the effects of spirituality that is not Judeo-Christian in origin. Specifically, they reported that an intensive 10-day Vipassana meditation program housed in a minimum-security prison resulted in significantly lower substance use and alcohol-related consequences relative to self-selected control inmates. Also at 3-month follow-up the inmates who participated in the Vipassana meditation also reported significantly higher optimism scores and lower levels of psychiatric problems relative to controls. The Vipassana meditation protocol consisted of long hours of silence, teaching of Buddhist principles including the Four Noble Truths, and instruction in meditation.

Spiritually Based 12-Step Therapy

Twelve-step treatment is the final spiritual intervention to be addressed in this section. Placement of this intervention in this section, separate from our review on Alcoholics Anonymous, reflects the important albeit frequently forgotten distinction between formal 12-step treatment and community-based 12-step programs [5]. (See Ferri et al. [11] for an example of how confusing the two can lead to erroneous conclusions.) To be sure, both 12-step entities introduce and facilitate progress through the 12 steps of Alcoholics Anonymous and strongly encourage long-term Alcoholics Anonymous meeting attendance. In this regard, both 12-step entities can be regarded as sharing a common spiritual focus, e.g., 11 of the 12 steps makes reference to God or a Higher Power, and spiritual concepts such as acceptance, surrender, meditation, and belief in a Higher Power are the central content of the steps.

It is the *practice* of the prescribed 12-step behaviors that most clearly distinguishes community-based Alcoholics Anonymous and formal treatment, and these differences in practice fundamentally influence both the interpretation and impact of working the 12 steps. Some of the more obvious examples of how the two 12-step entities differ include: Community-based Alcoholics Anonymous encourages sponsorship to aid an Alcoholics Anonymous neonate through the 12 steps while formal 12-step treatment offers no analog to this important sponsor-sponsee relationship. Continuing Alcoholics Anonymous meetings are led by a non-professional member of the group and cross

talk in meetings is strongly discouraged. Just the opposite conditions are found in group-based therapy in formal 12-step treatment, with further distinctions made by the use of evidence-based treatment manuals [42]. And, finally, confrontation to accept the label of alcoholic frequently occurs in 12-step treatment (i.e., denial is a concept developed within the treatment context in response to this practice) while in community-based Alcoholics Anonymous the individuals elects if, when, and how, self-labeling of "alcoholic" is appropriate. Beyond the scope of this discussion, it is also important to note that 12-step treatment shares several features incorporated within cognitive behavioral therapy [34].

With this background, the focus of this section is to review those studies that investigated the independent effect(s) of the spiritual emphasis in formal 12-step treatment. To begin, several studies have investigated the plasticity of "Alcoholics Anonymous-specific" cognitions that are foundational to spirituality as it is expressed in 12-step programs. Morgenstern and Bates [41] for example, reported that cognitive shifts promoted by 12-step therapists at residential and intensive outpatient treatment centers did predict later improvement, e.g., commitment to abstinence, but others did not, e.g., negative expectancies. Interestingly, they also reported that severity of cognitive impairment did not influence or moderate the extent of desired cognitive shifts, yet more impaired individuals did not appear to benefit from such cognitive shifts to the extent of those who were less impaired. Likewise, using a composite measure of 12-step disease model beliefs Finney et al. [13, 14] found modest increases among 970 veterans assigned to 12-step treatment in Alcoholics Anonymous -related cognitions during therapy, but such changes did not explain later abstinence rates. Finney also reported that 12-step therapy led to a significant pre-post gain in the percentage of individuals endorsing an alcoholic identity (7% gain).

Project MATCH was one of the largest and most rigorous prospective studies of the efficacy of 12-step therapy to mobilize spiritual/religious practices and beliefs [50, 51]. At 12-month follow-up, no group differences were found in measures of drinking intensity and frequency of abstinent days between 12-step, cognitive behavioral, and motivational enhancement therapies although 12-step therapy did have a significantly higher rate of total abstinence relative to cognitive behavioral therapy and motivational enhancement therapy at 12 months. Tonigan and Miller [56] sought to identify those aspects in the 12-step facilitation that accounted for the relative parity in increased days abstinence and reductions in drinking intensity. No support was found for 12-step therapist emphasis upon total abstinence as an explanation for the relatively good outcomes in the 12-step condition although these therapist did endorse the goal of abstinence more than cognitive behavioral therapy and motivational enhancement therapists. Likewise, intended cognitive shifts in perceived powerlessness and loss of control over alcohol did occur within the 12-step treatment, but these shifts did not explain drinking outcomes at 12 months. Finally, a primary objective for the 12-step facilitation counselor was the encouragement of client spiritual development. As intended, at the end of 12 weeks of therapy, 12-step facilitation clients reported significantly higher God consciousness scores [6] relative to cognitive behavioral therapy and motivational enhancement therapy clients. Virtually no relationship, however, was found between increased God consciousness at the end of treatment and proximal abstinence 6 months after treatment, days to first drink and heavy drinking day, or 1-year total abstinence. Thus, while 12-step facilitation therapists were effective in evoking increased God awareness, this increase appeared to be unrelated to subsequent increases in abstinence.

Robinson and colleagues [53] have recently reported positive findings between increased spirituality and abstinence among 12-step-treated adults ($N = 123$), and some of the unique features of this study warrant special attention. As background, they recruited 154 adults with alcohol use disorders who were presenting for 12-step outpatient treatment and, following consenting procedures, administered a baseline assessment that included an array

of spirituality/religiousness measures along with semi-structured interviews for measuring alcohol consumption. Eighty percent of the sample was contacted and interviewed 6 months after recruitment and the assessment battery was re-administered. In this naturalistic study significant pre-post gains were reported on 5 of 10 spirituality/religiousness measures, nearly all of which were different than those measures described earlier in this section: Purpose in Life ($d = 0.26$), Positive religious coping ($d = 0.14$), Forgiveness ($d = 0.24$), Daily spiritual experiences ($d = 0.19$), and spiritual/religious practices ($d = 33$). Isolating the effects of spiritual gains in predicting the presence or absence of heavy drinking at 6 months by first controlling for gender, baseline heavy drinking, and pre-post changes in Alcoholics Anonymous involvement, they found that two spirituality/religiousness measures sustained their prognostic value in predicting abstinence, gains in purpose in life and daily spiritual experiences. This set of findings represents one of the rare examples of mediated spirituality/religiousness effects as defined by Baron and Kenny's [3] criteria. Why gains in spirituality/religiousness measures explained reductions in heavy drinking in the Robinson et al. [53] sample but not in previous investigations is unknown. Methodologically, earlier investigations used continuously scaled measures of drinking while the Robinson et al. group employed a dichotomous measure of relapse to heavy drinking over the 6-month period (yes/no). Further, the Robinson et al. team used spirituality/religiousness change scores in spite of voiced concerns that such techniques are prone to regression artifacts. Nevertheless, all investigations approached the topic of study with (1) standard recruitment and design choices, (2) psychometrically sound measures, and (3) achieved good follow-up rates.

In general, then, the weight of evidence suggests that cognitive shifts congruent with Alcoholics Anonymous ideology can be successfully mobilized in 12-step therapy. Demonstrations of such shifts have included beliefs in the disease model, endorsement of the alcoholic identity, commitment to abstinence, and a belief in a Higher Power. Applying a scotch verdict, the relative importance of these shifts is mixed, at best, in accounting for the generally good outcomes associated with 12-step therapy. The question is not decided, however. Work by Robinson et al. offers the possibility that previous studies have employed measures that were insensitive to the processes of interest.

Religiosity/Spirituality as a Moderator in 12-Step Therapy

Propst [52] reported that the effectiveness of cognitive behavioral therapy for depression was significantly enhanced for religiously oriented individuals when spiritual matters were discussed within therapy sessions. Here, a person's spirituality/religiousness orientation moderated the effectiveness of an evidence-based approach. In the treatment of alcoholism and addictions the moderator role of spirituality has not yielded as straightforward findings. At face value, for example, it would seem that spiritually focused treatments, e.g., 12-step program, would be received more favorably and be more effective for like-minded people.

Two investigators have examined this issue within the context of a randomized clinical trial. Connors et al. [7] essentially made this prediction when they argued that self-reported religiosity of an alcoholic would moderate the effectiveness of 12-step outpatient and aftercare therapy [50, 51]. The composite measure of spirituality/religiousness included responses to questions about the practice and frequency of prayer, meditation, and formal practice of religious attendance and reading of Holy Scripture. They predicted that alcoholics higher in endorsement of spirituality/religiousness would be more comfortable with the spiritual aspects of the 12-step therapy. Enhanced comfort with the 12-step model would become manifest in higher treatment retention, stronger therapeutic bond, and greater satisfaction with treatment, each of which is a positive and significant predictor

of increased abstinence after treatment. On the basis of drinking outcome no support for this matching hypothesis was found. Likewise, no support was found that comfortability with spiritual/religious beliefs and practices led to higher 12-step treatment retention, satisfaction, or therapeutic bond relative to individuals lower in spiritual/religious values.

Within the same study, Tonigan and colleagues [58] applied a more general and inclusive definition of spirituality in predicting a differential response to 12-step therapy. In particular, they computed a difference score that represented current perceived meaning in life after subtracting the seeking of life meaning [9]. Unlike the comfortability hypothesis, they reasoned that alcoholics high in meaning seeking (but perhaps not very high on spirituality/religiousness) would find the spiritual focus of the 12-step therapy more engaging and, hence, more effective. Consistent with the work by Connors et al. [7] no support was found for a differential response to 12-step therapy based upon the general measure of clients' meaning seeking when judged by percentage abstinent days or drinking intensity for the 12 months after treatment.

Several naturalistic studies have approached the question of whether client spiritual/religious beliefs and practices moderated treatment effectiveness. Oumilettee et al. [43], for example, made a similar prediction as Connors et al., with the key distinction that sampled alcoholics were veterans, and participants were not randomized to treatments. Here, substance abuse treatment programs were classified according to their dominant therapeutic orientation, i.e., cognitive behavioral, 12-step and milieu therapy, and matching of client characteristics and provider types was self-selective. Using similar spirituality/religiousness measures as Connors, (e.g., Religious Beliefs and Behaviors) [6] they, too, reported that 12-step treatment response was unrelated to baseline spirituality/religiousness status. Finally, Kaskutas et al. [24] investigated the role and influence of spiritual/religious practices and beliefs upon long-term sobriety and Alcoholics Anonymous involvement among 587 men and women presenting for treatment at private and public facilities in California. Although the sampled treatment centers represented a broad spectrum of services and therapeutic orientations nearly all encouraged 12-step attendance and included 12-step induction strategies as part of their services. At 3-yer follow-up no association was found between length of continuous sobriety and spirituality/religiousness endorsement at baseline.

Finally, Kelly et al. [25] conducted a unique single-group longitudinal 3-year study of substance-abusing adults who presented for intensive outpatient treatment (N = 227). Here, individuals were assessed at intake and at 1-, 2-, and 3-year follow-ups. In addition to concluding that mutual-help participation contributed to positive outcomes during the follow-up phase of the study Kelly et al. [25] tested several prospective hypotheses about the role and influence of religious/spiritual variables in recovery.

In sum, findings from both randomized clinical trials and naturalistic studies appear to have arrived at the same conclusion, namely that spiritual/religious practices and beliefs are relatively inert in the context of being offered a spiritually based 12-step program. Contrary to predictions, then, endorsement of spiritual/religious practices and beliefs does not seem to provide an advantage to a substance abuser when they are assigned to 12-step therapy. Conversely, substance abusers that report less interest in spiritual/religious practices and beliefs do not appear to be placed at a disadvantage when assigned to 12-step therapy. It should be stressed that almost all of the studies reviewed in this section relied on self-reported spirituality/religiousness status, generally a single item asking whether one was religious, spiritual, agnostic, or an atheist. Well known, single item responses lack reliability, and it is not clear whether more comprehensive spirituality/religiousness measures collected at the onset of 12-step treatment may offer a different picture than the one presented here. At this time, however, the limited evidence suggests that spiritual/religious beliefs and practices are relatively unimportant when determining whether or not

to assign substance abusers to spiritually based 12-step therapy.

Section III

Religiosity/Spirituality and Community-Based 12-Step Programs

Few topics in addiction research generate as much controversy as the question, does community-based Alcoholics Anonymous work and how, especially as a stand-alone intervention? Well documented, a majority of treatment seeking adolescents and adults in the United States report exposure to community-based 12-step programs prior to entering treatment. Likewise, in a survey of treatment providers, Kelly et al. reported that a majority of treatment providers encourage Alcoholics Anonymous attendance during and after inpatient and outpatient treatment, regardless of provider therapeutic orientation. Further, rates of referral to 12-step programs by treatment providers appear to be similar regardless of the nature of substance use dependency, e.g., alcohol, cocaine, and opioid dependency [62]. Given the widespread acceptance of the 12-step model and approach by the clinical community in the United States, why, then, has there been such reticence, ambivalence and, at times, outright hostility by researchers about community-based Alcoholics Anonymous?

The nexus of the conflict lies in Alcoholics Anonymous' pronouncements that alcoholism is a physical, emotional, and spiritual malady, that total abstinence is necessary for recovery, and that spiritual practices provide the foundation for sustained sobriety [1]. Disagreement, then, about Alcoholics Anonymous is rooted in ideological conflict. Derived from Judeo-Christian doctrines [29], the 12 steps of Alcoholics Anonymous are a concise statement of the prescribed and sequential program for recovery, and the 12 traditions are the blueprint for how the fellowship of Alcoholics Anonymous ought to be conducted. Both sets of prescriptions rest upon spiritual principles, and make frequent reference to the value of prayer and meditation, and the existence of God or a Higher Power. Tonigan and colleagues [60] point to five spiritual axioms in the core Alcoholics Anonymous literature: (1) the existence of a transcendent power, (2) the need to develop a personal relationship with God, (3) a belief in mysticism, (4) daily reaffirmation of a God relationship, and (5) the belief that emotional discord signals a departure from spiritual principles. At face value, the spiritual axioms of Alcoholics Anonymous are innocuous and would likely be accepted—with perhaps minor revision—by most theologians. Likewise, the emphasis in Alcoholics Anonymous upon incorporating these spiritual axioms into daily living is not unique, but the steadfast belief in the necessity of doing so to sustain sobriety is unique to 12-step programs.

Community-Based 12-Step Programs and Abstinence

Four of 5 meta-analyses [10, 15, 28, 60, 58] have concluded that Alcoholics Anonymous participation is predictive of increased abstinence although findings are mixed about improvements in other areas, e.g. psychological functioning. In general, effect size estimates of Alcoholics Anonymous-related benefit range between $d = 0.18$ and $d = 0.33$ which fall into the small to moderate range of "intervention" effect. The difficulty in addressing the question of benefit solely based upon community-based Alcoholics Anonymous is that a vast majority of the literally hundreds of empirical studies on Alcoholics Anonymous have been based upon treatment seeking adult samples [10]. Thus, the impact of treatment often confounds investigations into the unbiased benefit of Alcoholics Anonymous. Traditionally, two strategies have been used in an effort to isolate the influences of Alcoholics Anonymous, one statistical and the second based upon conducting distal follow-ups to minimize the direct and indirect influence of formal treatment, e.g., 5–10 years after treatment. Both strategies have important limitations although

both strategies have, to their credit, employed prospective designs. Statistical approaches to control for confounding treatment and self-selective factors, for example, may fail to adequately model all relevant factors. Alternatively, treatment-seeking substance abusers typically have frequent encounters with treatment over time, and is not clear how effective, if at all, distal follow-ups eliminate the influence of formal treatment on client functioning. Keeping these caveats in mind, these two approaches have tended to yield findings in agreement with those generated through the use of treatment-seeking samples, namely that 12-step participation is helpful in reducing problematic drinking for many alcohol abusers. Interested readers should review Kelly et al. [25], Moos and Moos [40], Connors et al. [7], and Kaskutas et al. [23] for exemplars.

What Spiritual Practices Predict Benefit?

Positive albeit modest associations between Alcoholics Anonymous meeting attendance and abstinence have been reported in most meta-analyses [10, 15, 60], and many investigators have reported that measures of commitment to, and involvement in, prescribed Alcoholics Anonymous behaviors are even stronger and more positive predictors of increased abstinence [38, 62]. While these Alcoholics Anonymous meeting and composite measures of Alcoholics Anonymous participation have utility, they do not shed light on the relevance, if any, on the specific spiritually focused behaviors that contribute to increased abstinence. Unfortunately, given the centrality of spirituality to 12-step programs it is surprising how few of these prescribed behaviors have been isolated and studied.

A majority of Alcoholics Anonymous-exposed individuals practice the steps of Alcoholics Anonymous and step work is routinely encouraged in Alcoholics Anonymous meetings [58]. Further, in a cross-sectional study of four Alcoholics Anonymous groups it was reported that steps 1–3, typically regarded as the surrender steps, and 10–12 (maintenance steps) were discussed significantly more often than steps 4–9 (action steps) [55]. Finally, in a second cross-sectional study Horstman and Tonigan [18] reported that Alcoholics Anonymous groups that were perceived to be more supportive and expressive were also judged to endorse the practicing of the 12 steps more frequently than Alcoholics Anonymous groups perceived to be more aggressive and less supportive. Here, Alcoholics Anonymous member perceptions of the social dynamics of Alcoholics Anonymous groups were assessed using the Group Environment scale [39]. It would appear, then, that practicing of the 12 steps is common in Alcoholics Anonymous that such practice frequently focuses upon those steps that endorse the existence of a benevolent deity, and that the extent that such discussion occurs in an Alcoholics Anonymous meeting is influenced by the perceived social dynamics of an Alcoholics Anonymous group.

Few studies have investigated the actual benefit associated with doing the 12 steps. Patton [48] conducted a single group longitudinal study ($N = 769$) of individuals who had received inpatient treatment at Hazelden. Twelve months after treatment a significant positive association was found between completing steps 6-12 and total abstinence. Likewise, to the question, "do you do step work?", a significant and positive relationship was reported between answering *yes* to this question and complete abstinence at 12-month follow-up ($r = 0.22$). In a second longitudinal study of a Hazelden sample ($N = 592$), Kammeier and Anderson [22] reported that there was no relationship between working steps 1-4 and abstinence at a 24-month follow-up, yet there was a significant and positive relationship between self-reported "step work" and total abstinence. Continuing, as part of a psychometric project Gilbert [17] recruited 183 veterans receiving substance abuse treatment to participate in a 12-month study. Here, Gilbert reported that completing step 1 during the first 3 months post-discharge significantly and positively predicted days sober at the 6- and 12-month

follow-ups. Finally, Tonigan and Miller [56] reported that, among 226 outpatients who had received treatment 3 years earlier, the number of steps completed at 3 years was significantly and negatively predictive of the amount of alcohol consumed at the 10-year follow-up. In general, then, these studies suggest that working through the steps is beneficial in reducing alcohol consumption although it must also be acknowledged that those individuals who heed the prescription to do step work are self-selected and may be more motivated and have a better prognosis.

Progression through the 12 steps of Alcoholics Anonymous is most commonly achieved with the guidance of a sponsor, a fellow Alcoholics Anonymous member who has already completed the 12 steps. In this context, a sponsor is a spiritual mentor and the acquisition of a sponsor signals a conscious decision to work the spiritual program of Alcoholics Anonymous. What is known about the benefits of acquiring a spiritual mentor in Alcoholics Anonymous? In a retrospective analysis of the Project MATCH study, Pagano et al. [44] reported that sponsorship led to a significant reduction in relapse rate at 1 year, e.g., 60% versus 78%. Kaskutas et al. [23] have likewise reported that having a sponsor was one of the few Alcoholics Anonymous-prescribed behaviors that predicted reductions in substance abuse, here in a community-based sample. Kaskutas et al. [23] have also reported findings that suggest that there may be indirect benefits associated with sponsorship, namely that Alcoholics Anonymous members with sponsors tend to have triple the rate of Alcoholics Anonymous meeting attendance than Alcoholics Anonymous members without sponsors. Given the documented advantage of continued Alcoholics Anonymous attendance to sustain long-term abstinence [40] this indirect benefit is worthy of further study.

An emerging line of research has addressed the related question of whether helping others in 12-step programs, a prescribed spiritual activity in Alcoholics Anonymous, benefits the helper as well as the person helped. In a retrospective study of 11 Alcoholics Anonymous members with long-term sobriety, for example, Pagano et al. [45] reported that, for these Alcoholics Anonymous members, helping other alcoholics increased with time, and that such helping was felt to enhance the quality of sobriety. In a second cross-sectional study Zemore and Kaskutas [63] reported findings similar to Pagano. Specifically, Zemore and Kaskutas found that among 198 recovering alcoholics in Alcoholics Anonymous that a composite measure of helping (Sponsorship and step work) was more strongly and positively related to length of sobriety than was a composite measure of Alcoholics Anonymous involvement.

Summary and Future Directions

Religiosity and spirituality are associated with improved health-related functioning, especially with regard to mental health. As described in this chapter, the relationship between spirituality and addiction is unique and quite distinct from other mental health problems. Except in rare cases, for example, few clinicians would conclude that the onset of depression was the process of spiritual bankruptcy. In the treatment of substance abuse in the United States, however, the dominant therapeutic model embraces this belief. As such, a majority of treatment providers will uniformly refer individuals to 12-step programs during and after treatment.

Distinctions between the religiosity and spirituality constructs are frequently blurred in addictions research, with many investigators failing to adequately define the constructs if they make any attempt at all. The point was stressed when presenting four popular measures of spirituality/religiousness constructs in this chapter that each construct is multidimensional in nature, and dimensions within each construct appear to have differential sensitivity to the effects of spiritual interventions and in predicting positive outcome(s). In this regard, investigators and practitioners need to be keenly aware of the subtle complexities in what, at first glance, appears

to be self-evident and face valid measures. The measurement of meaning in life exemplifies some of these complexities. On one hand, few would argue that the belief in, and practice of, religious/spiritual behaviors can offer feelings of contentedness and purpose. However, a sense of well-being can as easily result from non- religious/spiritual practices. General measures developed to assess changes in broadly defined spirituality are especially prone to such measurement confounding.

Strong evidence indicates that 12-step treatment is equally effective as more research-based interventions for substance abuse, including therapies that combine psychosocial interventions with pharmacotherapy, e.g., naltrexone. The factors accounting for this parity, however, are only beginning to be understood. Most often, efforts to understand the role and influences of religiousness/spirituality in recovery from addiction adopt one of two conceptual models. The deficit model of spirituality has clear linkages to the 12-step spiritual paradigm and posits that the spiritual void created by addiction ultimately must be filled in order to avoid relapse. In fact, the distinction made in 12-step literature between abstinence and sobriety suggests that spiritual growth is even necessary to achieve well-being. The coping model of religiousness/spirituality is gaining popularity among addiction researchers, and some of the implications of this model were identified. Foremost, the coping model does not imply that religiousness/spirituality development is essential for recovery, but the model does posit that such growth may offer individuals the means to more positively interpret and adjust to negative affect. In this light the coping model of religiousness/spirituality is wholly compatible to, and can be integrated with, cognitive behavioral and relapse prevention strategies.

Religious/spiritual measures have been used as dependent, independent, moderator, and mediator variables in addiction research. Reviewed in some detail in this chapter, there is strong evidence that psychosocial interventions can produce desired shifts in religious/spiritual measures. In both 12-step and non-12-step religious/spiritual interventions, for instance, significant gains have been reported in religious/spiritual beliefs, cognitions, and practices. Such gains in clients' beliefs and practices appear to occur in both individualized and group therapy and for alcoholics and polysubstance abusers. Mostly negative findings have been reported, however, about the effectiveness of religious/spiritual interventions to produce, as independent variables, reductions in substance use. To date, efforts to assess the effectiveness of a spiritual guide [36] have not produced desired effects on a reliable scale, and while 12-step therapy is effective it does not appear to be the result of the spiritual focus of the formal intervention. Important exceptions were identified. Work by Robinson et al. [53] using new religious/spiritual measures and with Vipassana meditation, for instance, offer promising possibilities about the use of religious/spiritual interventions in the treatment of addiction.

The consistent absence of a moderator effect in religious/spiritual research in addictions can be viewed several ways. On one hand, client-treatment matching offers an efficient way to improve treatment effects through the appropriate assignment of individuals with different characteristics to different kinds of interventions. Findings that some clients fared better in spiritually focused interventions than others would have thus provided important information. The lack of evidence for client-treatment matching, using a diverse number of religiousness/spirituality measures of client characteristics, is also good news for practitioners in the United States. Specifically, this information suggests that the assignment of clients low on religious/spiritual beliefs and practices to a spiritually based intervention does not place them at a serious disadvantage. It is estimated that about 6–9% of the population in the United States is atheistic, and their proportional representation among alcohol and polysubstanc abusers is unknown. Findings suggest that this infrequently studied group of substance abusers is not at higher risk of poorer outcomes when assigned to 12-step therapy relative to non-atheists.

The effectiveness of community-based 12-step programs as a stand alone intervention is not entirely clear because of standard sampling procedures in mutual-help research. With this caveat, strongest support for the effectiveness of spiritually focused practices in Alcoholics Anonymous was found for the guidance provided by having and or being a sponsor and for completing prescribed Alcoholics Anonymous steps. Cross-sectional work indicated that encouragement to do step work is associated with Alcoholics Anonymous groups that are more cohesive and supportive and that some steps are endorsed more than other steps. While some confidence can be placed on the findings that step work is relatively common in Alcoholics Anonymous, the findings about the conditions in which they are (or are not) stressed requires prospective study. Current prospective findings offer three relatively firm evidence-based recommendations: (1) encouragement to attend Alcoholics Anonymous meetings is important, especially during early efforts to reduce drinking, (2) encouragement to become engaged in prescribed Alcoholics Anonymous behaviors beyond that associated with simple meeting attendance increases the prospect for Alcoholics Anonymous-related benefit, (3) acquiring a sponsor reduces later relapse, and (4) religious/spiritual orientation of the client, while important, may not be important in determining whether or not to refer to Alcoholics Anonymous. Awaiting replication with prospective studies, it may be the case that helping other Alcoholics Anonymous members as prescribed in the Alcoholics Anonymous literature also increases Alcoholics Anonymous-related benefit for the helper.

At the beginning of the chapter the cautionary statement was made that ongoing 12-step research funded by the National Institute on Alcohol Abuse and Alcoholism may qualify the findings and recommendations in this paper. Currently, for example, there are at least six large-scale longitudinal studies of 12-step programs in the United States, and many of them are specifically investigating the mechanisms that account for Alcoholics Anonymous-related benefit. Clearly, findings from these studies will produce several new chapters on the narrative of the relative importance of spirituality in recovery. Also mentioned earlier, several excellent evidence-based monographs on 12-step programs in particular and spirituality in general have just been published. Perhaps the soundest recommendation that can be made is that readers interested in this topic need, over the next decade, to become actively engaged in the scholarly empirical literature that is focused on religiousness/spirituality and addictions.

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Ear Acupuncture in Addiction Treatment

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Contents

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Introduction

Acupuncture is currently used in the treatment of addictions by approximately 2,500 addiction treatment programs. Clinical evidence supports that it is effective in ameliorating withdrawal and craving symptoms associated with alcohol, opiate, and cocaine dependence, as well as symptoms associated with most other addictions. Acupuncture for cocaine dependence has been particularly recognized as an important innovation since there are presently no established pharmaceutical treatments for cocaine dependence. Acupuncture is used by programs as a foundation for later psychosocial recovery. It is a non-verbal, non-threatening, "first-step" intervention that has an immediate calming effect on clients regardless of the specific substance used and regardless of whether a coexisting

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_61,

psychiatric disorder has been diagnosed. Initial participation with acupuncture has been found to improve participants' overall treatment retention and to facilitate their subsequent involvement. In most programs, clients receive 3–5 ear acupuncture points while seated together in a large group room so that a substantial number of individuals can be treated conveniently. This safe and cost-efficient procedure has gained increasing acceptance from agencies responsible for overseeing addiction treatment. Evidence for the benefit of acupuncture in coexisting psychiatric conditions and other behavioral health settings also will be presented. This chapter will describe the practical use and research findings relating to acupuncture for addiction. Mechanisms of action that involve physiology and psychosocial process will be covered.

Acupuncture Basics

History and Method

Acupuncture is a major component of the ancient tradition of Chinese medicine. The principles and goals of this form of treatment have remained constant through time. The textbook that is still used today, the Nei Jing, was written 2,000 years ago. Acupuncture was used by numerous nineteenth century U.S. practitioners, including Sir William Osler, "the father of modern medicine", and the imminent physician/chemist Franklin Bache, the grandson of Benjamin Franklin. In the early 1970s, American interest was renewed when relations with China were opened. Most U.S. states have acupuncture licensing laws. Acupuncture is recognized by established medical organizations in virtually every part of the world. Veterinary medical journals cite many examples of objective clinical success, including treatment of potentially lethal arthritis in horses and congenital hip dysplasia in dogs. Effective treatment of animals is usually cited as proof that acupuncture is not merely a placebo procedure.

Acupuncture consists of the stimulation of specified locations on the surface of the body that alters and improves bodily function. The Chinese term for a treatment location is *xue*, which means opening. The traditional Chinese names for these locations often refer to flow on the surface of the earth such as valley, marsh, crevice, or stream. In the West, the term point is used. Acupuncture points are physiologically distinct from the immediate environment; they have less electrical resistance and, therefore, greater electrical conductivity. The points are warmer than the surrounding area by 0.1–0.2 of a degree. The difference in warmth and electrical activity can be detected by the human hand as well as by instruments. A painful response to pressure may also be used as a point indicator. The precise location of these phenomena varies within a small area that corresponds to the acupuncture point as denoted on an acupuncture chart. Descriptions of the location and functions of these points have remained fairly constant through the centuries.

Acupuncture points can be stimulated by various means: touch, movement, heat, electricity, and needling. Health-related procedures such as acupressure, shiatsu, reiki, and tai ji chuan work on the same principles as acupuncture even though no needles are used. Needling is the most convenient and efficient means of stimulating acupuncture points.

Acupuncture needles are stainless steel shafts of varying length and thickness. The handle of the needle usually has an additional spiral winding made of copper. The needles may be cleaned, sterilized, and re-used, as is the case with surgical equipment. Most Western facilities use the needles once and discard them. Acupuncture needles are provided in convenient sterile packages. Needles are inserted with a brief but steady movement. Ear needles penetrate 1/8 inch, contacting the cartilage if it is present in that location. Needles are twirled 180 degrees for smoother insertion. The client may feel a momentary sensation like a pinch. Occasionally, there is a brief, sharper sensation that may cause the client to complain. The procedure is nearly painless and causes the rapid

onset of a gratifying sense of relaxation. On first exposure, most clients express fear of the pain of needle insertion and are confused by the idea that little needles can cope with their big problems. This fear is easily solved by letting prospective clients observe others undergoing the actual process of treatment. It is a mistake to rely on leaflets and verbal explanation alone.

What the Clients Experience

Clients may notice local paresthesia effects such as warmth and tingling. There may be sensations of warmth, electrical movement, or heaviness in other parts of the body, although these reactions are more typical of body acupuncture rather than ear acupuncture. Clients may feel quite sleepy after each of the first several treatments. This reaction is part of the acute recovery process and passes readily. A few individuals develop a headache at the end of a treatment session. Shortening the length of the session or reducing the number of needles resolves this problem. Rarely, a needling reaction occurs in which the client feels dizzy and light-headed and may actually faint. This reaction (postural hypotension) also occurs in many medical and dental settings. When it occurs, one should remove the needles and help the client lie on a flat surface. The syncope will resolve within a few minutes, and the client will exhibit relaxed behavior as though the full-duration treatment had been given. Needling reactions occur more often in persons with a relatively labile autonomic nervous system. Fortunately, these reactions are quite rare in the treatment of addiction. Clients should be told to eat before coming for treatment in order to reduce the possibility of a needling reaction.

The insertion of acupuncture needles never causes bleeding. Hence, there is no need for special blood contact precautions during application of treatment. Based on our experience, treatment sites in the ear bleed about 1% of time after the needles are removed. Thus, 10–20% of clients will have such a reaction. There are several methods that are being used to cope with this problem in terms of appropriate risk management precautions. Commonly, clients are asked to remove their own needles and place them directly in a sharps container. Staff may remove needles by only touching the handle and giving the client a cotton pad to use if bleeding is noted. A small hematoma may also occur. Staff may press each location with a Q-tip as necessary. Most gloves do not provide dexterity in grasping small needles. It should be noted that ear needles are inserted so shallowly that about 10% fall out during the period of treatment. Therefore many needles must be retrieved which have fallen on the individual's clothing. Even wearing gloves will not protect staff who might try to search for such needles. Hence, clients must be instructed to locate any fallen needles and discard them properly. Often programs use a needle count procedure. Clients place needles in a paper cup or bowl so that staff can verify that all needles are present before they are discarded in the sharps container. This procedure is particularly appropriate if acupuncture is conducted in a room that is used for other purposes.

Suggested Physiological Mechanisms

There have been many efforts to determine the underlying physiological mechanisms of acupuncture. Some of the efforts were based on the misleading assumption that acupuncture is primarily a treatment for pain relief. Many acupuncture functions, such as autonomic and gastrointestinal effects, are independent of any aspect that relates to pain. In other cases, such as the treatment of frozen shoulder, pain is actually temporarily increased after successful acupuncture needling. More accurately, acupuncture is frequently an effective treatment for the circulatory, neurological, or inflammatory causes of pain.

Acupuncture charts have a superficial resemblance to Western neuron anatomical charts. The functions of the meridian channels on acupuncture charts differ substantially, however, from those of nearby peripheral nerve trunks. Ear acupuncture is a particularly clear example in

this regard. The acupuncture chart of the external ear identifies more than a hundred separate acupuncture points. These points relate primarily to different body locations and to various organic functions. One can easily verify some of these correlations by noting that the shoulder point on the ear shows abnormally low electrical resistance in patients with shoulder injuries, as does the ureter point in patients who are passing a kidney stone. The simple innervation pattern of the external ear cannot be used to explain these effects.

Researchers have noted the following variety of specific physiological effects associated with acupuncture [3]. It has been reported that acupuncture at traditional points produced dramatic effects in electroencephalogram, galvanic skin resistance, blood flow, and breathing rate. Various studies have linked acupuncture to the production of endogenous opiate peptides, such as beta-endorphin and metenkephalins, and it has been speculated that this is a physiological mechanism behind the treatment's effects on withdrawal discomfort. Acupuncture also has been related to changes regarding other neurotransmitters, including corticotropin and cortisol levels, serotonin, and norepinephrine. The impact of these neurotransmitters in addiction and behavioral health is well established. They are thought to be of key importance in understanding drug and medication effects in addiction and psychiatry. A review of research linking endogenous opiate peptide production to optimal immune system functioning concluded that acupuncture appears to have beneficial effects on the immune system. Substantial literature thus exists supporting that acupuncture has a variety of neurochemical and other physiological effects.

It should be noted that certain medications—namely, methadone, corticosteroids, and benzodiazepines—seem to suppress part of the acupuncture effect. Individuals taking these medications in substantial quantity experience clearly less relaxation effect during treatment and may have a slower response to treatment. Nevertheless, acupuncture is an effective treatment for secondary addiction in high-dose methadone recipients and in reducing benzodiazepine withdrawal symptoms. Acupuncture is also widely used to treat adrenal-suppressed individuals who need to be weaned off corticosteroid medication. This may suggest that part of the initial relaxation response is endorphin and steroid dependent but that the more important mechanisms relate to a different type of process.

Acupuncture effects have been documented in a wide range of organisms. Needling the stem of a plant at a low resistance point will correlate with a rapid increase in the temperature of the tips of the leaves as measured by thermography. Needling a point of normal resistance will produce no such effect (A. Eory, unpublished findings discussed at a Society for Acupuncture Research meeting, 1995).

It is too restrictive to define acupuncture mechanisms in terms of highly evolved structures such as the human brain and the endocrine system. Rather, it seems clear that acupuncture involves the primitive and pervasive functions that are common to all life. Such functions include circulation on a microscopic level, homeostasis, wound healing, immune function, and micro-neurological functioning. Acupuncture has an obvious impact on the autonomic nervous system that is an example of a relatively primitive and homeostatic system in human beings. Acupuncture seems to enhance the integrity of these basic life functions. Pharmaceutic medicine, at best, can only suppress one or more parts of these systems. The Society for Acupuncture Research meets yearly to discuss these issues of mechanism and research. Acupuncture research may provide a window of opportunity for us to enhance our understanding of basic and pervasive vital processes [18].

National Acupuncture Detoxification Association Protocol

Lincoln Hospital Experience

Acupuncture treatment for drug and alcohol problems was primarily developed at Lincoln

Hospital, a New York City-owned facility in the impoverished South Bronx. The Lincoln Recovery Center is a state-licensed treatment program that has provided more than 800,000 acupuncture treatments in the past 34 years. Dr. Yoshiaki Omura was the consultant who began the program [15].

Lincoln Hospital has trained more than 7,000 clinicians, usually referred to as acupuncture detoxification specialists, in the past 20 years. The National Acupuncture Detoxification Association was established in 1985 to increase the use of the Lincoln model and to maintain quality and responsibility in the field. Registered trainers from the National Acupuncture Detoxification Association have trained many thousands of acupuncture detoxification specialists. The Center for Substance Abuse Treatment, part of the Substance Abuse and Mental Health Services Administration, publishes a series of Treatment Improvement Protocols. In 2006, the Center for Substance Abuse Treatment's Treatment Improvement Protocol #45 on "Detoxification and Substance Abuse" included the use of acupuncture in its best practice guidelines for the treatment of addiction.

Initially, in 1974, Lincoln used Dr. H.L. Wen's method, applying electrical stimulation to the lung point in the ear [25]. Lincoln was a methadone detoxification program at that time; therefore, acupuncture was used as an adjunctive treatment for prolonged withdrawal symptoms after the 10-day detoxification cycle. Participants reported less malaise and better relaxation in symptom surveys. Subsequently, twice-daily acupuncture was used concurrently with tapering methadone doses. Reduction in opiate withdrawal symptoms and prolonged program retention were noted.

It was accidentally discovered that electrical stimulation was not necessary to produce symptomatic relief. Simple manual needling produced a more prolonged effect. Participants were able to use acupuncture only once a day and still experience a suppression of their withdrawal symptoms. A reduction in craving for alcohol and heroin was described for the first time. This observation corresponds to the general rule in acupuncture that strong stimulation has primarily a symptom-suppression or dispersing effect and that gentler stimulation has more of a long-term, preventive or tonification effect.

Gradually the acupuncture protocol was expanded by adding the shen men (spirit gate), a point known for producing relaxation. Other ear points were tried on the basis of lower resistance, pain sensitivity, and clinical indication during a several-year developmental process. The author added the sympathetic, kidney, and liver points to create a basic five-point formula (Fig. 1). Numerous other point formulas using body acupuncture points were tried on an individual basis without any significant improvement.

A standard acupuncture textbook [10] describes the functions of each of the five points in the basic formula as follows: *Sympathetic* is used for numerous diseases related to disruption in both sympathetic and parasympathetic nervous systems. It has a strong analgesic and relaxant effect upon internal organs, and it dilates blood vessels. *Shen men* regulates excitation and inhibition of the cerebral cortex. It produces sedative and anti-allergy effects and

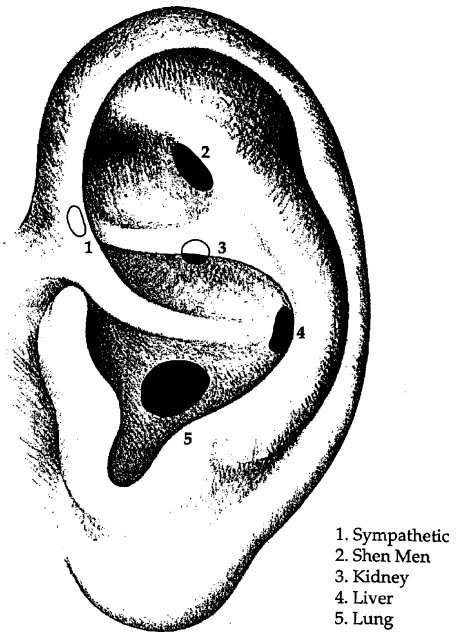

Fig. 1 Acupuncture point locations for National Acupuncture Detoxification Association protocol

is used for many neuropsychiatric disorders. *Lung* is used for analgesia, sweating, and various respiratory conditions. *Liver* is used for hepatitis, anemia, neuralgia, muscle spasms, and eye diseases. *Kidney* is a strengthening point for the cerebrum, hematopoietic system, and kidneys. It is used for neurasthenia, lassitude, headache, and urogenital problems. Traditional Chinese theory associates the lung with the grieving process, the liver with resolving aggression, and the kidney with willpower, coping with fear, and new growth.

Clinical Value of a Standard Protocol

The value of using one standard group of acupuncture points became increasingly clear. The standard formula seemed to be equally effective for different drugs of abuse and at different stages of treatment. Participants responded better when acupuncture treatment was administered quickly without an intrusive, diagnostic prelude. Since acupuncture produces a homeostatic response, it was not necessary to adjust the formula for mood swings, agitation, or energy.

From the point of view of Chinese theory, using a single basic formula for such generally depleted individuals is appropriate. In traditional Chinese medicine, the lack of a calm inner tone in a person is described as a condition of empty fire (*xu huo*) because the heat of aggressiveness burns out of control when the calm inner tone is lost. It is easy to be confused by the empty fire that many addicts exhibit and to conclude that the main goal should be the sedation of excess fire. Addicts themselves take this approach in the extreme by using sedative drugs. The empty fire condition represents the illusion of power, an illusion that leads to more desperate use of substances and to senseless violence. Acupuncture helps those with this condition to restore their inner control.

A group setting enhances the acupuncture effect. A group size of less than six members seems to diminish symptom relief and retention significantly. Clients receiving acupuncture in an individual setting are often self-conscious and easily distracted. These problems are more evident in the management of new clients. General acupuncture treatment sessions need to last 20–25 min. Because chemically dependent individuals are more resistant and dysfunctional, they should be instructed to remain in the acupuncture group setting for 40–45 min so that a full effect is obtained. The atmosphere of the treatment room should be adjusted to fit varying clinical circumstances. Programs with a significant number of new intakes and/or socially isolated individuals should use a well-lit room and allow a moderate amount of conversation to minimize alienation and encourage social bonding. On the other hand, programs with relatively consistent clientele who relate to each other frequently in other group settings should dim the lights and not allow any conversation in order to minimize distracting cross-talk. Background music is often used in the latter circumstance.

The location of ear points and the technique of insertion can be taught effectively in a 70-h apprenticeship-based program. Most acupuncture components can be staffed by a wide range of addiction clinicians such as counselors, social workers, nurses, medical doctors, and psychologists. Training must include a clinical apprenticeship because coping with the individual distractions and group process is more important and more difficult to learn than the technical skill of repetitive needle insertion. Each clinician can provide about 15 treatments per hour in a group setting. General supervision should be provided by licensed or certified acupuncturists. This arrangement allows for acupuncture to be integrated with existing services in a flexible and cost-effective manner.

Numerous states have enacted specific acupuncture detoxification specialist laws. These states include New York, Vermont, Connecticut, Maryland, Virginia, Tennessee, Georgia, South Carolina, Indiana, Missouri, Louisiana, Texas, New Mexico, and Arizona. Other states have specific arrangements that allow nurses and counselors to provide National Acupuncture Detoxification Association acupuncture services. According to Substance Abuse and

Mental Health Services Administration statistics [21], acupuncture is used in more than 900 state-licensed chemical dependency programs. Almost all of these programs are located in states with acupuncture detoxification specialist laws. The limited availability of fully licensed acupuncturists (or physicians) and the expenses of hiring such providers seem to be limiting factors.

Summary of National Acupuncture Detoxification Association Protocol

The National Acupuncture Detoxification Association model can be summarized and defined as follows: (1) Clinicians use three to five ear acupuncture points including sympathetic, shen men, lung, kidney, and liver. Three points (sympathetic, shen men, and lung) are used in third-world settings to save money without any apparent loss of effectiveness. (2) Treatment is provided in a group setting for 40–45 min. (3) Acupuncture treatment is integrated with conventional elements of psychosocial rehabilitation. (4) Several components of the Lincoln program are frequently combined with acupuncture in other treatment facilities. These items include: a supportive non-confrontational approach to individual counseling; an emphasis on Narcotics Anonymous and other 12-step activities early in the treatment process; an absence of screening for appropriate clients; the use of herbal sleep mix; the use of frequent toxicologies; a willingness to work with court-related agencies, and a tolerant, informal, family-like atmosphere [19].

The author developed an herbal formula known as sleep mix, which is used in most acupuncture for addiction settings and many other health care settings as well. The formula includes chamomile, peppermint, yarrow, skullcap, hops, and catnip. These are inexpensive herbs, traditionally used in Europe, that are reputed to calm and soothe the nervous system and tend to stimulate circulation and the elimination of waste products. The herb formula is taken as a tea on a nightly basis or frequently during the day as symptoms indicate. Sleep mix can be used for the treatment of conventional stress and insomnia as well as providing adjunctive support in addiction treatment settings. Sleep mix is particularly appropriate for the management of alcohol withdrawal symptoms. Individuals receiving conventional benzodiazepine treatment will often voluntarily refuse this medication if sleep mix is available.

Lincoln has used a reiki circle for the past 10 years. Reiki is a type of therapeutic touch that is related to acupuncture. A reiki circle can involve 20 people if several practitioners are involved. Reiki provides similar benefits to National Acupuncture Detoxification Association acupuncture. In addition, reiki is more socially interactive and helps clients learn more about their own process of change. Lincoln and many programs use magnetic beads for weekend treatments. The beads are attached to a square of adhesive. They are usually placed on the lung point, the shen men point, or the back of the ear in a "reverse shen men" position. Only one point should be used bilaterally. Beads remain in place for 1–2 weeks if necessary. In addition to addiction-related treatment, beads have been used for general stress relief and for attention-deficit hyperactivity disorder and other childhood problems. A pilot study at Reed Academy in Framingham, Massachusetts shows potentially promising results for autism spectrum disorders [17].

Controlled Studies

Randomized Placebo Trials

H. L. Wen, MD, of Hong Kong was the first physician to report successful use of acupuncture treatment of addiction withdrawal symptoms [25]. He observed that opium addicts receiving electro acupuncture as post-surgical analgesia experienced relief of withdrawal symptoms. The lung ear point was used. Subsequently, Wen conducted several basic clinical pilot studies that formed the basis of subsequent research.

Results from available placebo-design studies support the conclusion that acupuncture's

effectiveness in facilitating abstinence with alcohol, opiate, and cocaine abusers is not due to a simple placebo effect [3]. Seven published studies involving animal subjects (i.e., mice or rats) indicate that electro acupuncture reduces opiate withdrawal symptoms with morphine-addicted subjects. In these studies, experimental and control animals show behavioral differences regarding rodent opiate withdrawal symptoms, such as hyperactivity, wet dog shakes, and teeth chattering. Each of these studies notes significantly fewer withdrawal symptoms with subjects receiving electro acupuncture relative to controls. Significantly different hormonal and beta-endorphin levels post-electro acupuncture are noted between experimental and control subjects in several of these studies.

A number of controlled studies have been conducted on human subjects using various modified versions of the Lincoln Hospital ear point formula. Washburn and colleagues [24] reported that opiate-addicted individuals receiving correct site acupuncture showed significantly better program attendance relative to subjects receiving acupuncture on placebo sites. Two placebo-design studies provide strong support regarding acupuncture's use as a treatment for alcoholics. Bullock and colleagues [7] studied 54 chronic alcoholics randomly assigned to receive acupuncture either at points related to addiction or at nearby point locations not specifically related to addiction. Subjects were treated in an inpatient setting but were free to leave the program each day. The setting also provided frequent 12-step meetings and a supportive atmosphere typical of an aftercare facility.

Throughout the study, experimental subjects showed significantly better outcomes regarding attendance and their self-reported need for alcohol. Significant differences favoring the experimental group were also found regarding: (1) the number of self-reported drinking episodes, (2) self-reports concerning the effectiveness of acupuncture in affecting the desire to drink, and (3) the number of subjects admitted to a local detoxification unit for alcohol-related treatment. Bullock et al. [5] replicated Bullock et al. [7] using a larger ($n = 80$) sample over a longer (6-month) follow-up period. Twenty-one of 40 participants in the treatment group completed the 8-week treatment period as compared with 1 of 40 controls (Table 1). Significant differences favoring the experimental group were again noted. Placebo subjects self-reported over twice the number of drinking episode reported by experimental subjects. Placebo subjects were also re-admitted to the local hospital alcohol detoxification unit at over twice the rate of experimental subjects during the follow-up period.

Table 1 Completion rates in Hennepin study

	Treatment group	Control	p Value
Phase I (daily acupuncture for 2 weeks)	37 (92%)	21 (52%)	0.001
Phase II (3 times a week for 4 weeks)	26 (65%)	3 (7%)	0.001
Phase III (twice a week for 2 weeks)	21 (52%)	1 (2.1%)	0.001

Adapted from Bullock et al. [5] (The Lancet), with permission from Elsevier

Research Problems

There are several potential distortions of research data that are particular to acupuncture detoxification studies. Controlled studies must often rely on "soft outcomes" including interim measurements from questionnaires or short-term attendance or toxicology. Acupuncture is not "Valium in a needle". Conventional researchers usually assume that acupuncture has an exclusively sedating effect. They assume that treatment success can be measured by responses on a one-time, one-dimensional questionnaire that equates more relaxation with a greater treatment effect. The reality of National Acupuncture Detoxification Association acupuncture is quite different. It has a balancing effect, which includes arousal and increased energy in some treatment. Some other acupuncture treatments lead to a moderate sense of well-being; the significant effects primarily occur hours or days after treatment. The most important effects of acupuncture detoxification have little to do with

immediate sedation effects. Meditation and rejuvenation are very different from sedation.

Addiction treatment is not merely the suppression of the indications of illness. Most people in the field agree that best outcome of addiction treatment is the development of self-responsibility. We focus our effort so that the client takes charge of his or her own recovery. This situation is very different from the conventional model in which there is an active pharmacologic agent and a passive client. From the point of view of research design, clients' own efforts become an unwanted variable. How do we know whether the medicine did it or the client did it?

Note the results of the pilot study from Reed Academy cited in this chapter [17]. Halfway through the study, four boys decided that they wanted to "take control of their lives" and have the magnetic beads removed. Statistically, they were removed from the study database. Clinically, however, they continued to do well and gained a level of success that had not seemed possible before. This effect is widely accepted in the outcome evaluation of long-term treatment. Clients who drop out of therapeutic communities after 6 months are seen to have a comparable success rate to those who complete the whole program. Self-actualization, not simple obedience, is the more significant trait. Many forms of treatment do not fit easily with the process of self-actualization. Other forms of treatment—acupuncture, 12-step, Drug Court, for example—fit easily with a client's growing independence.

The social context for a research study is often a critical variable that is overlooked. The pilot study for the Cocaine Alternative Treatments Study at Yale [1] showed promising results. In this case, acupuncture was embedded in a well-functioning methadone program, and the link between the participants, the program, and the study was constructive. When the large Cocaine Alternative Treatments Study was done, the Yale site data showed no significant effect. The intervention and controls were identical; the variable was a less functional social bond between the program and participants, which led to the need to pay research participants in order to get enough of them [13].

It is often difficult to design or identify a social context that will be appropriate to test a claim that acupuncture is an effective supportive context-dependent treatment. The Cocaine Alternative Treatments Study tested an inappropriately optimistic claim that acupuncture can reduce cocaine use as a virtual stand-alone treatment [12]. The Fairview Study by Bullock and colleagues [6] sought to measure a treatment enhancement where little enhancement was possible due to the already comprehensive schedule in that rehab program.

Placebo Points May Be Active

The five National Acupuncture Detoxification Association points are not the only acupuncture points for acupuncture detoxification. Several points can give about the same effect. This causes problems when researchers look for placebo points. Konefal et al. [9] examined the efficacy of different acupuncture point protocols with individuals who had various alcohol and other drug problems. Subjects ($n = 321$) were randomly assigned to one of three groups: a one-needle auricular treatment protocol using the shen men point; the five-needle Lincoln protocol, or the five-needle Lincoln protocol plus selected body points for self-reported symptoms. All groups showed an increase in the proportion of drug-free urine tests over the course of treatment. Subjects with the single needle protocol, however, showed significantly less improvement compared with the other two groups.

During the trial-and-error search conducted at Lincoln Hospital for a more effective ear acupuncture formula for addiction treatment, it was clear that a large number of points had some effect on acute withdrawal symptoms. Ear acupuncture charts indicate that all areas on the anterior surface of the ear are identified as active treatment locations. Using a placebo or sham acupuncture technique is actually an effort to use relatively ineffective points in contrast to the

conventional use of totally ineffective sugar pills in pharmaceutical trials. Sham points are usually located on the external helix or rim of the ear, although there is no consensus about the level of effectiveness of this procedure. Bullock's alcoholism studies used highly failure-prone subjects and, hence, may have revealed the difference between active and sham points more effectively.

Landmark Shwartz Study

While focusing on the complexities of randomized controlled double-blind studies, it is easy to forget that a controlled study is never more than an approximation of reality. Real-life surveys tend to have explicit "hard" outcomes that represent prolonged significant change. Consequently, the large Boston Target Cities Study conveyed more potentially valid information than any of the randomized controlled studies than have been done on acupuncture detoxification [16].

Shwartz et al. [16] surveyed 8,011 complete treatment episodes that were totally blinded because no "study" was being conducted. Low-volume studies must be carefully monitored (controlled) because relatively small variations can create significant distortions in the results. Surveying a high volume of treatments tends to minimize this problem.

The Shwartz study used data from the federally funded Target Cities program, which provided assessment and referral of all detoxification patients in Boston during 1993–1994. Consequently, Target Cities provided a uniquely convenient database for referral and subsequent referral comparison. At the time of the study, Boston had three outpatient detoxification programs that used acupuncture instead of pharmaceutical medication. These were long-standing programs, so the study measured outcomes from existing established programs rather than a new or experimental design. Shwartz and colleagues compared the recidivism rates of the three outpatient detoxification programs with the recidivism of four residential detoxification programs. Recidivism is defined as re-admission for detoxification within 6 months of discharge from the prior admission for detoxification.

Of 8,011 individuals discharged during the study period, 6,907 (86%) had their first detox discharge from an inpatient program and 1,104 (14%) from an outpatient acupuncture program. As might be expected, the acupuncture group tended to be more educated, employed, and well housed. The modality of outpatient acupuncture treatment was selected by the clinical referral staff. Participants had to be educated about acupuncture before they agreed to this modality.

Shwartz et al. [16] took the necessary step of matching 740 of the acupuncture recipients with a similar group of residential patients with similar baseline characteristics. So, 67% of the acupuncture recipients with a similar group of residential patients were able to be included in the matched sample. The outcomes of the study were fairly clear-cut. The odds that an acupuncture recipient was re-admitted with 6 months were 71% of the odds that a residential patient was re-admitted (p= 0.02; 95% CI, 0.53–0.95). Acupuncture appeared particularly beneficial for those individuals with a primary alcohol diagnosis (odds 0.53) (Table 2) and those with two or more detox admissions in the past year (Table 3). Looking at the overall database, repeat recent detox admissions are the primary predictor of recidivism.

The characteristics of the two modalities being compared in the Shwartz study need to be examined. Residential detoxification lasts about 1 week and billed at $850–$900 in Boston in 1993. Most individuals are referred to other treatment after referrals. Outpatient detoxification has an initial intensive period of daily treatment and then a stabilization period up to a total average duration of 4 months.

Outpatient detoxification involves a lot of individual and group counseling as well as acupuncture. Acupuncture is valuable in the initial retention of clients and helping the client to be calm and receptive to benefit from counseling and social support. Target Cities processed a mixed group of addicts (alcohol 42%, cocaine and crack 33%, and heroin 24%). Outpatient use

Table 2 Percentage of clients re-admitted to residential detox or acupuncture within 6 months and the multivariate model odds ratio associated with acupuncture re-admission as a function of primary drug

		Residential detox		Acupuncture	Multivariate model
Primary drug	*n*	% re-admitted	n	% re-admitted	Odds ratio[a]
Alcohol	2,919	37.3	358	10.9	0.53 (0.29–0.98)
Cocaine	1,122	31.0	183	19.7	1.03 (0.52–2.04)
Crack	1,099	28.8	223	21.5	0.97 (0.54–1.74)
Heroin	1,699	40.6	210	31.4	1.11 (0.63–1.96)

[a]Odds ratio associated with acupuncture admission (95% confidence interval)
Reprinted from Shwartz et al. [16], with permission from Elsevier

Table 3 Percentage of clients re-admitted to residential detox or acupuncture within 6 months and odds ratio associated with acupuncture as a function of number of detox admissions in the year preceding the index admission

Admissions in year preceding the index admission	*n*	Residential detox % re-admitted	*n*	acupuncture detox % re-admitted	Multivariate model Odds ratio
No acupuncture admissions	3,781	0.0	821	0.0 (0.64)[a]	–[b]
1 residential detox admission	1,326	65.6	113	72.6 (0.13)	1.37 (0.89–2.12)[c]
≥2 residential detox admissions	1,518	89.4	61	78.7 (0.01)	0.47 (0.25–0.88)[c]
1 acupuncture and no residential detox admissions	124	78.2	69	40.6 (<0.01)	–

[a]Numbers in parentheses under % re-admitted are the *p*-values for a test of the null hypothesis that re-admission rates of residential detox and acupuncture clients are similar
[b]Too few re-admission cases to develop a model
[c]Odds ratio (acupuncture clients compared with the reference group of residential detox clients) and 95% confidence interval for the odds ratio
Reprinted from Shwartz et al. [16], with permission from Elsevier

of pharmaceutical agents is not a useful method of detoxification for most of this population, especially the cocaine subgroup.

Residential detoxification is more expensive than outpatient detoxification. The greater cost is usually justified by greater retention. Inpatient treatment is thought to have more impact on the individual so that further treatment will be sought. This study does not reveal how many successful referrals were made by the residential programs. However, the net effect of those referrals has been measured by the recidivism rate. Outpatient acupuncture treatment is less expensive and more flexible than residential detoxification. Showing that outpatient detoxification is even equally effective on a large-scale review has clear policy implications. This finding is especially pertinent because the outcomes are better with the most common drug of abuse (alcohol) and for the most problematic subgroup (multiple prior admissions).

Tweed Study

An article from the Centre for Addiction and Mental Health in Toronto showed that acupuncture is an effective supportive treatment in a comprehensive treatment program for women with concurrent mental health and substance use problems. The Jean Tweed Centre in Toronto provides a 21-day residential/day treatment program for women experiencing problems with alcohol and/or drugs. Women are either self-referred to the program or referred by others, such as physicians and self-help groups. The structured program offers daily therapeutic activities that address diverse aspects of women's

psychological and physical health. These aspects include group and individual therapy, addiction education, self-esteem, anger management, family and relationships, recreation and leisure in recovery, women's health, life skills, relapse prevention, relaxation, stress management, sexuality, assertiveness training, journal writing, nature walks, reading, and self-reflection [8].

A National Acupuncture Detoxification Association acupuncture component was added to the basic program for eight 21-day cycles. As a control, five cycles were monitored without the acupuncture enhancement. Randomizing participants within each cycle was not possible because almost all of them wanted the acupuncture experience once they saw it. By alternating cycles, the control participants were unaware of acupuncture in any manner. The control participants were given a time for meditation and reflection comparable to the time the other participants spent on acupuncture.

The most commonly abused substance was alcohol (44%). Demographics showed 40% employed, 10% university graduates, and 64% single or separated. Anxiety and depression were the primary mental health findings. Women with psychotic symptoms were excluded from the unit. Results showed that women receiving acupuncture (n=185) reported having reduced physiological cravings for substances, felt significantly less depressed and less anxious, and were better able to reflect on and resolve difficulties than women in the control group ($n = 101$).

Possible Broader Range of Effectiveness

National Acupuncture Detoxification Association acupuncture can have an effect on symptoms not related to addiction. A British researcher, Beverley de Valois, used National Acupuncture Detoxification Association acupuncture as a treatment for hot flushes and night sweats in women using adjuvant hormonal treatment for breast cancer. Women who had had the treatment were invited to retrospective focus groups. Most of the 16 attendees found that acupuncture was helpful and relaxing. Many reported a reduction in hot flush frequency as well as improvements in overall emotional and physical well-being [23].

Impact on Different Abuse Patterns

Acupuncture is being used in numerous diverse treatment settings. Outcome reports have been published only to a limited degree because of the journals' emphasis on placebo-controlled studies. Unless otherwise noted, these outcomes are based on clinical experiences at Lincoln Hospital or personal observation of other programs made by the author.

Opiates

Opiate addiction was first treated by Dr. Wen in Hong Kong and has been treated at Lincoln Hospital since 1974. Acupuncture provides nearly complete relief of acute observable opiate withdrawal symptoms in 5–30 min. This effect lasts for 8–24 h, and its duration increases with the number of serial treatments provided. Clients often sleep during the first session and may feel hungry afterward. Clients who are acutely intoxicated at the time acupuncture is administered will behave in a much less intoxicated manner after the session. Surprisingly, these clients are gratified by this result, in contrast to reports of discomfort after naloxone administration.

Acupuncture for opiate addiction is typically administered two to three times daily in acute inpatient settings. Alternatively, it may be administered only once a day with clonidine or methadone on an outpatient basis. Many individuals do well on once-daily acupuncture because they taper their illicit opiate usage over a 3- to 4-day period. Heroin addicts usually seek detox to reduce the size of their habit, so this arrangement fits their immediate goals. The addition of an acupuncture component to an opiate detoxification program typically leads to a 50% increase

in retention for completion of the recommended length of stay.

Alcohol

Directors of the acupuncture social setting detox program conducted by the Tulalip Tribe at Marysville, Washington have estimated a yearly saving of $148,000 due to less frequent referrals to hospital programs. Inpatient alcohol detoxification units typically combine acupuncture and herbal "sleep mix" with a tapering benzodiazepine protocol. Individuals report fewer symptoms and better sleep. Their vital signs indicate stability, and, hence, there is much less use of benzodiazepines. One residential program in Connecticut noted a 90% decrease in diazepam use when only herbal "sleep mix" was added to their protocol.

Retention of alcohol detox patients generally increases by 50% when an acupuncture component is added to conventional settings. Some alcoholics who receive acupuncture actually report an aversion to alcohol. Woodhull Hospital in Brooklyn reported that 94% of the individuals in the acupuncture supplement group remained abstinent as compared with 43% of the control group who only received conventional outpatient services [11]. The widely quoted controlled study by Bullock et al. [5] showed 52% retention of alcohol-dependent individuals as compared with a 2% sham acupuncture retention rate.

Cocaine

Cocaine addiction has provided the most important challenge for conventional treatment because there are no significant pharmaceutical agents for this condition. Acupuncture recipients report more calmness and reduced craving for cocaine even after the first treatment. The acute psychological indications of cocaine toxicity are visibly reduced during the treatment session. This improvement is sustained for a variable length of time after the first acupuncture treatment. After three to seven sequential treatments, the anti-craving effect is more or less continuous as long as acupuncture is received on a regular basis.

Urinalysis outcomes were examined for Lincoln Hospital patients using cocaine or crack who had more than 20 treatment visits and were active during the 1-week study period in March 1991. At Lincoln, patients typically provide urine samples for testing during each visit. Of the entire study group of 226 individuals, 149 had more than 80% negative tests during their entire treatment involvement. Of those remaining, 39 had at least 80% negative tests during the 2 weeks prior to data collection.

Methamphetamine

Methamphetamine users experience similar dramatic increases in treatment retention. Hooper Foundation, the public detoxification center in Portland, Oregon, reported 5% retention of methamphetamine users prior to the use of acupuncture and 90% retention after adding acupuncture to their protocol. Increased psychological stability and decreased craving were cited.

Methadone

Individuals on methadone maintenance receive acupuncture in a number of different settings. They report a decrease in secondary symptoms of methadone use such as constipation, sweating, and sleep problems. Typically, there is a substantial drop in requests for symptomatic medication. Treatment staffs usually notice decreased hostility and increased compliance in methadone-acupuncture clients. The most important impact of acupuncture in maintenance programs is reduction of secondary substance abuse—primarily involving cocaine, even in clients with minimal motivation [14]. Reductions in secondary alcohol use are also frequently described. Acupuncture is effective with individuals on any dosage level of methadone.

Lincoln Hospital used methadone and acupuncture together from 1974 to 1978. Several hundred individuals on methadone maintenance were detoxified during that period using tapered doses of methadone and acupuncture. Based on our previous non-acupuncture experience, we observed that clients were much more comfortable and confident when they received acupuncture. Even though clients regularly complained about withdrawal symptoms, there were very few requests for a dosage increase. The large majority completed the entire detoxification process and provided at least one negative toxicology report after the cessation of methadone.

Methadone dosages were decreased 5–10 mg/week, with a slower schedule during the final 10 mg. Starting levels of methadone ranged from 20 to 90 mg, with a median of 60 mg. Acupuncture was provided 6 days per week and continued up to 2 months after the last methadone dose. Although many of these participants had been referred for administrative or mandatory detoxification due to secondary drug use, toxicologies were usually drug-free after the first 2–3 weeks of treatment.

Methadone withdrawal is notable for unpredictable variations in symptoms and significant post-withdrawal malaise. Symptoms such as depression, low energy, and atypical insomnia are quite difficult to manage without acupuncture. Clients are usually fearful and have considerable difficulty participating in psychosocial therapy during the detoxification period. Acupuncture is particularly valuable in the methadone-to-abstinence setting because clients' future well-being depends on their ability to utilize psychosocial support during the detoxification period.

Marijuana

At Lincoln, we have had a significant number of primary marijuana users seeking care. These individuals usually report a rapid reduction in craving and improved mental well-being. Secondary marijuana use is usually eliminated along with the detoxification of the primary drug (e.g., cocaine).

Tobacco

The use of the National Acupuncture Detoxification Association protocol can be helpful in residential treatment where the clients are unable to continue using tobacco. Its use in a 90-day inpatient, tobacco-free, dual-diagnosis treatment program demonstrated improved retention in treatment, with longer length of stay and improved participation in those individuals who received the needles. The use of acupuncture appeared to help both those planning to smoke and those wanting to stay quitting after discharge. For those planning to smoke as soon as possible after discharge, significantly more (57%) completed the program successfully if they had 8 or more acupuncture detoxification sessions versus <8 sessions ($p<0.05$). Those receiving needles reported significant improvement in sleep, anger, pain, concentration, and energy compared with those not receiving needles. Combined with education, acupuncture detoxification allows individuals to move forward in their stage of change regarding tobacco use after discharge [20].

For those in outpatient treatment who are motivated to quit smoking, the National Acupuncture Detoxification Association protocol can be very helpful. Bier et al. [2] demonstrated that the combination of acupuncture with education resulted in an effectiveness rate of 40% cessation and 53% post-treatment reduction in total cigarettes smoked. This result is comparable to that produced by pharmacological treatment of nicotine addiction combined with behavioral support.

Clinical Effectiveness

Retention and Recidivism

The beneficial effects of acupuncture in cocaine treatment often lead to dramatic increases in

retention of cocaine users. Women in Need, a program located near Times Square in New York, reported the following outcome figures in their treatment for crack-using, pregnant women: (1) Individuals with conventional outpatient treatment averaged three visits/year. (2) Those who received acupuncture in addition to conventional treatment averaged 27 visits/year. (3) Participants in an educational component in addition to acupuncture and conventional treatment averaged 67 visits/year. Those averaging three visits/year would be unlikely to participate in an educational component. Therefore, it seems likely that the increased retention correlated with acupuncture set a foundation for successful participation in the educational component.

Acupuncture detoxification programs report substantial reduction in their recidivism rates. Hooper Foundation cited a decrease from 25 to 6% in comparison with the previous non-acupuncture year. Kent-Sussex Detoxification Center (in Delaware) reported a decrease in recidivism from 87 to 18%.

Substance Abuse Recovery (Flint, MI) noted that 83% of a group of 100 General Motors employees were drug- and alcohol-free productive workers a year after entering acupuncture-based treatment. Most of them had repeated prior attempts at treatment and frequent relapse. Everyone in the 17% failure group had fewer than five program visits. Seventy-four percent of the success group continued to attend Alcoholics Anonymous and Narcotics Anonymous meetings after completing the treatment program. Programs specifically designed for adolescents, such as the Alcohol Treatment Center in Chicago and a Job Corps-related program in Brooklyn, have shown retention rates comparable to adult programs.

Frequency and Duration of Treatment

Acupuncture treatment is generally made available to clients 5–6 days per week. Lincoln offers treatment during an 8-h period, but many smaller programs offer acupuncture during 1- to 2-h periods each day. Morning treatment hours seem to be more beneficial. Active participants will receive treatment three to six times per week. Initially, acupuncture should be defined as an expected part of the program. If one describes acupuncture as a voluntary or optional part of the program, this description is not useful to a crisis-ridden addicted person. Such a person cannot handle choice and ambivalence effectively. Initially, clients need direction and clarity. They should be asked to sit in the treatment room without needles if they are unsure about receiving acupuncture. New clients will learn about acupuncture from other more experienced clients, and they will observe the process of treatment on a first-hand basis. Sometimes a client will be willing to try just one or two needles at first. Eventually, a high percentage will be active participants.

The duration of acupuncture treatment depends on many factors. Inpatient programs will want to stress acupuncture in the beginning for detoxification and stabilization and prior to discharge for separation anxiety. Outpatients in a drug-free setting typically receive acupuncture for 1–3 months on an active basis. About 10% of these outpatients will choose to take acupuncture for more than 1 year if possible. Such individuals usually have significant difficulties bonding on a psychosocial basis.

Lincoln Hospital used to provide acupuncture 7 days a week for the benefit of those in crisis. Eventually, it became clear that full weekend coverage did not appreciably improve clinical results. Individuals who began the treatment program on Friday had essentially the same outcomes as those who began the program on Monday. Acupuncture is not primarily a dose-related phenomenon, as is pharmaceutical treatment. Acupuncture more appropriately represents a qualitative service comparable to a schoolroom class or psychotherapy session.

People who are using acupuncture appropriately should be allowed to choose how often they receive acupuncture treatment. Duration of the effect of each individual treatment increases as the person becomes more stable. Since this

treatment is a private personal process, it should come under the client's control as soon as possible. Some clients will discontinue acupuncture too quickly, but they should be able to learn from the resultant loss of well-being in order to make better decisions in the future. Participation in acupuncture is a different kind of decision from participation in group or individual psychotherapy.

Effect on the Whole Treatment Process

Relapsing individuals are often able to continue to be involved in acupuncture even though they are no longer constructive participants in psychotherapy. Acupuncture recipients do not tend to burn their bridges as quickly; hence, retention and eventual success are increased in an acupuncture-based program.

A wide range of clients can be accepted for the initial stage of treatment because there is no verbal motivational requirement. Also, acupuncture is effective for most drugs and a wide range of psychological states. A low-threshold, easily staffed program can be established for new clients. Ambivalent street-wise individuals find the acupuncture setting almost impossible to manipulate. The setting is so soothing and self-protective that even extremely anti-social people are able to fit in. Problems relating to language and cultural differences are diminished. For new clients, frequent acupuncture treatment permits the gradual completion of assessment on a more accurate basis. Clients can be evaluated and triaged according to their daily response to treatment and testing rather than merely on the basis of the initial interview.

The tolerant, non-verbal aspect of acupuncture facilitates retention during periods when the client would otherwise be ambivalent, fearful, or resentful within a more intense verbal interpersonal setting. Ear acupuncture makes it easy to provide outpatient treatment on demand, without appointments, while the client is being acclimated to the interpersonal treatment setting. Clients are often willing to be tested even when they know that their toxicology result is positive, thereby showing respect for the value system of the overall treatment process. Those same individuals may be unable or unwilling to share their crisis and failure verbally until they have time to reach more solid ground. In the acupuncture setting, time is on our side.

Acupuncture has many characteristics in common with 12-step programs such as Alcoholics Anonymous and Narcotics Anonymous. It uses group process in a tolerant, supportive, and present-time-oriented manner. Participation is independent of diagnosis and level of recovery. Both approaches are simple, reinforcing, nurturing, and conveniently available. The emphasis on self-responsibility is common to both systems. In practice, acupuncture provides an excellent foundation for 12-step recovery. Clients seem less fearful and more receptive when they first enter the meetings. The traditional advice—listen to learn and learn to listen—fits this model well. Acupuncture reduces "white knuckle sobriety" considerably. There is less guarding and a greater ability to support each other warmly. The increased ability to use 12-step meetings provides more stable support for continuing treatment on an outpatient basis.

AIDS-Related Treatment

Easy access and better retention encourage the outpatient management of difficult clients with less need for additional drugs or services. One can select times for hospitalization more appropriately. An outpatient continuum also facilitates primary health care management for AIDS, tuberculosis, and sexually transmitted diseases. Acupuncture is used in a large proportion of AIDS prevention and outreach programs in New York and London, as well as other cities. These facilities include needle exchange and harm reduction programs and recovery readiness and pre-treatment programs, as well as health service providers for people with HIV and AIDS. In relation to addiction treatment, each of these

programs faces similar dilemmas. Their clients are likely to have ever-increasing addiction-related problems; however, these clients minimize their need for help. Furthermore, the clients are often overwhelmed by problems relating to immune deficiency. Acupuncture is uniquely appropriate entry-level treatment because it is convenient, relaxing, and not dependent on any mutually agreed-upon diagnosis or treatment plan. Acupuncture also provides treatment for emotions such as fear and depression. Many of these clients may be ashamed and confused, not knowing how to describe their ever-changing feelings in a conventional therapeutic context.

Maternal Treatment

The use of acupuncture has led to a considerable expansion of treatment services for cocaine- and crack-using women. The Lincoln program was cited as a model innovative program for prenatal care in a monograph, *Hospital and Community Partnership*, issued by the American Hospital Association in 1991.

The average birth weight for babies at Lincoln with more than 10 maternal visits is 6 pounds, 10 ounces. The average birth weight for less than 10 visits is 4 pounds, 8 ounces, which is typical of high-risk cocaine mothers. There is a high correlation between clean toxicologies, retention in the clinic program, and higher birth weights. Seventy-six percent of our pregnant intakes are retained in long-term treatment and give birth to non-toxic infants.

Premature birth is a serious health risk. The Hospital of St. Raphael in New Haven used the Lincoln acupuncture model for 8 years. The director of obstetrics, Dr. Wilfredo Requero, reported a drop in perinatal death rate from 18.5 to 7.1 from 1990 to 1992 following the use of acupuncture and other innovative outreach techniques. Special acupuncture-based components have also been developed for women with children in long-term foster care in the Drug Strategies Institute program in Baltimore. Acupuncture is used during high-risk prenatal home visits conducted by public health nurses in Washington state.

Female clients are often trapped in destructive and exploitative relationships and, therefore, have special difficulty with any therapeutic relationship. A consistently tolerant and non-confrontational approach prepares the way to establish a trauma survivor support service for clients at an early sobriety stage of recovery. The supportive atmosphere makes it relatively easy for clients to keep children with them during treatment activities. The acupuncture point formula used for addictions is also specific for the kind of emotional and muscular guarding associated with early sexual trauma. These clients will suffer intermittent crises and experience profound challenges to their physical and spiritual identity. All of their relationships will be strained and transformed. Acupuncture is a very appropriate adjunct to trauma survivors' support work.

Criminal Justice-Related Treatment

Individuals referred by court-related agencies often enter treatment in total denial or with a basic conflict with the referring agency. The non-verbal aspect of acupuncture allows the intake staff to get beyond these protests and offer acupuncture for stress relief, instead of forcing the issue. Using acupuncture, one is able to wait until the clients feel more comfortable and less threatened so they can admit their addiction and ask for help.

Addicts have trouble with discipline. They need order in their lives but cannot develop internal structure. Addicts also have trouble liking themselves. They are depressed and depersonalized and cannot accept good things. The end result is self-destruction and adherence to a masochistic lifestyle. The ability to like oneself builds the foundation for internal discipline. Acupuncture provides significant advantage in meeting the paradoxical requirement of tough love. Verbal interpersonal intensity is reduced. Clients feel that their immediate needs and

their urges toward independence have been satisfied. A tolerant, flexible atmosphere exists. Acupuncture delivered in a consistent and caring manner provides the basis for the love side of the equation. The foundation for the development of more effective discipline has been set.

Frequent urine testing provides an objective non-personalized measure of success that can be accepted equally by all parties. In this system, the counselor is the good cop and the urine machine is the bad cop. The counseling process can be totally separated from the process of judgment and evaluation. Discipline is separated from the difficulties of interpersonal relationships. Within this context, discipline or leniency by the judicial authority leads to constructive not escapist behavior. Positive toxicology results are primarily used to require a more prolonged or intense commitment to treatment.

The well-known Drug Court program in Miami uses the acupuncture-based model that we have described. This program diverts thousands of felony drug possession arrestees into treatment each year. More than 50% of these individuals eventually graduate from the program on the basis of providing 90 consecutive negative toxicologies over the period of a year or more. Drug Court diversion and treatment programs have been established in thousands of settings nationwide. This expansion represents a valuable increased commitment to addiction treatment throughout the U.S. The majority of the largest and oldest Drug Court programs (Miami, Broward, Las Vegas, and Portland) used acupuncture as a primary component of their protocol. Acupuncture is also being used in many jails and prisons in the U.S. and abroad. A follow-up study in Santa Barbara, California, for example, showed that women who received acupuncture were 50% less likely to be rearrested after being released from the county jail [4]. Sex offenders in a maximum security prison in Oak Park Heights, Minnesota received acupuncture on a regular basis. There was a significant reduction in anger and violent intrusive sexual fantasies as compared with a control population (P. Culliton and L. Leaf, personal communication, 1996).

Coexisting Mental Health Problems

Serious and Persistent Mental Illness

There is little substantive published literature on the use of acupuncture in the treatment of primary psychiatric problems. During the past 20 years at Lincoln Hospital, we have noted numerous effects of acupuncture on clients with coexisting addiction and psychiatric conditions. Agitated individuals fall asleep routinely while receiving acupuncture. Those with chronic paranoia have a higher-than-average retention rate. We have seen many examples in which grossly paranoid addicted persons have made special efforts to access acupuncture treatment. Our clients do not express paranoid ideas about acupuncture although they may remain otherwise quite paranoid. These clients experience a gradual reduction in psychiatric symptoms as well as a typical response in terms of craving and withdrawal symptoms. Psychotropic medication does not interact with acupuncture. Clients should remain on psychotropic medicines while using acupuncture since the improved level of compliance that correlates with acupuncture often makes the process of medication more reliable and effective.

A pilot program used acupuncture according to the Lincoln model in the public mental health system in Waco, Texas with a goal of reducing the rate of re-hospitalization. Highly disturbed, non-compliant, drug-addicted individuals with serious and persistent mental illness were deliberately selected for this trial. Rates of hospitalization dropped from 50 to 6% in the group of 15 participants. Harbor House, a residential program for mentally ill substance abusers in the Bronx, reported a 50% reduction in psychiatric hospitalization in the first year of acupuncture utilization. Their dropout rate during the first month of treatment decreased 85%. The participants in Waco, Texas participated more enthusiastically. They listened better and were more cooperative. The context of treatment became even more important to these individuals.

Acupuncture has an obvious advantage in the treatment of mentally ill substance abusers, especially those with serious and persistent mental illness. Mentally ill substance abusers have particular difficulty with bonding and verbal relationships. Acupuncture facilitates the required lenient supportive process, but, at the same time, it provides an acute anti-craving treatment that is also necessary. The use of acupuncture can resolve the contradictory needs of mentally ill substance abusers.

In the last decade, the National Acupuncture Detoxification Association acupuncture protocol has been used widely in large general psychiatric hospitals in Germany and Scandinavia. In Sweden, hospitals typically request training for 50–150 nurses. Training is conducted for 24 nurses at a time. One Swedish nurse summarized the changes: "Acupuncture reduces anxiety even for patients who are waiting for hours in the emergency unit. With quite aggressive people we use acupuncture. It seems to reduce hallucinations and make them less frightening. The more paranoid the patient is, the greater the effect from acupuncture. Depressed patients often get more active. Their anti-depressant medications seem to work better. Prescriptions for benzodiazepines are often reduced."

Dr. Elizabeth Stuyt of Pueblo State Hospital in Colorado reported similarly that "the worse patients seem to do better with acupuncture" [20].

Trauma and Violence

The World Trade Center in New York City was attacked on September 11, 2001. St. Vincent's Hospital became the receiving hospital where volunteer medical personnel gathered. As the stress intensified, a nurse from the hospital's alcoholism program offered their acupuncture protocol for stress relief for staff and visitors. More than 1,000 people received the ear acupuncture protocol during the next 2 weeks. This response led to a realization that this protocol has a much wider applicability than just addiction-related treatment. A full-time acupuncture service is still used by the New York City Fire Department for 9/11-related stress. Acupuncturists were invited to New Orleans after hurricane Katrina, specifically to treat homeless police and fire personnel. These treatments have been so successful that the medical board and the State of Louisiana are planning to have all first responders have access to ear acupuncture training.

In recent years the ear acupuncture protocol has been used in a wide variety of settings: parenting classes (Washington), suicide prevention in border security forces (India), schools for violent youth (England), recovery programs for commercial sex workers (San Francisco and Ethiopia), street children (Mexico, Peru, and Philippines), victims of sexual abuse (U.S.), and menopause-like side effects of tamoxifen (U.K.).

Ear acupuncture was used for stress relief for the inmates of Dartmoor Prison (U.K.) in the 1990s. Correction officials discovered a dramatic reduction of inmate violence and a greater interest in drug-free dormitories. Support for acupuncture spread quickly through the prison system. By 2006, 130 prisons in England were using ear acupuncture. More than 500 correctional officers have been trained to provide ear acupuncture in the prisons. The atmosphere between the officers and inmates has changed very positively as a result of this systemic transformation.

Psychosocial Mechanisms of Action

Personal Behavior

It is essential to understand acupuncture's psychological and social mechanisms of action to use this modality effectively. Acupuncture has an impact on the individuals' thoughts and feelings that is different from conventional pharmaceutical treatments. Subsequently, one can discuss how the use of acupuncture has a valuable and profound impact on the dynamics of the treatment processes as a whole. We should emphasize

that acupuncture for addictions is provided in a group setting. The new acupuncture client is immediately introduced to a calm and supportive group process. Clients describe acupuncture as a unique kind of balancing experience. "I was relaxed but alert. I was able to relax without losing control." Those who are depressed or tired say that they feel more energetic. This encouraging and balancing group experience becomes a critically important basis for the entire treatment process.

The perception that a person can be both relaxed and alert is rather unusual in Western culture. We are used to associating relaxation with somewhat lazy or spacey behavior and alertness with a certain degree of anxiety. The relaxed and alert state is basic to the concept of health in all Asian culture. Acupuncture encourages a centering, focusing process that is typical of meditation and yoga. Therapists report that clients are able to listen and remember what we tell them. Restless impulsive behavior is greatly reduced. On the other hand, discouragement and apathy are reduced as well. It is a balancing, centering process.

One of the striking characteristics of the National Acupuncture Detoxification Association acupuncture treatment setting is that each client seems comfortable in his or her own space and thinking process. One client explained, "I sat and thought about things in a slow way like I did when I was ten years old." Acupuncture treatment causes the perception of various relaxing bodily processes. Clients gradually gain confidence that their minds and bodies can function in a more balanced and autonomous manner. A hopeful process is developed on a private and personal basis, laying a foundation for the development of increasing self-awareness and self-responsibility.

Addiction is about trading present experience for past and future realities. Addicted individuals hang onto the present because the past and future seem to offer nothing but pain. Unfortunately, conventional treatment efforts tend to focus on assessment of past activities and planning for the future. Clients are obsessed by present sensations and problems. They often feel alienated and resentful that we cannot focus on their immediate needs. Acupuncture is one of the only ways that treatment staff can respond to a client's immediate needs without using addictive drugs. We can meet clients in the present time reality—validating their needs and providing substantial relief. Once a comfortable day-to-day reality support is established, we can approach past and future issues with a better alliance with the client.

The nature of recovery from addiction is that individuals often have quickly changing needs for crisis relief and wellness treatment. Many persons in recovery have relatively high levels of wellness functioning. Even so, a crisis of craving or past association may reappear at any time. Conventional treatment settings have trouble coping with such intense and confusing behavioral swings. Often merely the fear of a possible crisis can sabotage clinical progress. Acupuncture provides either crisis or wellness treatment using the same ear point formula. The non-verbal, present-time aspects of the treatment make it easy to respond to a client in whatever stage of crisis or denial may exist.

Internal Change

Clients readily accept that it is possible to improve their acute addictive status. They seek external help to provide hospitalization and medication for withdrawal symptoms. The challenge develops when they encounter the necessity for internal change. Addicts and others perceive themselves as being unable to change from within. Their whole life revolves around powerful external change agents. Each addict remembers countless examples of weakness, poor choices, and overwhelming circumstance that led to the conclusion that they cannot help themselves become drug-free. Indeed, many influential members of society agree that once an addict, always an addict.

Many of the complicating factors in our clients' lives echo this challenge of past internal failure. Persons leaving prison are confronted

with a bleak uncaring world. Their own feelings of inadequacy frequently become so overwhelming that a return to prior drug and alcohol use may occur within hours of release. When a person learns that they are HIV positive, their self-esteem drops precipitously. A drug-abusing seropositive person typically feels punished for past weaknesses by their HIV status. How can such a person have the confidence to seek out internal personal strength in the future?

Victims of incest and childhood abuse are well known to have been robbed of an internal sense of value. Their innermost physical and emotional responses have become sources of betrayal. It is not surprising, therefore, that a large majority of female addicts have been injured in this way.

All of us pass through a period of fearful internal inadequacy during the process of adolescence. Powerful trends of self-doubt and internal vulnerability are manifested at that time. No amount of external support will eliminate the need to confront internal fears on a private, personal basis. Hopefully, adolescents gradually learn to accept and appreciate themselves. They may also learn to rely on internal resources in their efforts to improve their circumstances. This archetypal challenge of adolescence is echoed in the struggle to become drug-free, as well as countless other efforts to become more internally resourceful and resilient in daily life. The question "does treatment work?" is comparable to asking whether internal self-discovery and re-definition are possible.

Acupuncture provides uniquely valuable assistance in coping with this challenge of internal redefinition. Clients often begin acupuncture treatment seeking external escape and sedation as they do when they use drugs. When there is a rapid calming effect, they often assume there was some sort of chemical agent in the acupuncture needle. After a few treatments, they come to the astonishing conclusion that acupuncture works by revealing and employing their internal capability rather than by inserting an external chemical. Individuals begin to realize that their mind is capable of calm, focused thoughts on a regular basis. There seems to be no indication of permanent damage to their thinking and consciousness. On the contrary, their ability to listen, think, and learn seems to be growing steadily each day.

Inevitably, a critical point will be reached. The newly drug-free individual will enter treatment one day with the feeling that "I don't deserve to be relaxed today because of all the bad things that I have done in the past." Such feelings frequently sabotage early treatment achievements. In an acupuncture program, however, the client realizes that his or her mind can become calm and clear even in the face of such overwhelming feelings of inadequacy. This lesson demonstrates that change based on internal resources is possible. In other words, successful treatment is possible. Regular participation in acupuncture helps a client take advantage of his or her internal resources much faster than conventional treatment processes. This effect contributes to the calm, cooperative atmosphere in most acupuncture settings. It reduces dropouts based on fears of failure and low self-esteem that typify the early stage of treatment.

Foundation for Autonomy

The use of acupuncture sets a foundation so that clients can have more autonomy in developing their own plan of treatment. A calmer, less resentful atmosphere is created. The tolerant, self-validating process helps individuals find their level and type of involvement in a productive manner. Clients must choose to talk sincerely with their counselor just as they must choose to avoid temptation and return to the program each day. These choices may fluctuate widely and be mistaken at times, but such independence is the only path toward growing up. When a program properly encourages structure but ignores the client's own independence efforts, these actions undermine future success. Acupuncture creates a better atmosphere so that treatment staff can spend their energies helping clients make choices rather than being fatigued by trying to impose authority on a resistant clientele.

One can describe acupuncture as a foundation for psychosocial rehabilitation. In the beginning of treatment, building a proper foundation is very important. If we are building on a weak, "sandy" personality, work on the foundation may take many months or years before it is strong enough to support any significant psychosocial treatment efforts. However, once a foundation is established, the focus of treatment should shift away from acupuncture toward building a "house" of psychosocial recovery on that foundation. When one of our clients testified at city council hearings, she described how important it was to attend daily Narcotics Anonymous meetings and barely mentioned acupuncture. For an individual with 3 months sobriety, this emphasis was appropriate. Of course, during her first 2 weeks in our program, she was quite angry and ambivalent and was only able to relate to the acupuncture component of the program.

Non-verbal Therapy

Acupuncture is a non-verbal type of therapy. Words and verbal relationships are not necessary components of this treatment. We do not mean that the therapist should not talk with the client. Verbal interaction can be quite flexible so that a client who does not feel like talking can be accommodated easily and naturally. Acupuncture will be just as effective even when the client lies to us.

The most difficult paradox in this field is the common reality that addicted persons usually deny their need for help. Such individuals do not say anything helpful to the treatment process. Nevertheless, resistant clients often find themselves in a treatment setting due to referral or other pressures. Using acupuncture can bypass much of the verbal denial and resistance that otherwise limit retention of new and relapsed clients. Addicts are frequently ambivalent. Acupuncture helps us reach the needy part of their psyche that wants help. Acupuncture can reduce stress and craving so that individuals gradually become more ready to participate in the treatment process.

Addicted individuals often cannot tolerate intense interpersonal relationships. Using a conventional one-to-one approach often creates a brittle therapeutic connection. It is easily broken by events or any stress. Clients have difficulty trusting a counselor's words when they can hardly trust themselves. Even after confiding to a counselor during an intake session, clients may feel frightened and confused about expanding that relationship. Many of their concerns are so complex and troublesome that talking honestly about their lives could be difficult in the best of circumstances. The ambivalence typical of addicts makes it easy to develop misunderstandings. All of these factors support the usefulness of non-verbal techniques during early and critical relapse phases of treatment and critical periods of relapse.

A woman who was 6 months pregnant entered our clinic several years ago. She said, "I can't tell you much about myself because my husband is out in the street with a baseball bat, he'll hit me in my knees if I say too much." We provided an emergency acupuncture treatment and conducted a simplified intake interview. Two weeks later, this client told us, "This is my husband. He doesn't have a drug problem, but he is nervous. Can you help him?" Both of them received acupuncture that day. The woman needed non-verbal access to treatment because of real physical danger. Overprotective spouses often forcefully oppose all social contacts outside the marriage. This client was protected because there was no premature verbal bonding that would have threatened the husband. The whole process was so supportive that the husband was able to trust his wife and seek help himself. Like many fearful people, he was literally unable to make any verbal approach on his own.

A certain mistake in treatment interaction should be highlighted. One should avoid reverbalizing the acupuncture interaction. Anxiety and depression are common indications for acupuncture. However, it is a mistake to require that the client admit to anxiety or depression in order to qualify for acupuncture. Addicts who have significant anxiety or depression will

usually not admit these feelings. They will avoid anyone who asks such questions. At a later stage of sobriety and recovery, talking about these feelings will be important, but at an early stage of treatment, verbalizing these feelings can lead to dropout. Likewise, it is not productive to ask clients why they have missed a previous acupuncture session. Use the advantage that acupuncture will be effective even if we don't know the issues involved.

Improving Treatment Program Function

Treatment programs without acupuncture are compelled to screen for individuals who are able to talk readily with authority figures. Many verbally needy clients become quite dependent on the program and quite involved with numerous staff members. Such individuals may be the focus of many conferences, but they are often too needy to remain drug-free outside the hospital. In contrast, acupuncture-assisted intake can retain clients who are relatively more paranoid, independent, assertive, and hostile. Noisy, troublesome individuals who are frustrated with the world and with themselves actually may be more likely to sustain a drug-free lifestyle than those with verbal dependency needs.

Acupuncture helps a program develop an underlying environment of acceptance, tolerance, and patience. There is ample space for the ambivalence and temporary setbacks that are a necessary part of any transformation. Clients can have a quiet day by attending the program and receiving acupuncture without having to discuss their status with a therapeutic authority figure. Since acupuncture reduces the agitated defensive tone in the whole clinical environment, clients are able to interact with each other on a much more comfortable level. Their increased ability to listen to others and accept internal changes have a profound effect on the quality and depth of communication in group therapy sessions and 12-step meetings. Being a sympathetic witness to a description of past tragedies can be easier to achieve in a setting that is not charged with defensive self-centered associations. The primary community agenda can focus on the acceptance of each person and a tolerant encouragement of change rather than coping with defensive and antagonistic interactions.

Clinical Examples

Using acupuncture can be a catalyst for unique personal development, as the following two examples show.

(1) The author was demonstrating ear acupuncture at a dual-diagnosis program in a university medical center. The clients were able to see sample acupuncture treatments, but they were not specifically introduced to me. After sitting for a few minutes, one woman asked me in a strong voice, "Does this treatment help incest survivors?" I answered "sometimes". The client volunteered for the treatment and soon after she fell asleep. Later on, she asked me if she could talk to the local professional acupuncturists who were sitting nearby. She said, "This treatment helps me; I want to make an appointment in your office. . . . I can pay for the treatment." I was impressed and shared this experience with the rest of the staff.

    The staff replied that they could have made the appointment and could have paid for the treatment. The process of observing and requesting acupuncture was part of this client's survival process. She was able to express herself and make decisions on her own. A potentially cumbersome therapeutic and case management issue was resolved by the client's healthy initiative.

(2) The author was visiting an outpatient treatment program run for the Cook County Jail in Chicago. As an effort to reduce overcrowding, jail officials would release 50 pre-trial inmates per month to a brief intervention program. Part of the program was

a large acupuncture group. One of the participants came to me and said, "Do you see the blue ribbon on my belt? That means I belong to XXX gang. I have to kill anyone with a red ribbon on his belt, like this guy in YYY gang walking toward us." I didn't know what to do. "Why are you telling me these things?" I said. The two men met in the middle of the room. They gave each other a big hug. "This is a peace zone," they said. "Who made it a peace zone?" I said. "We did," they replied. Gang members are separated in jail lockup, but referral to the program had not taken that simple measure. The acupuncture led to self-affirming, gentle communication and a simple special outcome that no amount of counseling could have achieved.

Conclusion: Clients' Own Stories

To really know the power of acupuncture in the treatment of addiction, listen to clients who have experienced it as part of their recovery transformation:

> Acupuncture has gotten me where I don't have a really manic life and I'm not depressed. I'm able to deal with everything that comes my direction because I have a lot of support also. I am energized, not miserable. I feel great about myself. I can smile today and the smile has feelings behind it. Acupuncture has hooked me up spiritually. I found my higher power—God—and he leads me each and every day.
>
> I was into prostitution and pornography—a violent woman. I behave differently today. I live with principles that I believe were ignited, sparked in me with acupuncture. As cumulative as acupuncture is, it has reached me in this level that I am able to change my beliefs more comfortably. I am given courage to take a look at my beliefs and empower myself, and now empower other women. I stand under reality strong truth that women can recover, and I know that acupuncture is the most valuable tool I know for recovery.
>
> Talking to [counselors], getting acupuncture treatment—hate, anger, jealousy, vengefulness, vindictiveness, all that changed into compassion and love. The acupuncture treatment just helped the process change in the detoxin (sic) and everything.
>
> Someone helped me find a simple way to just be with my self long enough to see what I need to work on—where I was wounded and how I could heal. And it is like a quiet way for one person to help to give treatment to another person. Acupuncture is a way to help sand the rough edges of what is going to be changed. It will give you a place to take all your other things into, and help create the change [22].

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Part X
Computer Modeling

In Silico Models of Alcohol Kinetics: A Deterministic Approach

Marc D. Breton

Contents

Introduction

In recent years, the mathematical representation of physiological systems and its use in computer simulations have come of age. Initially restricted to pharmacokinetics and pharmacodynamics studies, they are now used in many different fields of medicine—e.g., diabetes and metabolic syndrome—to explore previously inaccessible metabolic markers, develop candidate treatments, and even obtain authorization of regulatory agencies for clinical research, therefore bypassing animal testing. The field of alcohol addiction is of particular interest for such applications; it is both very developed (e.g., in modeling the dynamics of ethanol in blood or the diffusion from blood to brain tissues) and in its infancy, with only two simulation studies in the past 20 years [3, 4]. It also requires modeling of behavioral system and medication effects that are not yet mainstream (see Chapter "In Silico Models of Alcohol Dependence Treatment: Stochastic Approach"). In this chapter, we present several published and novel models of ethanol blood distribution, leading to simulation studies linking system-level characteristics to clinical outcomes.

Mechanisms of Alcohol Intoxication

Ethyl alcohol, also known as ethanol, is the substance found in alcoholic beverages. It is a colorless liquid that mixes in all proportions and, therefore, is readily distributed throughout the body in the aqueous bloodstream after consumption. Also because of this water solubility, it readily crosses important biological membranes, such as the blood-brain barrier. After it reaches the brain, alcohol affects multiple molecular targets, some of which remain unknown. In particular, alcohol causes gamma-aminobutyric acid receptors to remain open longer, allowing

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_62,

more chloride ions to enter brain cells and, therefore, causing relaxation, sedation, and overall inhibition of brain activity. At low concentrations, alcohol sensitizes the glutamate system, which stimulates areas of the brain associated with pleasure such as the cortico-mesolimbic dopamine system. With chronic exposure to alcohol, the brain undergoes long-lasting biochemical changes including neurological adaptation of the ion channels. Alcohol also is responsible for structural changes in the brain, such as loss of neuronal mass and brain shrinkage, which, in turn, is responsible for impaired cognitive function. Interestingly, the maximum quantity of alcohol consumed, such as in binge drinking, seems to be a better predictor of alcohol-related impairment. Hence, understanding the elimination process of alcohol will, to a certain degree, help us predict the extent of the neurological adaptation that takes place with chronic alcohol use.

Alcohol Metabolism

When we consume alcohol, the majority of it is absorbed from the small intestine (approximately 80%) and the stomach (approximately 20%). Generally, drinking more alcohol within a certain period of time will result in increased blood alcohol concentrations due to more alcohol being available for absorption into the bloodstream. More than 90% of the alcohol that enters the body is completely metabolized in the liver. The remaining 10% is not metabolized and is excreted in the sweat, urine, and breath. There are several routes of metabolism of alcohol in the body. The major pathways involve the liver and, in particular, the oxidation of alcohol by alcohol dehydrogenase to produce acetaldehyde, a highly toxic substance. The second step is catalyzed by acetaldehyde dehydrogenase. This enzyme converts acetaldehyde to acetic acid, a non-toxic metabolite. Acetic acid is eventually metabolized to carbon dioxide and water. Another system in the liver oxidizes ethanol via the enzyme cytochrome P450IIE1. This microsomal ethanol-oxidizing system seems to play a more important role at higher concentrations of ethanol.

Individual Differences in the Rate of Alcohol Metabolism

There are genetic variations in the P450E1 enzyme system that lead to individual differences in the rate of ethanol metabolism among people [5]. The rate of alcohol metabolism depends, in part, on the amount of metabolizing enzymes in the liver, which varies among individuals and appears to have some genetic determinants. After the consumption of one standard drink, the amount of alcohol in the drinker's blood usually peaks within 30–45 min. (A standard drink is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits, all of which contain approximately the same amount of alcohol.) The concentration of alcohol in the entire body, including the brain, is always less than that in the blood; human tissues contain a much lower percentage of water compared with the blood. However, organs having a rich blood supply, such as the brain, will quickly reach alcohol diffusion equilibrium with arterial blood. This explains why most people experience intoxication very quickly after taking a couple of drinks and then sober up rapidly as other bodily tissues with less blood supply, such as the muscle, start to absorb alcohol from the blood, meaning that less alcohol is circulating in the bloodstream.

Methods: Mathematical Modeling of the Pharmacokinetics of Ethanol

Ethanol elimination has been assumed to exhibit a zero-order metabolism, which means that constant amount of alcohol is eliminated per unit of time regardless of blood levels. However, a number of studies have identified that

elimination of ethanol follows different clearance models including first-order kinetic and a combination of zero- and first-order kinetic together. This, coupled with individual genetic differences, makes it hard to predict blood alcohol concentration based on total amount of alcohol consumed [12]. Since the early twentieth century, efforts have been directed toward the understanding of alcohol dynamics in humans and, more specifically, the blood concentration of ethanol.

Numerous models have since been devised, beginning with the early Widmark zero-order model assuming a constant clearance rate β_0 (equation (1)) and modeling the human body as one compartment (concentration, or blood alcohol level, BAL(t) and constant volume V) [14] (Fig. 1).

$$\frac{\partial BAL}{\partial t} = -\beta_0 BAL + \frac{D(t)}{V} \tag{1}$$

where $D(t)$ is the dose of ethanol received. This zero-order model is still commonly used in forensic sciences for its ease of use and the relative simplicity of its structure (very few parameters, easily identifiable). Nonetheless, this oversimplification of the clearing process of ethanol is responsible for additional variability in the model coefficients, within and more importantly between subjects. It is this between-subject variability, in particular, that makes the Widmark model ill defined for simulation purposes.

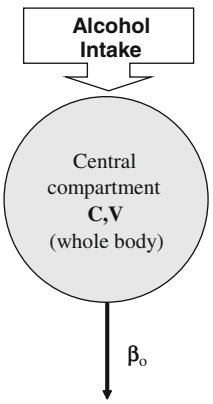

Fig. 1 Widmark's zero-order model

A deeper understanding of the processes involved and novel measuring tools have allowed more precise measurement and understanding of ethanol pharmacokinetics and the development of more complex non-linear multi-compartment models [7–9, 11]. Most of these models are compartmental—e.g., they represent the human body as a set of homogeneous (i.e., the ethanol concentration is the same everywhere) compartments of specific concentration and volume linked by diffusion or rate-limited pathways. The study of ethanol kinetics in vivo has led to a better representation of the ethanol-aldehyde-acetate process, leading to Norberg's model of alcohol dynamics [8] (Fig. 2), which introduces a Michaelis-Menten rate of alcohol clearance—a common enzyme-catalyzed, rate-limited clearance model; see Equation (2).

$$\begin{cases} \dfrac{dC_B}{dt} = -\left(CL_R + CL_d\right) C_B - \dfrac{V_{\max} C_B}{K_m + C_B} \\ \dfrac{dC_T}{dt} = -CL_d \left(C_T - C_B\right) \end{cases} \tag{2}$$

where C_B stands for blood ethanol concentration, C_T is the tissue concentration, CL_R is the renal clearance, and CL_d is the diffusion constant.

It is now widely accepted that alcohol clearance is a Michaelis-Menten controlled reaction—an enzyme-enhanced chemical reaction with limited supply [6]. These previously introduced models allow for a mathematical description of alcohol clearance following intravenous alcohol injection (Fig. 3).

Though it is able to represent closely the clearance processes of ethanol in blood, this type of model is often unwieldy compared with the first-order Widmark model. The larger number of parameters and the non-linearity of the model make the parameter estimation procedure difficult and sometimes yield imprecise estimates. For example, $V_{\max}$ and K_m are often highly correlated, as are the variances of their estimates. These numerical limitations can be alleviated by proper design of clinical data collection—e.g., the ethanol dose should be greater than two standard drinks, and numerous samples should be obtained at low levels. These restrictions should

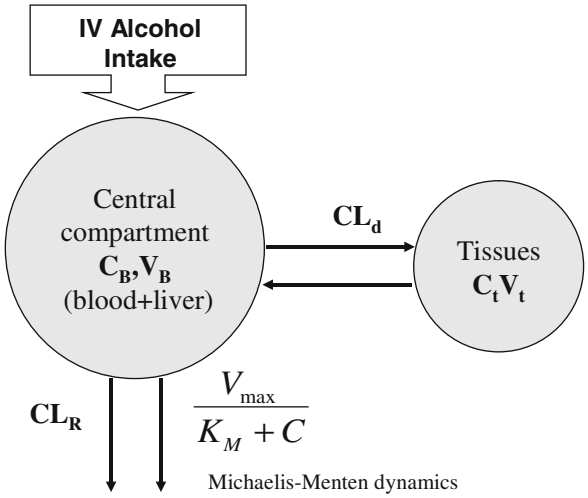

Fig. 2 Norberg's alcohol clearance model featuring Michaelis-Menten dynamics. Suitable for description of intravenous (IV) ethanol injection

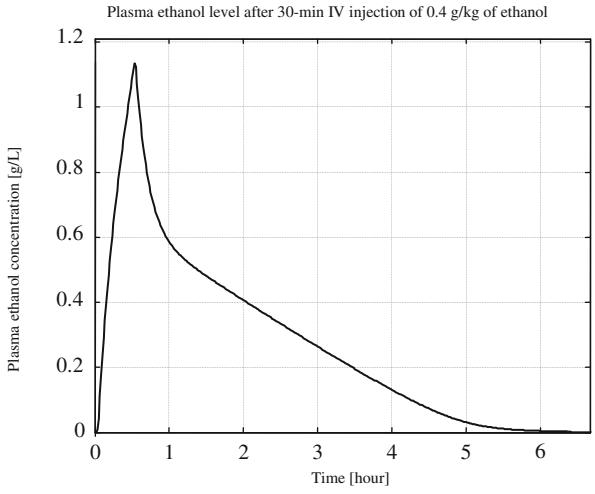

Fig. 3 Blood alcohol level following intravenous (IV) ethanol injection

be supplemented by specific numerical techniques such as initialization of the minimization procedure (see the section below) [9].

However, the dynamics of orally ingested alcohol has not been well quantified. The compartmental model in Fig. 2 cannot reproduce the dynamics of blood alcohol level presented in Fig. 4. In particular, the increase in blood alcohol level after alcohol ingestion is poorly described.

This is partly due to the slow diffusion of ethanol from the gastrointestinal tract to blood; whereas with intravenous injection the total dose of ethanol is immediately present in blood and its concentration is at equilibrium after a couple of minutes, orally ingested ethanol can take much longer to percolate fully from the digestive system to blood, therefore allowing for clearance even before the full dose has transferred to the blood. Modeling this process is difficult as ethanol diffuses to the blood from both the stomach and the intestines and at different rates; the speed of gastric emptying (and, therefore, the content and amount of what is ingested with alcohol) also plays a critical role in the dynamics of absorption.

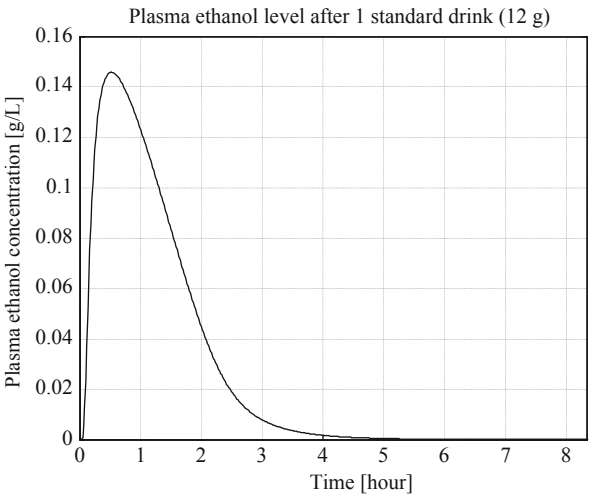

Fig. 4 Blood alcohol level following oral alcohol ingestion

The Minimal Model of Ethanol Kinetics

Here, we present a model directly derived from the work of Norberg (see above) but including a two-compartment model of the gastrointestinal tract. This allows us to make use of the simplicity of Norberg modeling, keeping the model complexity to a minimum (the number of equations and parameters to estimate), while also allowing for a semi-physiological representation of ethanol absorption and clearance, ultimately leading to the possibility of simulation of ethanol ingestion and finally drinking behavior.

Figure 5 presents the compartments included in the Minimal Model of Ethanol Kinetics. To represent properly oral alcohol intake, the model needs to include at least two compartments of the gastrointestinal tract: the stomach and gut. Following the minimal model approach, we do not need to add more compartments unless it is proven that the two-compartment gastrointestinal tract model is inherently insufficient. Further, the processes linking these compartments include one-way diffusions from the stomach and the gut into the bloodstream (ethanol in the blood cannot diffuse back to the gastrointestinal tract). Final assumptions of the model

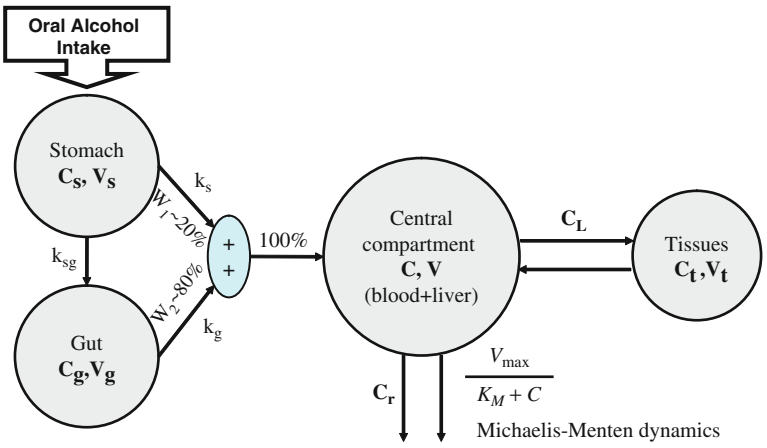

Fig. 5 The minimal model of ethanol kinetics following oral alcohol intake. The model allows the computation of the idiosyncratic Alcohol Sensitivity Index

include gastric emptying following an exponential decay with a certain half-life (e.g., 50 min [15]) and the proportion of gastric diffusion from the stomach W_S versus diffusion from the gut W_G (e.g., $W_S = 20\%$ versus $W_G = 80\%$ [1]).

The differential equations governing the processes depicted in Fig. 5 are as follows:

1. Ethanol is transported from the stomach to the gut with a rate constant k_{SG} and diffuses from the stomach into the bloodstream with a rate constant k_G.

$$\frac{\partial C_S}{\partial t} = \frac{1}{V_S W}\left(I(t) - k_S C_S - k_{SG} C_S\right) \quad (3)$$

2. Ethanol diffuses from the gut into the bloodstream with a rate constant k_G.

$$\frac{\partial C_G}{\partial t} = \frac{1}{V_G W}\left(-k_G C_G + k_{SG} C_S\right) \quad (4)$$

3. The total ethanol diffusion into the bloodstream is then given by the combination of diffusions from the stomach and the gut.

$$D(t) = k_G C_G + k_S C_S \quad (5)$$

4. Michaelis-Menten clearance of ethanol from the bloodstream occurs.

$$C(t) = \frac{V_m}{K_m + BAL(t)} BAL(t) \quad (6)$$

5. Two-way diffusion of ethanol between the bloodstream and tissues/liver occurs, including ethanol transport to the brain.

$$\begin{cases} \dfrac{\partial BAL}{\partial t} = \dfrac{1}{V_C W}(D(t) + CL_d(TAL(t) \\ \qquad\qquad -BAL(t)) - CL_r BAL(t) - C(t)) \\ \dfrac{\partial TAL}{\partial t} = \dfrac{CL_d}{V_T W}\left(BAL(t) - TAL(t)\right) \end{cases} \quad (7)$$

Identification of Model Parameters: From Population Averages, Through Individuals' Specific Profiles, to the In Silico Population

Population Averages

Using the previously described model, one can fairly easily extract the population average values from the literature. In particular, parameters common to Norberg's two-compartment model can be found in Norberg and colleagues [9]. Tuning of the gastric model is somehow more complex but can be done to reflect the generally admitted equilibrium between the stomach and gut of 20% versus 80% and the 50-min half-life of gastric emptying. While these values are enough to simulate the dynamics of ethanol and to extract interesting general characteristics of the addiction process, they do not reflect the large variability observed in vivo and, therefore, do not allow the study of a specific group of subjects and, *a fortiori*, a particular subject.

Subject-Specific Identification

We propose a clinical data collection based on the 20-point sampling protocol presented in Fig. 6. This protocol is similar to the standard profile used for determination of insulin resistance [2, 13] and is modified to account for the specifics of ethanol dynamics. Under this protocol, plasma blood alcohol level samples are collected at times $(t) = -30$, 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 300, 360, and 420 min. Time 0 is the time of initiation of oral alcohol intake. The total amount of ingested alcohol is equivalent to three standard drinks (45 g of ethanol), and, therefore, the average blood alcohol level profile of a person would be similar to the profile presented in Fig. 4. The blood alcohol level measurement prior to initiation of alcohol intake provides a baseline used for calibration; denser sampling is anticipated during the expected increase in blood alcohol

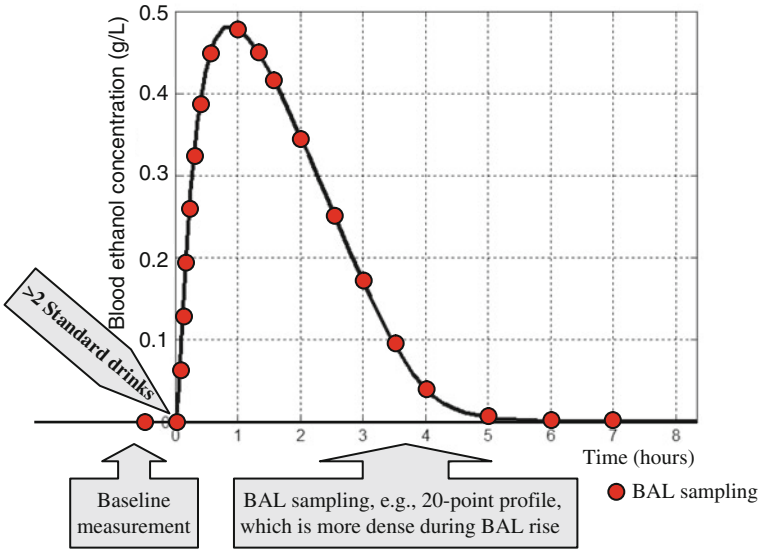

Fig. 6 Common features of a clinical testing protocol collecting data for an individual ethanol dynamics profile. The blood alcohol level (BAL) sampling can be done directly through blood samples, or using a breath analyzer

level, and less frequent sampling is anticipated during blood alcohol level decay.

A gradient search, simplex, or other nonlinear optimization technique is used to minimize the distance between the predicted blood ethanol concentration course of the model and the data collected as described above. Examples of distances include—but are not restricted to—the Euclidian norm (least square), infinite norm (maximum), and weighted least square, the most common being the Euclidian norm.

At convergence, the optimal parameters for this specific subject are fixed, and the model can be used to study the reaction of this subject to different scenarios, including some not easily reproducible in vivo (e.g., extreme/dangerous drinking).

In Silico Population

By repeating the procedure above on a large number of individuals, in different conditions (e.g., fasting versus fed, with a meal or not), we can start to understand the distribution of the model parameters—their mean, bounds, spread, and correlation with each other. With such a distribution, it then becomes possible to create an entirely simulated population spanning the entire (or a chosen subset of) space of possible reactions. In turn, this population can be used for simulated trials, as described in detail in Chapter "In Silico Models of Alcohol Dependence Treatment: Stochastic Approach".

Results: In Silico Studies of Blood Ethanol Time-Concentration

To illustrate the use of such models, we present in silico experiments reproducing key features of the ethanol metabolism system reported in the literature. The parameters of the Minimal Model of Ethanol Kinetics were first estimated using data available in the literature and from prior studies; then, the model was applied to study the behavior of the system during simulated drinking of 1 through >10 standard drinks dispersed randomly throughout an average day.

Experimental Setting of the Computer Simulation

The computer reproduced the system behavior over 72 drinking days. The simulation of a day of

drinking was based on the generation of a typical drinking day, taking into account the given average number of drinks per day. For example, with 4 preset drinks/day on average, the computer generated a 72-day sequence of drinking days with any number of drinks (i.e., between 1 and 15) dispersed throughout each day, amounting to 4 drinks/day on average.

This was done by modeling a drinking day as a Wiener stochastic renewal process, which means that the time between drinks is a Gaussian (normal) random variable. To follow a more reasonable pattern of drinking, we also limited the drinks to be between 7 A.M. and 11 P.M.—i.e., what we considered a standard daytime. The mean time between drinks was set at the ratio of the number of daytime minutes to the average number of drinks per day, and its coefficient of variation was set at 20%.

Each drink was standardized and set to be equivalent to a glass of wine—12 g of ethanol in 100 ml (3.5 oz)—consumed in 5 min. The simulation was run for 72 days (100,000 min) in a standard human model (i.e., a weight of 70 kg). The time course of blood alcohol level was recorded for each run. The range of average drinks per day was bounded between 1 and 15. Initial settings for identifying the Minimal Model of Ethanol Kinetics were adopted from the literature: $C_{max} = 0.1614$ g/L, $t_{max} = 47$ min, and AUC = 0.23 g × h/L (area under the curve) [5, 9, 10].

Two outcome measures were analyzed from this in silico experiment: the minimum of blood ethanol concentration over daytime and over 24 h. Each measure was calculated for each day between days 10 and 72, avoiding the initiation period of 9 days to allow the system to become stationary; the mean blood alcohol level was computed as well.

Figure 7 presents the minimum blood alcohol level during daytime as a function of the average number of drinks per day. In other words, the line represents whether or not the blood alcohol level would ever go down to zero during the day. The computer simulation shows that with up to 5 *drinks/day on average*, the minimum blood alcohol level during daytime is zero, indicating that the system reaches its steady (sober) state at least for a while during the day. Between 5 and 11 drinks/day, there is a linear increase of the minimum blood alcohol level (slope = 0.0235, $R^2 = 0.99$). After 11 drinks/day, the slope of the linear relationship increases dramatically to 1.71 ($R^2 > 0.99$).

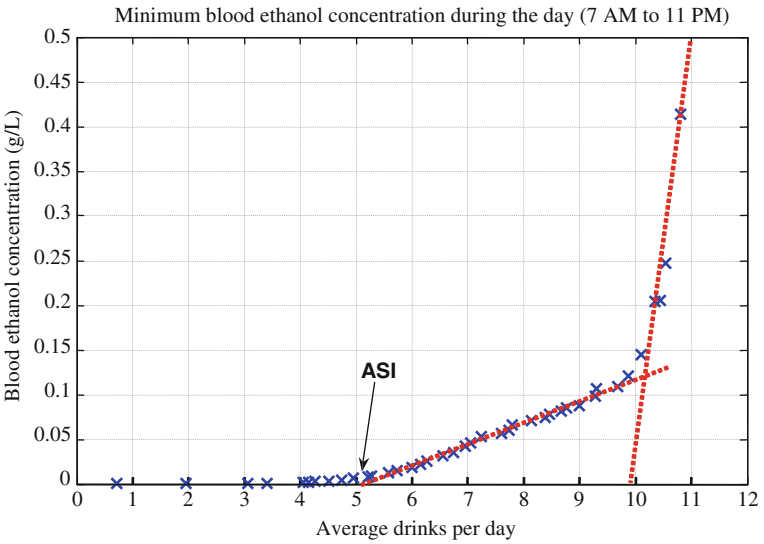

Fig. 7 Minimum blood alcohol level during daytime (7 A.M.–11 P.M.) as a function of average number of drinks per day. ASI = Alcohol Sensitivity Index

Thus, the computer simulation indicates that there are two well-defined threshold points defining abrupt system changes: 5 and 11 *drinks/day on average*. The first threshold point, at 5 drinks/day, indicates the transition of zero versus non-zero daily (7 A.M.–11 P.M.) blood alcohol level minimum. This means that with 4 drinks/day or less, the system is still capable of metabolizing fully the ingested alcohol, whereas at 5 or more drinks/day, there is always a certain residual amount of alcohol. From a system biology point of view, this first critical point indicates a phase transition from stable to unstable system dynamics. This is well visualized by the Poincaré plots in Fig. 8.

As seen in Fig. 8, 5 or more drinks/day would cause metabolic perturbations, never allowing the system to come to rest; the left panel represents a sustainable system dynamics, while the right panel represents a system that is clearly out of control.

This computer simulation result is consistent with—and to some degree explains at a system physiology level—the generally accepted understanding of heavy drinking defined as 5 or more drinks/day. *It appears that this critical value is not only an empirically established threshold but also an indication of an abrupt metabolic phase transition*.

To explain the second threshold value of 11 drinks/day, we need to look at the nighttime. As presented in Fig. 9, the minimum blood alcohol level during the night (11 P.M.–7 A.M., which was simulated as free of drinking) reaches zero for up to 11 drinks consumed during the day (7 A.M.–11 P.M.). When the number of drinks during the day exceeds 11, the system cannot metabolize the amount of consumed alcohol even during the nighttime hours, which are free of drinking.

Thus, 11 or more standard drinks/day results in a transition of the system dynamics to a higher blood ethanol value, which never goes down to zero. Because every morning there is still residual ethanol in the bloodstream, there is a very steep rise of blood alcohol level after 11 drinks/day. This explains the abrupt change in the slope of the dependence of blood alcohol level on average number of drinks per day depicted in Fig. 7.

Conclusion

In summary, the Minimal Model of Ethanol Kinetics is capable of reproducing (via computer simulation)—and to some degree explaining—the well-known empirical definition of heavy drinking, i.e., 5 or more standard drinks/day for men. The model also suggests other extreme situations, such as those that would occur with

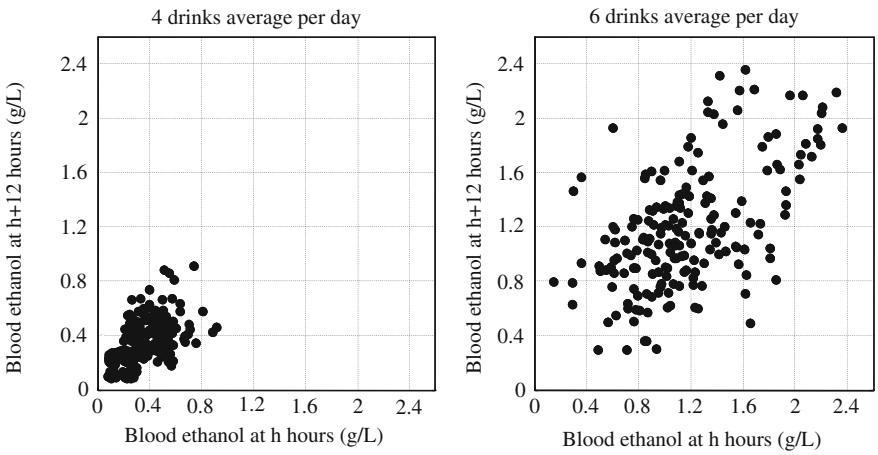

Fig. 8 System phase transition from stable to unstable dynamics indicated by Poincaré plots of the system attractor

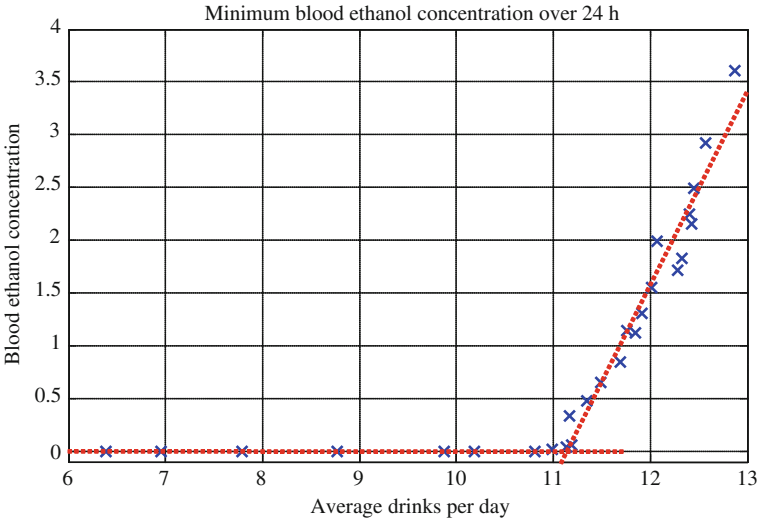

Fig. 9 Minimum blood alcohol level during the night (11 P.M.–7 A.M.) as a function of average number of drinks during the day (7 A.M.–11 P.M.)

more than 11 drinks/day, which theoretically should result in a protracted cognitive impairment due to continuous alcohol intoxication.

In this computer simulation, we used average parameters of alcohol metabolism. The Minimal Model of Ethanol Kinetics will allow for the computation of such parameters for each individual. This, in turn, is expected to facilitate the tailoring of individualized treatment.

This approach can be expanded to in silico studies of alcohol addiction, as presented in Chapter "In Silico Models of Alcohol Dependence Treatment: Stochastic Approach". With the creation of an in silico population, spanning the large observed variability in absorption and clearance of alcohol, it would become possible to study further drinking behavior as part of a high-order metabolic system, thereby applying long-held methods pertaining to system engineering to supplement/enhance well-known techniques used in the actual prevention/treatment of alcohol addiction. Further along, it will become possible to run preclinical testing of varied treatment strategies, as was done recently in the case of an artificial pancreas study, bypassing long-term animal studies and greatly accelerating the transition from medication development to human testing.

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In Silico Models of Alcohol Dependence Treatment: Stochastic Approach

Boris P. Kovatchev

Contents

Introduction

In the past two decades, computer simulation and computer-aided design have made dramatic progress in all areas of development of complex engineering systems. A prime example is the Boeing 777 jetliner, which has been recognized as the first airplane to be 100% digitally designed, assembled, and tested preflight in silico, e.g., in a computer simulation environment. This virtual design has eliminated the need for many costly experiments and accelerated immensely the development process. The final result has been impressive; the 777s flight deck and passenger cabin received the Design Excellence Award of the Industrial Designers Society—the first time any airplane was recognized by the society [4]. There is an enormous body of literature on computer simulation methods applicable to physics, engineering, economics, biology, metabolism, aerospace, meteorology and climatology, warfare, and just about any other subject of investigation that can be approximately described by a mathematical model. The review of this literature is beyond the scope of this chapter; here we will only mention a few biomedical modeling and simulation projects that are relevant to the topic at hand—in silico prediction of the effects of alcohol dependence treatment. For example, accurate prediction of the outcome of clinical trials has been achieved using the Archimedes diabetes model [10, 11]. Entelos, Inc., specializes in predictive biosimulation, introducing in its Physiolab suite in silico models for various physiological systems: cardiovascular, metabolic (diabetes), and others [27].

These in silico models are typically based on mathematical models of the studied physiological system, which are developed from extensive

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_63,

data collection examining underlying physiology in sufficient detail to allow for formal modeling. The models are then used to develop algorithms and software that power up simulation experiments. According to Winsberg [41], simulation experiments are typically classified with respect to the type of algorithm that they employ: "Discretization" techniques transform continuous differential equations into step-by-step algebraic expressions. "Monte Carlo" methods use random sampling algorithms even when there is no underlying indeterminism in the system. "Cellular automata" assign a discrete state to each node of a network of elements, and assign rules of evolution for each node based on its local environment in the network. In this chapter, we will utilize both discretization and Monte Carlo (or generally stochastic) methods, but first we will discuss three types of mathematical models of biosystems, classified according to the purpose of modeling: models to *measure*, to *simulate*, or to *control* the biosystem under consideration.

Models to Measure

The models to measure are generally simpler, allowing hidden relationships to be evaluated by estimating underlying parameters. Most of these models are compartmental; e.g., they represent the human body as a set of homogeneous compartments of specific concentrations and volumes linked by diffusion or rate-limited pathways. Classic examples include the Widmark Model of Ethanol Pharmacokinetics Assuming, which offers a straightforward interpretation with a constant ethanol clearance rate and the human body modeled as one compartment [40], and the more complex Minimal Model of Glucose Kinetics suggested by Bergman and Cobelli almost 30 years ago to measure insulin resistance in health and diabetes [5]. More recently, with the advent of the digital biology paradigm, various models to measure have been developed addressing pharmacokinetics, physiology, and human behavior. Deeper understanding of the processes involved and the development of novel measuring tools have allowed for more precise measurement of ethanol pharmacokinetics and the development of more complex non-linear models [28, 29, 30, 39]. The study of ethanol kinetics in vivo has led to a better representation of the ethanol-aldehyde-acetate process via the Michaelis-Menten rate of alcohol clearance introduced by Norberg [29]. It is now widely accepted that alcohol clearance is a Michaelis-Menten controlled reaction—i.e., an enzyme-enhanced chemical reaction with limited supply [39]. These and other pharmacokinetic models are discussed in detail in Chapter "In Silico Models of Alcohol Kinetics: A Deterministic Approach".

Models to Simulate

The models to simulate are maximal multiparameter models describing the complexity of the system as comprehensively as possible [7, 8]. For example, the recently published meal model of glucose-insulin dynamics is a descendant of the Minimal Model, which encompasses several metabolic subsystems including the gastrointestinal tract, renal function, hepatic glucose production, and others [7, 8]. When a maximal model is built, the computer simulation of the observed biosystem becomes possible, leading to in silico trials involving virtual "subjects" rather than real people. Such in silico trials can serve as precursors guiding expensive and time-consuming clinical investigations by outruling ineffective treatment approaches. For example, a recently developed simulator of the human metabolic system has received Food and Drug Administration approval and recognition for the preclinical testing of control strategies in artificial pancreas studies [21]. Using this simulator, the time for refining and safety testing of new algorithms that target the closed-loop control of diabetes has been reduced from years to several months [19, 24, 31]. Therefore, realistic computer simulation is capable of providing valuable information about the effectiveness, safety, and

limits of various treatments. Computer simulation allows experiments with extreme situations and testing of extreme failure modes that are unrealistic in animals and clinically impossible in humans. Besides extreme experiments, various treatment scenarios can be efficiently tested and either rejected or accepted for inclusion in future clinical experiments, which allows for rapid, comprehensive, and cost-effective clinical trial design. *We need to emphasize, however, that good* in silico *performance of a treatment does not guarantee* in vivo *performance. Computer simulation should* only *be used to reject inefficient treatments; it cannot confirm the efficacy of an intervention.*

Models to Control

External control of a complex technical or living system is generally achieved by control algorithms that are based on a certain mathematical representation of the system—a model to control—combined with the ability to observe the system in real time and make immediate decisions for correction of the system state. The models to control are typically simplified (frequently linearized) models that allow for rapid observation and computation of the corrective action. A prime example of medical devices that use adaptive control algorithms is the cardiac pacemaker, which in the past two decades has been incorporating automated control functions such as automatic capture and sensing control, self-adjusting rate response settings, sinus rhythm and atrioventricular conduction preference, and others [13, 17, 37, 42]. In diabetes, successful attempts at external closed-loop control have been made using various systems and algorithms, from cumbersome intravenous systems and implantable devices [1, 33, 36] to external subcutaneous control [15, 18, 38]. Relating control to simulation, comprehensive in silico testing of control algorithms is an efficient strategy if a model to control is tested against a much more complex model to simulate. In other words, the effectiveness of a controller can be judged if it is tested in realistic in silico conditions, which can be achieved by a comprehensive simulation model.

Formal Description of Human Behavior and Social Conditioning

In the context of in silico models of alcohol dependence treatment, applicable quantitative strategies include models to measure and models to simulate. In order to build such models, a formal mathematical description of human behavior and environmental conditioning is needed. However, the behavioral and social modeling field is still quite limited. Whilst several theoretical models based on internal somatic perception have been proposed [3, 22, 23], their heuristic approach has not permitted their development in sufficient mathematical detail to guide data analysis. For example, the stages of change described by the Transtheoretical Model of DiClemente and Prochaska [9] refer to a stochastic sequence—of readiness to change, stage of change status, temptation, and confidence—that has consistently shown predictive and explanatory ability for clinical outcome in alcohol dependence treatment studies. However, this sequence has not been identified as stochastic and has not been formalized to the extent that would permit computerized assessment and simulation. Another example can be provided in the context of non-specific treatment effects, such as the Hawthorne effect, which describes the tendency of an individual to change his or her behavior as a consequence of being observed or studied [26, 35]. While this effect provides evidence for the importance of environmental conditioning and external reinforcement for all stages of the progression of alcohol dependence—from acquisition of alcohol dependence, through treatment, to potential relapse—there is no formal description of environmental conditioning that would allow its inclusion in an integrated in silico model encompassing physiology, behavior, and social conditioning. Therefore, to advance the field, we have proposed a formal stochastic bio-behavioral

model of the sequence leading to self-regulation decision, in which the first three steps of the process were described by continuous variables while the decisions at Step 4 were binary [19]. The general concept is that decisions concerning self-regulation behaviors are often based on perception and appraisal of the body's internal state. Thus, the sequence preceding a certain action includes at least four sequential steps: internal condition perception environmental conditioning self-regulation decision. We have applied this general framework to evaluate the relationship between self-treatment behavior and the development of hypoglycemia in diabetics [6, 12], as well as the psycho-physiological factors associated with the attention impairment experienced by those with attention deficit hyperactivity disorder [20, 32, 34].

Combining Biology and Behavior In Silico

In this chapter, we view alcohol dependence and the response to alcohol dependence treatment as a recurrent bio-behavioral process developing in time. Such an approach captures the dynamics of sequential changes occurring during acquisition of alcohol dependence, successful treatment, or relapse. We will provide a rigid mathematical framework describing formally these dynamics. To do so, we first will introduce a stochastic model of behavioral and social conditioning describing the frequently random[1] effects of human behavior and social reinforcement. We then will merge this stochastic model with the deterministic model of alcohol metabolism described in Chapter "In Silico Models of Alcohol Kinetics: A Deterministic Approach". In combination, these two models provide the background for in silico interpretation of biology and behavior in their relationship to treatment effect. To represent formally behavioral and social conditioning, we will identify several sequential steps. Each step is represented by a probability distribution, and the set of these distributions across all steps regulates the feed-forward relationships of the process from internal condition to self-regulation decision. *Each person* is represented by an individual treatment effect profile, defined as the set of transition probabilities between the sequential steps of the model specific to that person. This model serves as a stochastic behavioral generator of events, each event being a drink, which is supplied as an input to an individualized model of alcohol metabolism. In other words, the in silico experiments with alcohol dependence treatment use behavioral and social parameters that serve as generators of metabolic disturbances to the system (person), which are then processed through an individualized metabolic model, thereby allowing the formal decomposition and reconstruction of the patterns of drinking behavior and their modulation by placebo or medication treatment. We will illustrate our proposed approach by re-analyzing data from a study of ondansetron for the treatment of alcohol dependence [16] and will include in the model the non-specific placebo effects that occurred before the active treatment phase of the study [32], with a special emphasis on the highly significant differences between heavy and non-heavy drinkers observed during the study.

[1] Here we need to make a distinction between the lay and scientific understanding of randomness: scientifically a random variable is a variable that can assume a set of values with certain probabilities comprising its distribution. For example, any constant is a random variable assuming its only value with probability 1 and all other values with probability 0. Other random variables have normal (Gaussian) distribution; others have uniform distribution, etc. The lay understanding of randomness typically refers to uniformly distributed variables that can assume any of multiple values with equal probabilities.

Methods

Recurrent Bio-Behavioral Process of Alcohol Dependence and Treatment

Figure 1 presents the general concept of the self-reinforcing recurrent bio-behavioral process

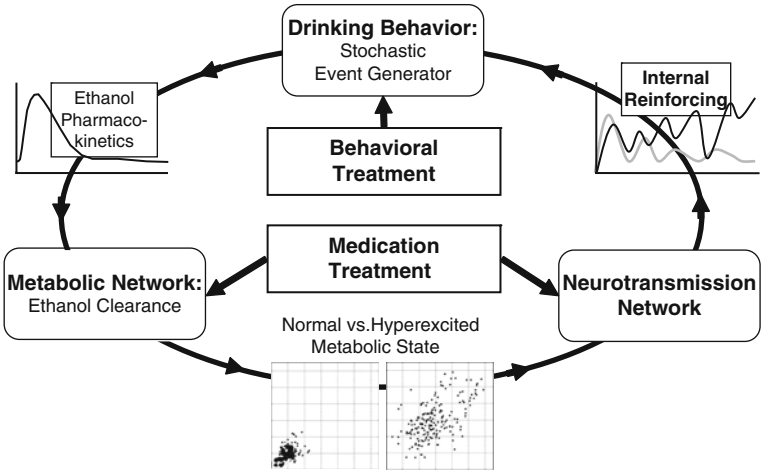

Fig. 1 Recurrent bio-behavioral process of alcohol dependence and treatment

describing the progression of alcohol dependence, its remission through medication or behavioral treatment, and potential relapse.

As presented in Fig. 1, the system (person) is represented by several blocks (components) linked via a circular pattern of sequential steps. First, a behavioral event generator actuates system disturbances (e.g., drinks), which cause metabolic disturbances that can be different for each person, depending on his or her individual parameters of alcohol pharmacokinetics. Further, when the metabolic network is subjected to recurrent stress, the intensity of stress determines whether or not a phase transition to a hyperexcited metabolic state would occur. (Metabolic phase transitions are discussed in Chapter "In Silico Models of Alcohol Kinetics: A Deterministic Approach".) A chronic hyperexcited metabolic state would influence the neurotransmission network, potentially leading to alcohol dependence. This in turn would result in a high degree of internal reinforcing (craving), which accelerates the behavioral event generator by triggering excessive drinking. Medication treatment would typically target the neurotransmission or the metabolic component of this recurrent process, while behavioral treatment would attempt to reduce the frequency of firing of the behavioral event generator. With this formal overall understanding, we shall now proceed to a mathematical description of the general components of the alcohol dependence process that would be used for its in silico representation and treatment evaluation: (1) a mathematical model of the human metabolic system specifically targeting ethanol kinetics; (2) a stochastic model of behavioral and social conditioning, and (3) a comprehensive population of in silico "subjects" spanning the observed in vivo inter-individual metabolic and behavioral differences.

In Silico Models of Ethanol Metabolism

As presented in the Introduction, several models of ethanol metabolism exist [28–30, 40]. Based on these models, we have proposed the Minimal Model of Ethanol Dynamics (see Chapter "In Silico Models of Alcohol Kinetics: A Deterministic Approach"). To properly represent oral alcohol intake, the model includes two previously unexplored compartments of the gastrointestinal tract—the stomach and gut (Fig. 2). Following the classic minimal model approach [5], we determined that we did not need to add more compartments. Further, the processes linking these compartments include one-way diffusions from the stomach and gut into the bloodstream. (Ethanol in the blood cannot diffuse back to the gastrointestinal tract.) The assumptions of

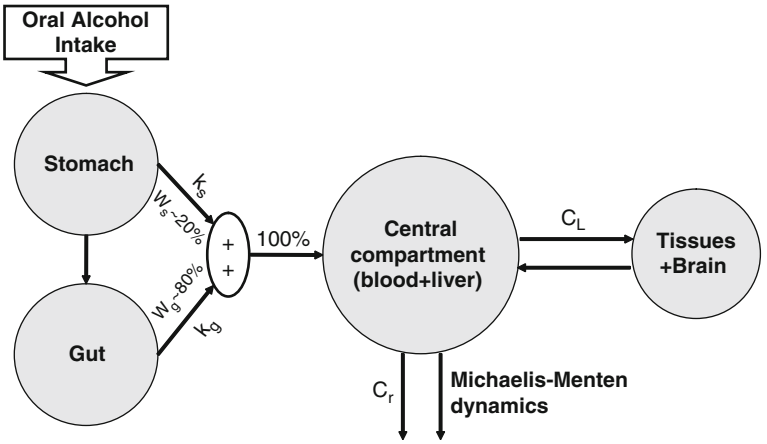

Fig. 2 The metabolic minimal model of alcohol dynamics following oral alcohol intake

the model include gastric emptying following an exponential decay with a certain half-life (rate constants k_s and k_g) and the proportion of gastric diffusion from the stomach, W_s, vs. diffusion from the gut, W_g (e.g., W_s=20% vs. W_g=80% [30]).

The alcohol clearance is represented by a Michaelis-Menten controlled reaction, e.g., an enzyme-enhanced chemical reaction with limited supply [25, 39], which has individual parameters (rate constant C_r) for each person. The mathematical details of this model and the process of its derivation and validation are discussed in Chapter "In Silico Models of Alcohol Kinetics: A Deterministic Approach".

Stochastic Model of Behavioral and Social Conditioning

Figure 3 presents the four steps of the alcohol intake self-regulation sequence introduced above: internal condition perception environmental conditioning self-regulation decision.

The basic idea behind the model of Fig. 3 is that its steps are linked by a *continuum of possible pathways*: i.e., there are a variety of possible perceptions of internal alcohol-induced neuromodulation (Step 1–Step 2); there is no single environment corresponding to a perception (Step 2–Step 3), and there is no uniquely predetermined decision arising from a specific environment (Step 3–Step 4). We, therefore, proposed a formal mathematical model in which the first three steps of this sequence are described by continuous variables, while the decisions at Step 4 are binary. In detail, the transition probabilities between Steps 1, 2, and 3 are modeled as conditional probabilities of a continuous outcome, given a continuous condition. The transition probabilities at Step 4 are conditional probabilities of a binary outcome, given a continuous condition. This reflects the clinical reality: the level of alcohol dependence, its perception, and environmental reinforcement are, by nature, continuous factors while the final decision to have or not to have another drink is binary—Yes/No. This model serves as a *stochastic behavioral generator of events*, each event being a drink that is supplied as an input to the metabolic model of Fig. 2. In other words, the in silico preclinical experiments use behavioral and social parameters that serve as generators of metabolic disturbances to the system (person), which are then processed through the metabolic model, thereby allowing the formal decomposition and reconstruction of the patterns of drinking behavior and their modulation by placebo or medication treatment. To be able to conduct in silico experiments, we need to describe our stochastic bio-behavioral model in algorithmic

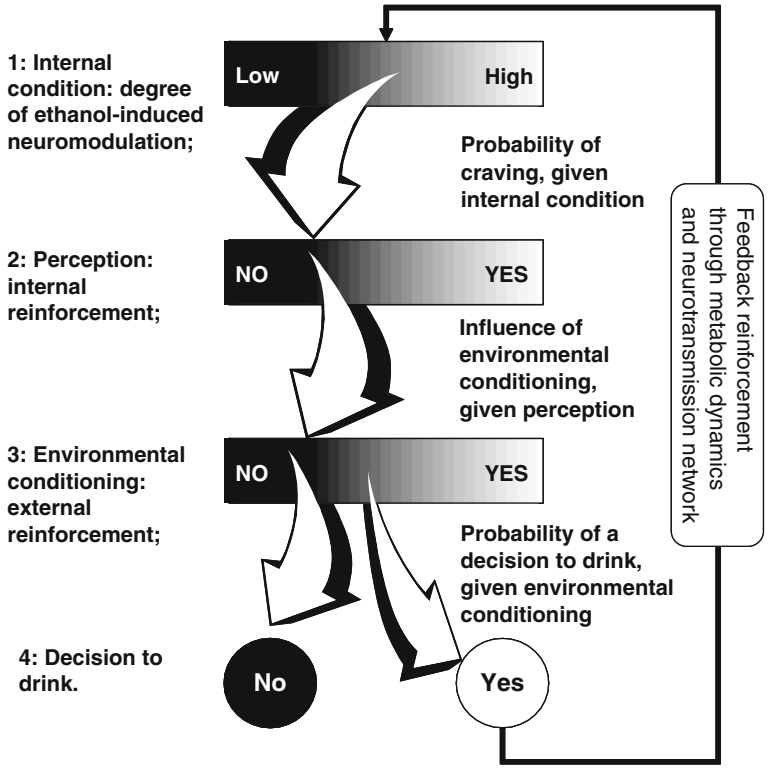

Fig. 3 Stochastic model of behavioral and social conditioning

terms. We use a discrete-time stochastic process ξ that goes through sequential steps. The basic building block of such a process is the *stochastic transition* from one step to the next, i.e., a transition that allows identical precursors at one step to have different consequences at the next, which is described by the following scheme: Suppose that at its Step n ($n = 1, 2, 3, 4$), the process $\xi(n)$ is described by a univariate or multivariate random variable x_n, having its values in some set X_n. Let S be a subset of X_n (we write $S \,\delta\, X_n$). A structure S_n of all subsets of X_n that satisfies certain conditions is called *σ-algebra* on X_n. A stochastic transition of the process ξ from X_n to its next stage X_{n+1} is defined by the conditional probabilities $P(\xi(n+1) = x_{n+1} \,|\xi(n) \in S)$ for any $x_{n+1} \in X_{n+1}$ and $S \in S_n$. The introduction of the structure S_n is a necessary mathematical complication, which makes the model capable of incorporating continuous as well as binary variables at each step.

Population of In Silico "Subjects"

Given the models in the previous sections, each person's ethanol metabolism is described via a set of several parameters (k_s, k_g, C_r, ...), and one set of fixed values of these parameters defines the metabolism of one in silico "subject". The in silico "population" is then derived by estimating the across-subject variance of these parameters and generating a number of parameter sets to span the metabolic diversity observed in vivo. Similarly, the behavioral and social specifics of each in silico "subject" are defined by an individual behavioral/social profile, e.g., by his or her own set of transition probabilities (p_1, p_2, ...) between the sequential steps of the model of Fig. 3 that are specific to that subject. The diversity of behaviors and social interactions of the in silico population is then described by diverse sets of transition probabilities.

While a comprehensive population of in silico subjects can be built only by collecting extensive data spanning the observed in vivo inter-individual metabolic and behavioral differences, to illustrate the proposed concepts we shall now use data derived from the database of a large clinical trial of ondansetron conducted at the University of Texas – Houston Health Science Center. This study had three clearly differentiated phases: (1) a 7-day baseline period, (2) a 7-day placebo treatment, and (3) several weeks of active ondansetron treatment. This sequential design made the collected data very suitable for interpretation via the sequential stochastic model of behavioral and social conditioning that is conceptualized here.

Subjects: Subjects were 321 DSM-III-R [2]–diagnosed alcohol-dependent individuals, who had: a mean age of 41.50 ± 1.34 years; a gender distribution of 73.81% male and 26.19% female; an ethnic distribution of 76.05% White, 22.10% Black, and 1.85% Hispanic and other; a social class [14] distribution of 39.25% I–III, 49.05% IV–VI, and 11.70% VII–IX, and a mean drinking level of 8.04 ± 5.80 drinks/day in the past 90 days prior to enrollment.

Procedure: This study received ethics approval from the Committee for the Protection of Human Subjects at the University of Texas – Houston Health Science Center. Subjects were recruited by newspaper or radio advertisement in the Houston area. Following recruitment, subjects were scheduled to return to the clinic to commence 1 week of placebo treatment with an inert pill to be taken twice per day for 7 days. After a study calendar week (7–10 days), subjects returned to the clinic to obtain their randomized double-blind medication (ondansetron) in doses of 1, 4, or 16 μg/kg twice daily or matching placebo for a further period of 11 weeks. For the purposes of this reanalysis, we selected the homogeneous subgroup of 87 subjects who were randomized to the 4-μg/kg twice daily ondansetron condition, and concentrated on their initial placebo period and 6 weeks of ondansetron treatment data. The complete results from this clinical trial have been published elsewhere [16].

Computational Algorithms

Given the theoretical basis established in this section, we deduce that each in silico subject is identified by two vectors: metabolic= $(k_s,\ k_g,\ C_r, \ldots.)$ and behavioral= $(p_1,\ p_2, \ldots.)$. The limits of the space occupied by these vectors are identified from literature and study data. The in silico population is, therefore, a population of vectors spanning this combined bio-behavioral space. Such an approach ensures unified numerical representation of physiological, behavioral, and social interactions, and enables the two-stage simulation procedure that we employ in this chapter:

Stage 1 – behavior: Computer-simulated idiosyncratic drinking patterns using the behavioral/social span of the set of vectors $\{(p_1,\ p_2, \ldots.)^1,\ (p_1,\ p_2, \ldots.)^2, \ldots, (p_1,\ p_2, \ldots.)^N\}$. Each of these patterns would result in a decision to drink or not to drink for each in silico subject. These decisions serve as behavioral event generators, and the generated events (i.e., drinks) are supplied to initialize the metabolic simulation model. In other words, the Stochastic Model of Behavioral and Social Conditioning creates the basic building block for in silico evaluation of treatment effect—the probability of a subject having a drink at any given point in time.

Stage 2 – metabolism: Computer-simulated idiosyncratic alcohol intoxication patterns using the span of the set of metabolic vectors $\{(k_s,\ k_g,\ C_r, \ldots.)^1,\ (k_s,\ k_g,\ C_r, \ldots.)^2, (k_s, k_g, C_r, \ldots.)^N\}$. This is done as follows: at each simulated drink for each in silico subject, this subject's metabolic model produces a specific trace in time of alcohol intoxication. The next simulated drink will come somewhere in this trace and, depending on this "individual's" specific metabolic and drinking behavior, will hit at different stages of alcohol clearance. If the simulated drinks are sufficiently infrequent so that this "individual" can fully metabolize the ingested alcohol, the system (subject) will remain in a subcritical drinking

pattern; conversely, if the drinks are too frequent, the system (subject) will transit to a super-critical pattern. Metabolic patterns are discussed in detail in Chapter "In Silico Models of Alcohol Kinetics: A Deterministic Approach".

This simulation procedure was programmed in MATLAB®, a high-level programming language widely adopted for technical computing.

Results

The following results are provided as an example of how the stochastic model can be applied.

Empirical Findings

The average number of drinks per day during the baseline period for the selected subgroup of 87 subjects was 8.01 (SD=5.28). Thus, the selected subgroup was representative of the entire study cohort, which reported an average of 8.04 (SD = 5.80) drinks/day for the 90 days prior to recruitment. During the placebo treatment period, the alcohol consumption in the selected subgroup was reduced to 5.03 (SD=4.64) drinks/day, followed by a further gradual reduction to 1.88 (SD=2.21) drinks/day after 6 weeks of active ondansetron treatment (F=56.1, p<0.0001) using repeated-measures analysis of variance. (This empirical pattern of passive and active reduction in drinking is included in Fig. 4.)

During the baseline period, 54 subjects (62%) in the illustrative subgroup were classified as heavy drinkers, consuming ≧5 drinks/day and ≧4 drinks/day for men and women, respectively. This classification had a significant ($F = 20.1$, $p < 0.001$) effect on the outcome from non-specific placebo treatment: the number of drinks per day in heavy drinkers changed from 10.70 (SD=5.02) at baseline to 6.06 (SD=5.31) at the end of the placebo period; in non-heavy drinkers, there was no change: 3.61 (SD=1.06) drinks/day at baseline vs. 3.65 (SD=2.94) drinks/day at the end of the placebo period. The difference between heavy and non-heavy drinkers became negligible during the first week

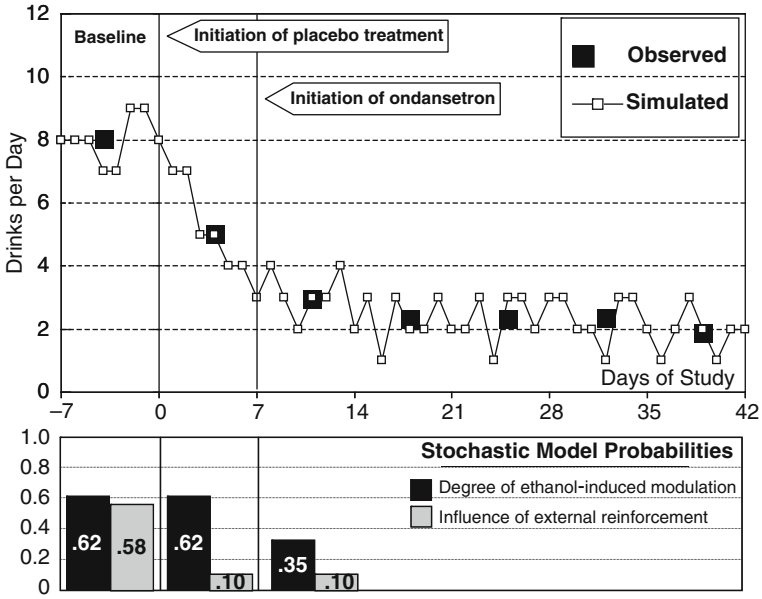

Fig. 4 Model-predicted and observed effect of placebo and ondansetron treatment

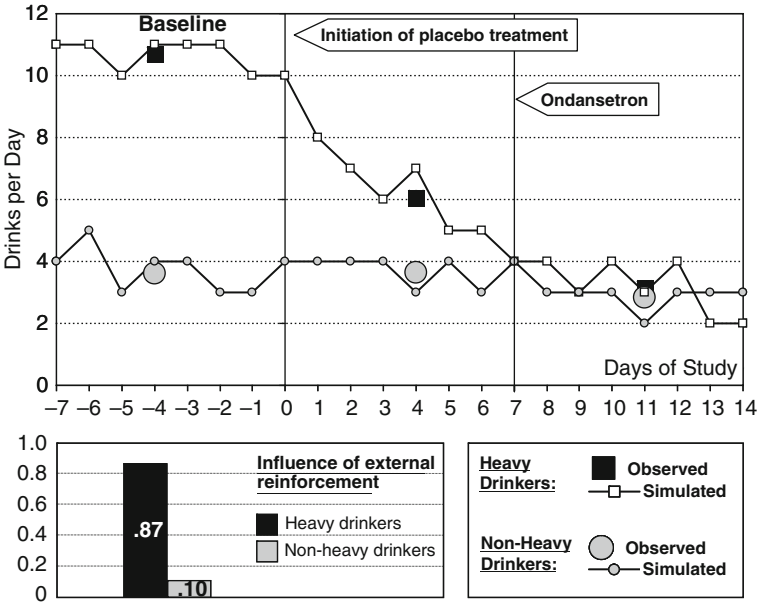

Fig. 5 Model-predicted and observed treatment effect in heavy and non-heavy drinkers

of active ondansetron treatment and remained negligible throughout the rest of the observation period. (The empirical patterns of these two groups are included in Fig. 5.)

In Silico vs. In Vivo Responses to Placebo and Ondansetron Treatment

To evaluate the closeness of in silico prediction to observed clinical outcome, we compared the computer-simulated and clinically observed patterns of treatment response. Throughout the simulation, we kept the metabolic parameters (Fig. 2) of the simulated "subjects" constant and used the stochastic model of Fig. 3 to decompose the observed drinking patterns into two sections explained by different model steps:

1) The response to initial placebo treatment was attributed to the influence of study enrollment, which was modeled as a reduction of the probability for environmental conditioning (Step 3 in Fig. 3) from its baseline value of 0.58–0.10. Because this effect occurs relatively quickly (within a week) and no active medication was provided, no other system changes were anticipated, such as feedback down-regulation through modulation of the neurotransmission system.
2) The response to ondansetron was attributed to neurotransmission changes influenced by the degree of ethanol-induced neuromodulation. This was modeled via reduction of the probability of Step 1 from its baseline value of 0.62–0.35.

Figure 4 compares the results of this in silico treatment experiment to the clinically observed treatment effects. Black squares represent the empirical pattern of baseline drinking (Days –7 to 0) and the pattern of drinking reduction due to placebo (Days 1 to 7) and ondansetron treatment (Days 8 to 42). The in silico-generated pattern (black line) follows closely these empirical observations, confirming that in silico experiments could provide realistic representation of treatment effect. The lower panel of the figure includes the change in environmental reinforcement probability, which is responsible for the "placebo" effect, and the reduction in the degree of ethanol-induced modulation describing the effect of ondansetron.

Modeling Idiosyncratic Treatment Response

The empirical results presented above suggest highly significant differences between heavy and non-heavy drinkers in their responses to placebo treatment, followed by a regression into a common pattern of response to ondansetron. Figure 5 focuses on the first three weeks of observation, where these idiosyncratic differences were most evident [32]. Following the assumption that the placebo effect is primarily due to reduced environmental reinforcement, we model the difference between these two groups of subjects via different probabilities at Step 3.

Indeed, environmental reinforcement probabilities of 0.87 and 0.10 for heavy and non-heavy drinkers allow for excellent simulated approximation of the observed empirical patterns of placebo response. (Note that the overall baseline probability of environmental reinforcement, 0.58, is the weighted sum of the probabilities in the two subject subpopulations.) As is empirically established and evident from Fig. 5, non-heavy drinkers (gray circles) were non-responsive to the effect of study enrollment. In contrast, heavy drinkers (black squares) appeared to be vulnerable to environmental conditioning effects, and, therefore, their response to placebo treatment was highly significant. Further, these two subject subpopulations were approximately equally responsive to the effect of medication, which explains the similarities in their patterns during the period of active ondansetron treatment. The environmental probabilities used for simulation are included in the bar graph in the lower section of Fig. 5.

Conclusions

The principal utility of in silico modeling efforts is three-fold. First, models allow the measurement of latent factors that cannot be observed directly but that frequently predetermine the behavior of a biosystem. A classical example is the Minimal Model of Glucose Kinetics suggested by Bergman and Cobelli almost 30 years ago to measure insulin resistance in health and diabetes [5]. Second, models allow for computer simulation and in silico studies involving virtual "subjects" rather than real people. Such in silico trials can serve as cost-effective precursors, guiding expensive and time-consuming in vivo investigations by ruling out ineffective treatment approaches. For example, a recently developed simulator of the human metabolic system has received Food and Drug Administration approval and recognition for the preclinical testing of control strategies in artificial pancreas studies [21]. Third, when a system (person) is adequately modeled, its control via engineering means becomes possible. Examples include cardiac pacemakers and, more recently, the artificial pancreas emerging as a means for control of blood glucose levels in diabetes.

The basic premise of in silico modeling of alcohol dependence is that alcohol dependence and the outcome of its treatment result from the action of a stochastic self-reinforcing bio-behavioral process, combined with each individual's metabolic specifics. In other words, the interplay between biology and behavior, which develops in a certain time frame, would trigger (with a certain probability) metabolic and neurobiological changes that in turn would reinforce uncontrolled or poorly controlled drinking behavior. Treatment would, therefore, be expected to modulate, attenuate, or reverse these changes with a certain level of probability. Such a quantitative approach has several potential advantages:

First, the overall treatment effect can be decomposed into meaningful steps, with each step serving as a target for a specific treatment. For example, Step 1 (internal condition) would reflect pharmacological treatment, while Step 3 (environmental conditioning) would reflect the placebo effect of study enrollment, or any type of socio-behavioral intervention. Such a decomposition of the treatment effect allows for better understanding of the time course

of treatment and the relationships among the various treatment components.

Second, the proposed model would allow for individualized treatment tailoring. For example, it appears that in heavy drinkers, environmental conditioning is a significant predictor of treatment response, while in non-heavy drinkers the effect of the environment is minimal. The effect of ondansetron is similar in the two groups but occurs faster in non-heavy drinkers.

Third, one of the advantages of a model-based investigation is that separate steps can be estimated in different studies and then the results can be integrated via the model. For example, neurotransmission or physiological parameters can be evaluated in animal studies and then related to human behavior parameters. That is, the proposed concept is *species invariant*, capable of bridging results from human and animal studies.

Most importantly, the stochastic process described here serves as an event generator of behavioral disturbances (i.e., drinks), which in turn influence the internal condition. Thus, the initial entry conditions for a person change with each repetition of the cycle presented in Fig. 1. This recurrence provides powerful tools for in silico analysis of the progression of alcohol dependence and treatment response, taking into account both biological and environmental factors.

To illustrate this concept, we conducted in silico experiments that reproduced patterns observed in a clinical trial of ondansetron. It became evident that placebo and ondansetron, as well as their interaction, contribute to the overall therapeutic response. There might, however, be other nonspecific effects that can affect clinical outcome and that we need to discover. Hence, the in silico model presented here is less developed than the metabolic models adopted for the study of diabetes. Nevertheless, this text represents an initial step to introduce the concept of in silico analysis to the area of alcohol dependence research. Because the first results appear promising and explanatory for the observed phenomena, we think that with the accumulation of data (both existing and from future clinical studies), in silico analysis would find its place in the arsenal of tools to help decipher the mechanisms that govern treatment response among alcohol-dependent individuals.

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Dynamic and Systems-Based Models for Evaluating Hypotheses Related to Predicting Treatment Response

Scott F. Stoltenberg

Contents

Introduction

Approaches to treating alcohol dependence are heterogeneous, ranging from group therapy in 12-step programs to pharmacotherapy. Such treatment heterogeneity is a reflection of client heterogeneity that results from the complex biopsychosocial architecture underlying multiple alcoholism types with different developmental trajectories [39].

While each treatment approach is successful in reducing the number of drinking episodes and the amount of alcohol consumed per episode, no single treatment approach is superior to the others in all cases. One size does not fit all when it comes to treatment for alcohol dependence. If no single alcoholism treatment is equally effective for all individuals who seek treatment, is there some way to identify those who will respond best to a particular treatment? In other words, is there some way to *personalize* treatment for alcohol dependence? While the relevant individual differences among treatment seekers have not been fully elucidated, it is likely that at least some of those relevant individual differences result from genetic variation in mechanisms crucial to etiology or to treatment response. In this sense, alcoholism treatment providers are in the same situation as much of the medical profession in the quest for personalized medicine. Also, while there is much to anticipate about developments in the area of personalized medicine, progress has not kept pace with the clamor. As interest intensifies in personalized medicine, it seems prudent to consider the ways in which investigators will endeavor to make sense of often conflicting empirical results in an effort to understand complex biological systems across levels of analysis from gene to physiological systems to treatment outcome. In this chapter, an approach is presented that focuses on genetic variation in neurotransmitter systems and utilizes dynamic system modeling to understand better the contribution of genetic variation to pharmacological treatment for alcohol dependence.

The goals of this chapter are to: (1) discuss personalized treatment and pharmacogenetics as it applies to alcoholism, (2) describe the Johnson Model of individual differences in response to pharmacological treatment for alcoholism, (3)

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_64,

discuss a dynamic control system model developed to examine the Johnson Model, and (4) discuss the potential for the use of control system modeling to test hypotheses regarding the pharmacogenetics of alcoholism.

Personalized Alcoholism Treatment

Substantial efforts to identify personal traits that can inform choice of alcoholism treatment have not yet borne fruit. The most notable of such efforts is Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity). Project MATCH was a large, multi-site psychotherapy trial that ran for over a decade and enrolled over 1,700 clients [22]. It was designed to test 21 matching hypotheses by assigning clients randomly to three treatment groups—cognitive behavioral therapy, motivational enhancement therapy, or 12-step facilitation—and measuring the associations among matching characteristics and multiple alcohol outcomes across five follow-up periods [4]. Project MATCH examined both primary (alcohol involvement, cognitive impairment, gender, meaning seeking, motivation, psychiatric severity sociopathy, support for drinking, and Babor's Typology) and secondary (alcohol dependence, anger, antisocial personality disorder, interpersonal dependency, Axis I psychopathology, Alcoholics Anonymous history, readiness to change, religiosity, self-efficacy, and social functioning) matching hypotheses [15].

Clients in each of the Project MATCH treatment conditions showed rates of improvement, as measured by drinks per drinking day and abstinent days, similar to other treatment studies [22]. Disappointingly, Project MATCH did not succeed at identifying personal traits associated with significant differences in treatment outcomes for the three alcoholism psychotherapies. Client anger, psychiatric comorbidity, and level of alcohol dependence were some of the client traits that provided limited prognostic utility [22].

Recently, a large trial to test alcoholism treatment matching hypotheses was conducted in the United Kingdom [34]. In the UK Alcohol Treatment Trial, investigators conducted 3- and 12-month follow-ups on clients ($n = 742$ at baseline) who were assigned to either motivational enhancement therapy or social behavior and network therapy. The matching hypotheses in the UK study included: (1) size of social network, (2) readiness to change/negative expectancies, (3) psychiatric severity, (4) anger, and (5) degree of alcohol dependence. The investigators found no evidence for matching effects on these client characteristics to the two types of treatment studied.

While this brief review of personalized alcoholism treatment is not exhaustive, it does provide powerful evidence that easily observable client characteristics do not appear to be useful for matching individual clients to particular psychosocial treatments. Much of the excitement regarding personalized medicine, however, has to do with a better understanding of the biological underpinnings of disease and disorder, as well as the promise of applying this understanding to improving pharmacotherapy by informed dosage practices, increased response rates, and a reduction in the number and severity of side effects. This area, known as pharmacogenetics, is the major thrust of personalized medicine and is reviewed in the next section.

Pharmacogenetics

Pharmacokinetics is an area of focus within pharmacogenetics that studies how genetic differences influence the bioavailability of an agent [19]. Individual differences in the rate of an agent's metabolism produce variability in treatment response and may be crucial in serious or fatal adverse reactions to the medication [27]. The cytochrome P-450 enzymes are located on organelles in liver cells and are one of the most studied components in agents' metabolism. Approximately 7% of Caucasians can be classified as "poor metabolizers" on the basis of their

genotype at the CYP2D6 polymorphism, which is known to be involved with the breakdown of many psychotropic medications [27]. The end result of metabolizing psychotropic agents at a slower than average rate is that higher levels of the agents remain in the bloodstream, effectively raising the dose to levels that could potentially be harmful.

Pharmacodynamics is an area of focus within pharmacogenetics that studies the ways in which genetic differences in the proteins at which medications act produce individual differences in treatment response [19]. An example of pharmacodynamic research that is important to psychiatry is the examination of the association between genetic variation in the gene that codes for the serotonin transporter and the response to depression treatment with selective serotonin reuptake inhibitors. Because reuptake of serotonin from the synapse via the serotonin transporter is the primary mode for inactivating serotonin's actions and because the serotonin transporter is the primary target of selective serotonin reuptake inhibitors, it is logical to assume that genetic variation that influences serotonin transporter function would also affect efficacy of selective serotonin reuptake inhibitor treatment.

For more than a decade, the most studied genetic polymorphism in psychiatric or behavior genetics has been the so-called 5-HTTLPR insertion/deletion in the regulatory region located upstream of the structural gene that codes for the serotonin transporter [32]. A recent search on PubMed for the term "HTTLPR" resulted in over 500 hits. The polymorphism is both functional and common, which makes it an excellent candidate for association studies. The "L" allele is a high-functioning allele that results in 2–3 times higher transcriptional efficiency than the "S" allele [20]. Recently, investigators have been using functional magnetic resonance imaging to study associations between the 5-HTTLPR genotype and the activity of different brain regions. Specifically, amygdala activity in response to fearful or threatening facial expressions is greater in individuals who carry at least one S allele compared with those with the LL genotype [11]. In addition, the functional connectivity between the amygdala and the prefrontal cortex is weaker in those who carry an S allele, which suggests that those individuals may be less able to dampen amygdala activity following an assessment of the potential threat [11].

Because the serotonin transporter is the primary target of selective serotonin reuptake inhibitors, it is of interest whether the 5-HTTLPR polymorphism is associated with a different response to selective serotonin reuptake inhibitor treatment. In a recent meta-analysis of 15 studies of selective serotonin reuptake inhibitor treatment for depression including a total of 1,435 subjects, the L allele was associated with better treatment outcomes [29].

In addition to response to selective serotonin reuptake inhibitor treatment for depression, the 5-HTTLPR polymorphism is also associated with differences in the personality trait of neuroticism [28], suicide [2], impulse control disorders [21], and eating disorders [8]. Importantly, in the context of the present chapter, a meta-analysis of 17 published studies examining the association between 5-HTTLPR polymorphisms and alcohol dependence showed that the S allele was associated with an increased risk for alcohol dependence and that this association was strongest in the presence of psychiatric comorbidity [6].

The pharmacogenetics of alcoholism presents a complicated picture with a plethora of molecular targets for both ethanol and the medications used in alcoholism treatment. An examination of the pharmacokinetics of alcohol reveals genetic variants in ethanol-metabolizing enzymes that are associated with different levels of risk for alcohol dependence and that vary across ethnic groups [5]. The well-studied enzymes in ethanol metabolism, alcohol dehydrogenase and aldehyde dehydrogenase, clearly affect the bioavailability of ethanol and a toxic by-product, acetaldehyde. Alcohol dehydrogenase converts ethanol to acetaldehyde, which is then quickly converted by aldehyde dehydrogenase to acetate. If these two conversions take place at similar rates, levels of the toxic acetaldehyde stay rather low in the blood. However, if the alcohol

dehydrogenase enzyme is "fast" or if the aldehyde dehydrogenase enzyme is "slow", toxic levels of acetaldehyde result. The medication disulfiram (Antabuse®) inhibits aldehyde dehydrogenase, and when an individual drinks alcohol while taking disulfiram, severe nausea and other aversive symptoms result. This reaction is similar to the "flushing" response that occurs when individuals with one or two copies of a mutant version of aldehyde dehydrogenase-2 that produces a non-functioning version of the enzyme drink alcohol.

The pharmacodynamics of alcohol is complicated by its many targets. Ethanol facilitates the activity of gamma-aminobutyric acid-A receptors, inhibits the activity of *N*-methyl-*D*-aspartate glutamate receptors, and, at high doses, inhibits many voltage-sensitive calcium channels. Ethanol also has direct influences on neurotransmission via serotonin, dopamine, and norepinephrine neurons and modulates opioid neuropeptides [17]. The endogenous opioid system is implicated in the rewarding effects of alcohol consumption and in alcohol craving [35]. Genetic variation at these many sites of action is likely to be responsible for variation in responses to ethanol exposure.

Both Project MATCH and the UK Alcohol Treatment Trial focused solely on psychosocial therapies and excluded pharmacotherapy to simplify the designs of such large complicated studies [4, 34]. Clearly, there are biologically based individual differences that are likely to influence treatment outcome. Interestingly, the Project MATCH investigators have recently begun to explore how variation in specific genes may prove to be predictive of drinking behavior and of the outcome of psychosocial treatment for alcoholism [1]. A "high-risk" genotype of the GABRA2 gene (A/A) was associated with less variability in treatment outcome and higher risks for drinking and heavy drinking.

The pharmacodynamics of agents used in alcoholism pharmacotherapy is also of interest. Examples of medications used for the treatment of alcoholism include: opiate antagonists (e.g., naltrexone); medications that interact with glutamate (e.g., acamprosate); modulators of both glutamate and gamma-aminobutyric acid systems (e.g., topiramate); agents that influence serotonin uptake (e.g., selective serotonin reuptake inhibitors), and those that modulate serotonergic function and, as a consequence, dopaminergic neurotransmission (e.g., ondansetron). There are known genetic variants for neurotransmitter system components (e.g., receptors and enzymes) in all of these systems in which medications to treat alcoholism might act.

In this section, I provide a general description of pharmacogenetics along with a more specific discussion of the pharmacogenetics of alcohol and of medications used to treat alcoholism. It is clear that there are sufficient pharmacogenetics targets to begin examining the best candidates empirically. In the next section, a pharmacogenetics theoretical model is described that takes important steps toward the goal of better understanding how genotypes can be used to identify the most effective pharmacotherapy for alcoholism treatment.

The Johnson Model

Because both the serotonin and dopamine neurotransmitter systems are intimately involved with alcoholism in ways that are complex and not yet fully understood, theoretical models focusing on the impact of genetic variation at the level of the synapse may provide a productive approach to understanding better the individual differences in response to alcoholism treatment. Such work combines empirical data from several different areas of study, such as human alcoholism treatment trials, candidate gene association studies, and pharmacological studies with both human and non-human animals. Alcoholism treatment trials can provide information regarding subjects' characteristics that are predictive of treatment response or of etiological significance. Candidate gene association studies can identify allelic variants associated with different alcohol phenotypes. The best of these candidates also will produce functional differences in the physiological systems

of interest and are often targets of pharmacological agents. Pharmacological studies provide evidence regarding the effects of agonists and antagonists on system function and on alcohol phenotypes. The development of theoretical models that attempt to elucidate the impact of variation at functional candidate genes on the response to pharmacological treatment for alcoholism is an important stage in a systematic approach to personalized alcoholism treatment. Johnson and Ait-Daoud [14] presented a theoretical model that was elaborated upon by Johnson [12] and aimed at better understanding the role of genetic variation in the serotonin transporter promoter region (5-HTTLPR) and differential response to two pharmacological treatments for alcoholism (hereafter called the Johnson Model). In this section, I provide details of this model, on which a subsequent control system model was based.

The development of the Johnson Model was motivated by the desire to understand better the contribution of allelic variation at components of neurotransmitter systems to individual differences in pharmacological alcoholism treatment response [12, 14]. As such, these efforts should constitute a pharmacodynamic approach because the genetic differences examined are hypothesized to influence the proteins at which the medications act [19].

Figure 1 presents the Johnson Model schematically. The main premise of the model is that relative serotonergic hypofunction, a result of efficient reuptake for individuals with the 5-HTTLPR LL genotype, produces an upregulation of serotonin-3 receptors and an enhanced "urge to drink". This heightened urge to drink is the result of dopaminergic activation due to the action of serotonin at postsynaptic serotonin-3 receptors on dopaminergic neurons.

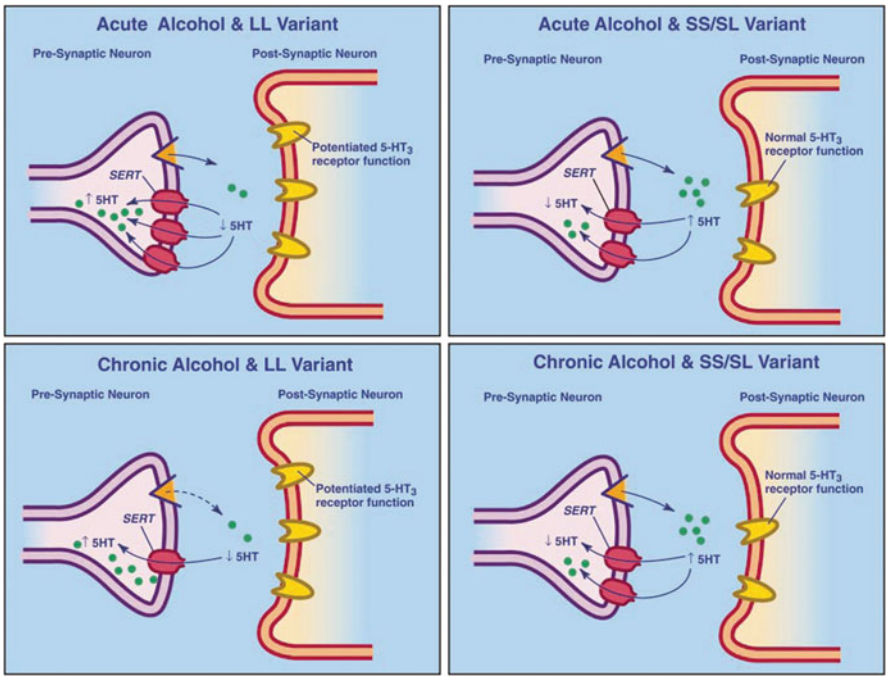

Fig. 1 The Johnson Model is a theoretical model, derived from empirical observations, that hypothesizes the mechanism of how variation in 5-HTTLPR genotype is associated with differences in the effectiveness of selective serotonin reuptake inhibitor and ondansetron alcoholism treatment. The LL genotype of 5-HTTLPR produces a hypodopaminergic state and potentiated serotonin-3 (5-HT_3) receptors on dopaminergic neurons, which results in an enhanced "urge to drink". 5HT, serotonin; SERT, serotonin transporter. (Figure reprinted with kind permission from Springer Science+Business Media: Johnson and Ait-Daoud [14], p. 335.)

Several lines of empirical evidence led to the Johnson Model (see references in Johnson [12] and Johnson and Ait-Daoud [14]):

1. The S allele of the 5-HTTLPR polymorphism is a common variant that is dominant to the L allele and reduces serotonin reuptake by approximately one-third via a reduction in the number of serotonin transporter proteins produced (i.e., it significantly influences serotonin neurotransmission).
2. Selective serotonin reuptake inhibitors bind to the serotonin transporter and block serotonin reuptake, enhancing serotonin neurotransmission.
3. Response to selective serotonin reuptake inhibitor treatment for alcoholism is better for those with late-onset alcoholism than for those with early-onset alcoholism.
4. Serotonin-3 receptors are located on mesocorticolimbic dopamine-containing neurons and are involved in the rewarding effects of alcohol.
5. Ethanol potentiates the activity of serotonin-3 receptors.
6. Response to alcoholism treatment with the serotonin-3 receptor antagonist ondansetron is better for those with early-onset alcoholism than for those with late-onset alcoholism.
7. Acute alcohol exposure increases serotonin function.
8. Chronic alcohol exposure decreases serotonin function.

The primary focus of the Johnson Model was to explain the observation that for individuals with early-onset alcoholism (assumed to be predominantly of the LL genotype), alcoholism pharmacotherapy with ondansetron was more effective than treatment with selective serotonin reuptake inhibitors. The efficacy of ondansetron was hypothesized to be due to its presumed effectiveness at reducing the rewarding effects of alcohol (via a reduction in dopaminergic activation due to serotonin-3 antagonism). The relative effectiveness of selective serotonin reuptake inhibitor pharmacotherapy for individuals with late-onset alcoholism (assumed to be predominantly carrying one or more S alleles) was hypothesized not to be due to serotonin-3 mechanisms. Rather, individuals with late-onset alcoholism and chronic selective serotonin reuptake inhibitor treatment were hypothesized to experience an "anti-rewarding effect" as a result of drinking alcohol because of a long-term inhibition of dopaminergic activity [12].

Because of the large number of components involved in the Johnson Model and the rather complex nature of the interactions among them, a systems-based model provides a platform for systematic testing of the model's hypotheses. In the next section, I use a dynamic systems-based model to examine the Johnson Model.

A Dynamic Systems-Based Model

Although control system modeling has a relatively long history, with Wiener's influential book on cybernetics first published in 1948 [37], it has not been widely used in behavior genetic analysis. However, with an increasing focus on the mechanisms of heredity-behavior relations made possible by advances in molecular genetics and neuroscience, it seems that control system modeling is poised to catalyze significant contributions to our understanding of how genes influence behavior.

The Johnson Model is well suited for implementation as a control system model because it considers the system as a whole that can be described by the levels or rates of specified parameters [9]. Levels are sometimes referred to as "stocks" or "states" and rates as "flows". For example, in the Johnson Model, the level of serotonin in the synapse can be considered a stock and the rate of serotonin reuptake determined by 5-HTTLPR genotype can be considered a flow. Control system models are dynamic models, in that they utilize difference or differential equations to account for change over time, deriving subsequent states of the system from the current state [9]. Control system models are particularly useful for modeling the influence

of genetic differences or of pharmacological intervention on neurotransmitter system function where feedback loops are known to occur and where epistatic interaction plays a role [31, 33]. It is important to keep in mind that these kinds of control system models are not intended to be exact replicas of the system being simulated. These models describe qualitative behavior of the actual system under varied parameter states that can simulate genetic variation or pharmacological manipulation. An important goal of the control system model is to help to identify leverage points—that is, components of the system that are key in controlling system function. Therefore, a complete catalog of every component of the system is not necessary. Similarly, in control system modeling there is little focus on scaling every parameter so that biological realism is obtained. On the contrary, one often works with standardized parameters so that matters of scale are de-emphasized. One is more concerned with the functional relations among the parameters than with the relative lack of biological realism.

One of the most favorable features of control system modeling using systems of differential equations is that when these equations are solvable and produce unique solutions, the toolkit of the mathematician can be brought to bear [33], such as fast, general-purpose differential equation solvers such as Berkeley Madonna [38]. Most importantly in the context of pharmacogenetics, one can examine the controllability of the system under study. That is, it may be possible to adjust the parameters of a system to move its functioning from an undesirable state to a desirable one [33]. In the context of the serotonin system, there is substantial empirical evidence that it is possible to manipulate system parameters either by the use of medications or by genetic techniques (e.g., constructing "knockout" lines of mice) to alter serotonin system function. Although a complete understanding of the dynamics of the serotonin system has not yet been achieved, the use of control system modeling may enable the systematic variation of parameters in silico to achieve empirically based controllability of the system. In other words, dynamic systems models such as this one may provide us with the platform on which we can build an empirically derived understanding of how to adjust system parameters with medication to move an individual's serotonin function into a desired state.

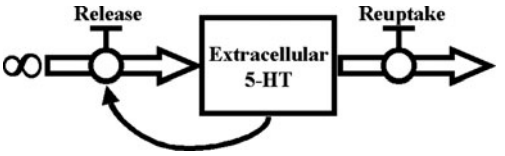

Fig. 2 A "stock and flow" diagram of a control system model of serotonin (5-HT) function. The stock of extracellular serotonin is increased by presynaptic neural activity (i.e., release) and is decreased by serotonin transporter-mediated reuptake. When extracellular levels of serotonin are above some threshold, somatodendritic autoreceptors (serotonin-1A) inhibit neural firing via a feedback mechanism. When presynaptic neural firing is enabled, terminal autoreceptors (serotonin-1B) control the serotonin release amount. The infinity sign represents an infinite reservoir for the production of serotonin

The model to test the Johnson Model [30] arose out of efforts to model presynaptic regulation of the serotonin system [31]. In that base model, presynaptic regulation of serotonin function was hypothesized to be controlled by three components, each of which varied genetically (see Fig. 2). These components included: the serotonin transporter that removes serotonin from the extracellular space via reuptake; the somatodendritic autoreceptor (serotonin-1A) that inhibits neural firing and, therefore, serotonin release, and the terminal autoreceptor (serotonin-1B) that influences the amount of serotonin released. Each of these components was hypothesized to have a "high" and a "low" functioning variant. The main outcome variable for this model of presynaptic regulation is the level of extracellular serotonin. Another outcome that can be considered is the firing rates of serotonin neurons.

As previously mentioned, the gene that codes for the serotonin transporter contains a variant in the upstream regulatory region (5-HTTLPR) that does not affect the structure of the serotonin transporter, but does affect the number of serotonin transporters produced. The S allele acts

in a dominant fashion so that individuals with one or two copies (i.e., SS or SL, the "low" functioning variant in the model) produce fewer serotonin transporters than those homozygous for the L allele (the "high" functioning variant in the model) [20]. The most commonly prescribed class of antidepressants, the selective serotonin reuptake inhibitors, bind to the serotonin transporter and block the transport of serotonin from the extracellular space to the intracellular space, where it can be either repackaged into vesicles for re-release or catabolized by monoamine oxidase. Lines of mice that have the structural gene for the serotonin transporter knocked out have been widely studied and have much to contribute to our understanding of pathways from gene to behavior [7, 23, 24].

The serotonin-1A somatodendritic autoreceptor is a key controller of the firing of serotonin-containing neurons [10]. When levels of extracellular serotonin are elevated, the serotonin-1A receptor inhibits neural firing. This type of feedback inhibition resembles the functioning of a thermostat that sends a signal to the furnace to turn off when the room temperature exceeds some set point. Such feedback mechanisms are well modeled with control system models. A recent study reported that a single nucleotide polymorphism in the serotonin-1A gene may be functional and is associated with the response to selective serotonin reuptake inhibitor treatment for depression [16]. Both agonists and antagonists for the serotonin-1A receptor have been identified and have been widely used to study the function of the receptor. Lines of mice have been developed in which the structural gene for the serotonin-1A receptor has been knocked out. These serotonin-1A knockout mice exhibit elevated anxiety-like behaviors when compared with mice with functioning serotonin-1A genes [26].

The serotonin-1B terminal autoreceptor controls the amount of serotonin released when neural firing occurs [10]. Therefore, the serotonin-1B receptor can be considered a second controller of serotonin release that has its effect only after the primary controller (serotonin-1A) has enabled neural firing (i.e., not inhibited firing). Both agonists and antagonists of the serotonin-1B receptor have been developed and have been used to study the function of the receptor. Lines of mice have been developed with the structural gene for the serotonin-1B receptor knocked out. These serotonin-1B knockout mice drink more alcohol and attack intruders more quickly and vigorously than wild type mice [3]. There is also evidence in human populations that genetic variation in the serotonin-1B gene is associated with early-onset alcoholism [18].

The starting point to simulate the Johnson Model was a relatively simple control system model of presynaptic serotonin function that focused on extracellular serotonin level and rates of serotonin firing [31]. The model included three main components: the serotonin transporter, the somatodendritic autoreceptor (serotonin-1A), and the terminal autoreceptor (serotonin-1B; see Fig. 2). To test the Johnson Model, only the function of the serotonin transporter was varied [30]. The functioning of the two autoreceptors was held constant because these controlling system components were not part of the Johnson Model. The functioning of the serotonin transporter was modeled as having a "high" and a "low" functioning variant to correspond to the LL and S/_ (i.e., SS or SL) genotypes, respectively.

From this basic model, extensions were added to accommodate the Johnson Model (see Fig. 3). Sixteen separate conditions were modeled that consisted of two levels of each of the following parameters: 5-HTTLPR genotype, alcoholism status, acute drinking status, ondansetron treatment status, and selective serotonin reuptake inhibitor treatment status (see Table 1).

In the model, the flow of serotonin into the extracellular space (i.e., release) was primarily influenced by acute drinking status. In the acute drinking conditions, the release of serotonin was doubled.

In the model, reuptake was primarily dependent on serotonin transporter functioning, which was affected by 5-HTTLPR genotype and selective serotonin reuptake inhibitor treatment status and, for the LL genotype condition, chronic alcoholism status. For the LL genotype, the reuptake

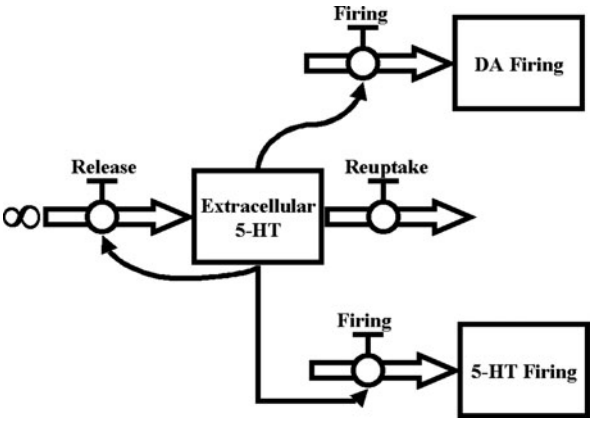

Fig. 3 A "stock and flow" diagram of the Johnson Model. This is an extension to the basic model presented in Fig. 2, with additions of counters to track both dopamine (DA) and serotonin (5-HT) firing rates. Both of these firing rates are dependent on extracellular serotonin level. The infinity sign represents an infinite reservoir for the production of serotonin

Table 1 Parameter values for conditions tested by Stoltenberg [30]

Condition	Genotype	Alcoholism	Drink	Selective serotonin reuptake inhibitor	Ondansetron
L	0.90	1.00	0	1.00	0
LD	0.90	1.00	1	1.00	0
LA	0.90	0.55	0	1.00	0
LAD	0.90	0.55	1	1.00	0
LAO	0.90	0.55	0	1.00	1
LAOD	0.90	0.55	1	1.00	1
LAS*	0.90	0.55	0	0.20	0
LAS*D	0.90	0.55	1	0.20	0
S	0.30	1.00	0	1.00	0
SD	0.30	1.00	1	1.00	0
SA	0.30	1.00	0	1.00	0
SAD	0.30	1.00	1	1.00	0
SAO	0.30	1.00	0	1.00	1
SAOD	0.30	1.00	1	1.00	1
SAS*	0.30	1.00	0	0.20	0
SAS*D	0.30	1.00	1	0.20	0

L LL genotype, *S* S/_ genotype, *D* drink condition, *A* chronic alcoholism, *O* ondansetron treatment, *S** selective serotonin reuptake inhibitor treatment

rate was set at 0.90, whereas for the S/_ genotype, the reuptake rate was set at 0.30. The selective serotonin reuptake inhibitor treatment condition further reduced reuptake by a multiplier, 0.20. Additionally, for those with the LL genotype, chronic alcoholism further reduced the reuptake rate by a multiplier, 0.55. So, for example, the LL, chronic alcoholic on selective serotonin reuptake inhibitor treatment had a reuptake rate of $0.90 \times 0.55 \times 0.20 = 0.099$. That is, 9.90% of the extracellular serotonin was removed at each time step of the model.

A simple counter was implemented to track the serotonin firing rate. The level of extracellular serotonin affected the serotonin firing rate. When the extracellular serotonin level exceeded a dynamic threshold, firing was inhibited (see Stoltenberg [31] for details about firing inhibition mediated by the serotonin-1A autoreceptor).

In general, the firing of dopaminergic neurons mediated by serotonin-3 receptor activation was modeled as a binary variable (i.e., either fire or not fire) with probabilities that were inversely proportional to the level of extracellular serotonin. However, when extracellular serotonin levels were very low, the probability of dopamine firing was increased, to model

the potentiation or upregulation of serotonin-3 receptors. Ondansetron treatment status reduced the probability of dopamine firing by half.

One of the first steps in the modeling process subsequent to model development is model validation. It is important to test whether the model produces output that is consistent with expectations. For example, the LL genotype should produce lower levels of extracellular serotonin than the S/_ genotype because the LL genotype has relatively higher reuptake rates, which should produce a relative reduction in serotonin levels in the synapse. For the Johnson Model simulation, we can identify the S/_ genotype as the standard (i.e., 100%) and the simulation produces extracellular serotonin levels for the LL genotype that are 39% of those produced by the S/_ genotype. Similarly, modeling a selective serotonin reuptake inhibitor should produce increases in extracellular serotonin levels because selective serotonin reuptake inhibitor treatment reduces reuptake rates. In the simulation, selective serotonin reuptake inhibitor treatment for the S/_ condition raised serotonin levels to 283% of baseline. A similar increase was observed in the LL genotype condition. Ondansetron treatment should reduce dopamine firing, which it did by approximately half in both the LL and S/_ genotype conditions. Acute drinking approximately doubled extracellular serotonin levels for both genotypes. In each case, the model provided output that was consistent with expectations, which provides a measure of confidence in the model's face validity.

The Johnson Model was motivated by an interest in improving our understanding of the mechanisms by which the 5-HTTLPR polymorphism may be associated with differential outcome of alcoholism pharmacotherapy with ondansetron and selective serotonin reuptake inhibitors. One of the important results of the simulation is that the LL genotype condition shows a dramatic difference in how reinforcing alcohol drinking is under ondansetron and selective serotonin reuptake inhibitor treatment. Figure 4 presents simulation data showing that under selective serotonin reuptake inhibitor treatment, alcohol drinking is more rewarding in the LL condition than it is under ondansetron treatment. Reward is operationalized as the difference in dopamine firing for the drink and no-drink conditions, such that higher levels of dopamine firing are considered more rewarding. That is, for those with the LL genotype,

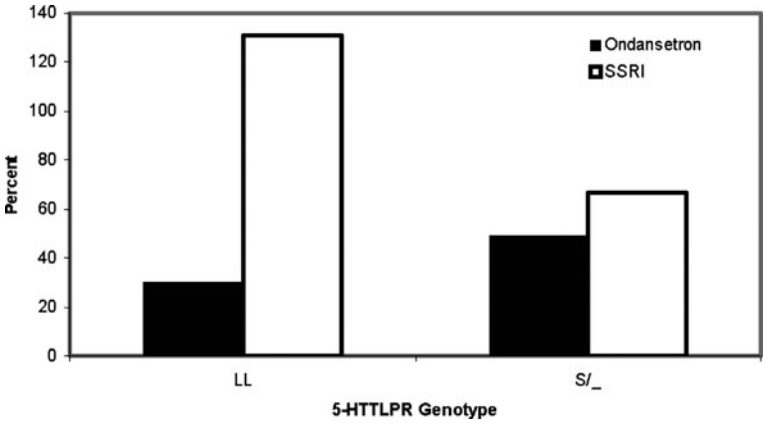

Fig. 4 The positive reinforcing effects of drinking alcohol are presented for groups defined by 5-HTTLPR genotype and treatment condition. The reinforcing effects of drinking alcohol are operationalized as the difference in dopaminergic activation between the drinking and no drinking conditions. For those with the LL genotype, drinking is relatively more rewarding in the selective serotonin reuptake inhibitor (SSRI) treatment condition than in the ondansetron treatment condition. For those with an S allele, little difference in reward is seen between the two treatment conditions

drinking in the selective serotonin reuptake inhibitor treatment condition is relatively more rewarding than drinking in the ondansetron treatment condition (see Fig. 4). It seems a reasonable interpretation that the ineffectiveness of selective serotonin reuptake inhibitor treatment for individuals with the 5-HTTLPR LL genotype is due to the reinforcing properties (i.e., capacity to activate dopaminergic neurons) of drinking. In contrast, under ondansetron treatment, drinking alcohol is not very reinforcing, which may explain the relative effectiveness of ondansetron treatment for those with the LL genotype. For those with the S/_ genotype, there is little difference in the reinforcing properties of drinking for the two treatment conditions. It may be that those with the LL genotype drink alcohol primarily for its rewarding properties, and, because ondansetron reduces the reward of drinking, it can be an effective treatment. Because selective serotonin reuptake inhibitor treatment actually increases the rewarding effects of drinking, for those with the LL genotype, it is ineffective as a treatment. The simulation results are consistent with the Johnson Model predictions regarding ondansetron treatment.

The simulation results for the selective serotonin reuptake inhibitor treatment conditions do not lend themselves to a simple interpretation. Figure 5 presents extracellular serotonin levels in both treatment conditions for both genotypes. The pattern of extracellular serotonin is similar for the LL and S/_ genotypes. Drinking raises serotonin levels across the board and, when coupled with selective serotonin reuptake inhibitor treatment, does so rather dramatically. It is worth noting that acute drinking raised serotonin to about the same level as did selective serotonin reuptake inhibitor treatment. Therefore, if an individual were to drink to raise serotonin into some "target zone", the same result could be accomplished by taking a selective serotonin reuptake inhibitor. The combination of drinking and selective serotonin reuptake inhibitor treatment raises serotonin levels substantially, perhaps to levels that could be considered aversive. For the LL genotype condition, the reinforcing effects due to dopaminergic activation may outweigh such aversive feelings. Because drinking is less reinforcing for the S/_ genotype group, the elevated serotonin levels may be aversive enough so that drinking is reduced under selective serotonin reuptake inhibitor treatment. These data seem to fit with a craving pathway model [36] such that those with the S/_ genotype experience relief craving and those with the LL genotype experience reward craving [30].

Such findings suggest questions that could be addressed empirically. Do individuals with the LL genotype drink primarily for alcohol's positive reinforcing effects? Do individuals with the S/_ genotype drink primarily for alcohol's

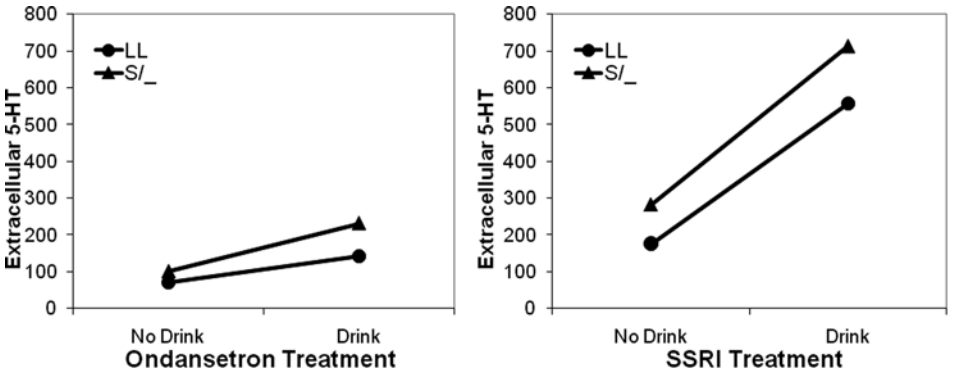

Fig. 5 Levels of extracellular serotonin (5-HT) across treatment and drinking conditions for groups defined by 5-HTTLPR genotype. Drinking raises serotonin levels for both ondansetron and selective serotonin reuptake inhibitor (SSRI) treatment, but the drinking-related increase is greater in the selective serotonin reuptake inhibitor treatment condition

negative reinforcing effects? Do individuals who drink for alcohol's positive reinforcing effects respond well to ondansetron treatment? Do individuals who drink for alcohol's negative reinforcing effects respond well to selective serotonin reuptake inhibitor treatment? Ondansetron does appear to reduce cue-induced alcohol craving [25] as well as other reinforcing effects of alcohol [13], but these effects might be specific to certain genotypes or alcoholism subtypes [13, 30].

In this section, a dynamic systems-based model was described as an example of how to incorporate genetic variation into mechanistic models of alcoholism treatment. The potential for the use of such control system modeling to test and to generate hypotheses regarding alcoholism pharmacogenetics has not yet been fully realized. Models such as these enable the systematic investigation of systems that have many parameters and in which components interact, thereby making predictions difficult. Dynamic control system models are relatively easy to construct using commercially available software such as STELLA (http://www.iseesystems.com/) or Berkeley Madonna (http://www.berkeleymadonna.com/). Both of these systems enable the user to build models with graphic interfaces and do not require the user to write systems of equations. These easy-to-use software packages enable the non-mathematician to engage in theoretically stimulating model building. Increased use of such modeling is likely to catalyze an increase in our understanding of the complex genetic architecture that underlies the etiology of alcoholism and the heterogeneity of alcoholism treatment response.

Modeling and the Personalized Treatment of Alcoholism

It is reasonable to envisage that future treatment of clients who present for alcoholism treatment might benefit directly from a personalized approach that utilizes a dynamic systems-based model. Such a model could make use of data obtained during the intake interview, such as age of onset and measures of severity and comorbidity, together with genetic data obtained from a buccal cell or blood sample, to characterize the specific dysfunction related to their disorder and to determine the most effective course of treatment.

Dynamic system models enable the researcher to utilize the full toolbox developed by mathematicians for solving and manipulating differential and difference equations. One of the most important properties of such equations is that they can often be shown to be controllable. The controllability of such systems of equations is of particular interest in terms of personalized medicine. If the system is controllable, then it may be possible to adjust parameters to move the system's current state into a desirable space. In the context of personalized alcoholism treatment, such controllability suggests that it may be possible to identify a combination of medications at specific doses that have a high probability of altering system function to, for example, reduce or eliminate the urge to drink in a particular individual. Such an approach to alcoholism treatment that is informed by biological mechanism, individual differences, and dynamic system models would be an important advance in personalized medicine.

While the systems involved have not been characterized fully, there is no question that genetic variation plays a significant role in the effectiveness of alcoholism treatments. The use of theoretical models, such as the Johnson Model, is an important first step in an empirically based, mechanistic understanding of the pharmacogenetics of alcoholism treatment. Dynamic systems-based models are important tools for systematically investigating complex systems across levels of analysis such as individual differences in alcoholism treatment response.

Conclusions

Personalized alcoholism treatment, while not yet a reality, is an important goal for researchers and treatment providers. Currently, the focus is

on identifying the relevant personal characteristics that will be of diagnostic and therapeutic utility. It is thought that treatment regimens based on specific characteristics of the individual seeking treatment will result in outcomes that are more rapid, more effective, and more long-lasting than treatment regimens not tailored to the individual. One approach to personalizing alcoholism treatment is to use the client's genotype for information about alcoholism subtype and relevant pharmacokinetic and pharmacodynamic states. Theoretical models that describe the relations between a person's genotype and the action of pharmacological agents are sorely needed to advance the science underlying personalized alcoholism treatment, and the Johnson Model is a step in the right direction. The Johnson Model proposes a mechanistic explanation of differential outcomes of pharmacological alcoholism treatment based on genotype. The simulation described in this chapter advances the study of personalized alcoholism treatment by providing a platform to facilitate systematic hypothesis testing and generation. Because the systems of interest are complex and cross levels of analysis, dynamic and systems-based models are likely to be of great utility in the quest to develop a rational and systematic approach to personalized treatment for alcoholism.

Acknowledgments This work was made possible by grants from the National Center for Research Resources (P20 RR016479) and the National Institute of Mental Health (R15 MH077654). The author thanks Dr. Parthasarathi Nag for helpful comments on an earlier version of this chapter.

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Part XI
Dependence in Specific Populations

Enhancing Positive Outcomes for Children of Substance-Abusing Parents

Karol L. Kumpfer and Jeannette L. Johnson

Contents

Introduction

The misuse of alcohol and other drugs has a significant impact on global health and economy as well as the well-being of children and families. It is estimated that around 48% of adults worldwide use alcohol and 4.5% use illicit drugs, though only about 15% misuse alcohol and drugs [4]. The greater the consumption of alcohol, the greater the harm done [7, 110]. It is of interest that Europeans have the highest amount of yearly alcohol consumption in the world. It is 2.5 times that of the world average

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The author Karol L. Kumpfer has supported by Grant DA10825 from the National Institute on Drug Abuse.

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_65,

[4]. Despite lower overall consumption levels in Northern European countries compared with Southern European countries where drinking small amounts of wine with meals is common, when Northern Europeans in Nordic counties drink they display more detrimental patterns of excessive use [79]. Alcohol and other drugs misuse has a wide impact on all strata of society, not just in terms of illness and disease, but also on violence and crime rates, workplace injuries and performance, and family stability and relationship breakdown. The cost of addictions in the United States is very high and is estimated at about $2,000 per person in economic costs related to lost revenue, taxes, treatment costs, criminal justice costs, fires, accidents, and other related costs [17].

Prevalence of Children of Substance Abusers

The substance misuse by adults does great harm to both themselves and society in general. Their children are impacted as well, often negatively, because many adult substance abusers are also parents. Substance abuse is a family disease because the addict affects those who live around him or her. Parental substance abuse is a public health concern due to its high prevalence and relationship to many negative child developmental and health outcomes. It is estimated that about 25% of children in the United States (19 million) under the age of 17 are exposed to parental alcoholism [42]. The estimate for the number of children of drug abusers in the United States is about 12.7%, or 9.2 million.

Children's Feelings and Beliefs About Parents' Substance Misuse

Recent studies [9–11] have reported on the child's perspective toward their alcohol or drug-using parents. These studies demonstrate three common themes: family role reversal, keeping the family secret, and coping strategies. These themes demonstrate the need for new approaches and interventions to support the development of children living in families where drug use is a problem. Children can feel confused and insecure when they do not understand their parents' erratic behavior and mood, which can be significantly impacted by the effect of alcohol or other drugs. Parents are often like "Dr. Jekyll and Mr. Hyde"—two different personalities. They tend to be more loving and humorous when using moderately, but can be anxious, paranoid, and use excessive punishment when in withdrawal from their drugs. Of course, the impact on personality of the parent depends on the drug of choice and other mental health problems. Excessive use of stimulants can make parents more agitated and dangerous to children, whereas heroin or depressant users tend to just get sleepy and groggy. Many children take on the parents' role for their younger siblings due to the incapacitating effects of some drugs.

Differences Between Children of Alcoholics and Children of Other Drug Abusers

There are many different combinations of substances that can be abused and patterns of parental chemical dependence that influence the lives of the children growing up in alcoholic or chemically addicted families [51]. First, the behavior surrounding the drug of choice differs. Unlike alcohol, the possession of heroin or cocaine is illegal, as is marijuana in most states. Children exposed to parents who abuse illegal drugs are also exposed to an aspect of life that children of alcoholics are not; using illegal drugs means that it is a criminal offense. The children who know about their parents' drug use must be involved in a shroud of secrecy, giving rise to a home environment that is veiled in fear, lest the cops find out about what their parents do. Unlike alcohol, which can be consumed openly and without fear of legal reprisal (barring certain restrictions), illicit drug use/abuse requires

great secrecy. For this reason, the child of an addicted parent must contend with the secretive illegal drug activity of their parent both at home and in the community. Second, unlike children of alcoholics, the AIDS epidemic directly confronts the children of addicted parents, especially if the parents are intravenous drug users. Loss of significant others due to AIDS-related illness may become more pronounced in the lives of these children. Addicted parents may have AIDS (or be HIV positive); friends of their parents may have AIDS, or babies in the community may be HIV positive. Third, the type of chemical dependence influences the type of childhood home environment, especially if the addicted parent abuses heroin or is involved with an insidious addiction to crack. Parents involved with deviant activities may invite adult friends into the home who are also involved with similar activities. The presence of adult antisocial role models is a strong possibility for children living with addicted parents. Home environment is a critically important variable in shaping cognitive skills, academic achievement, and psychosocial adjustment. Deviant home environments are the source for many childhood behavioral problems [114]. Finally, the effect of the drug on the parents' behavior is profound. Methamphetamine addicts act one way, and heroin addicts another. This affects the parental role and parental behavior profoundly.

Higher Risk for Addictions

Research suggests that children of addicted parents are at 2–9 times greater risk of becoming substance abusers as adolescents or adults [1, 23, 58] despite the positive and adaptive behavioral outcomes of many of these children [50]. Among adolescents, children of substance abusers misuse substances more than children whose parents are not substance abusers and escalate their use more steeply. As young adults they are more likely to be diagnosed with alcohol and drug abuse/dependence [21]. The risk for later substance misuse depends upon their degree of risk factors compared with protective factors including the extent of their family history of alcoholism, which includes whether one or both parents are abusers and the addiction severity, the type of alcoholism that runs in the family [115, 117], and the extent of their parents' antisocial behavior, health, and mental health problems. Gender differences also exist; for example, girls have increased vulnerability to the negative impact on later drug use of family environmental risks, which are high in families with substance-abusing parents [73].

Living with a parent who abuses alcohol or other drugs can have severe effects on every aspect of a child's life, including social acceptance, mental and physical health, and school performance [78]. Most studies find children of substance abusers to have elevated rates of psychological symptoms [26]. Beyond risk for addictive behaviors, children of substance abusers are also at higher risk for developing emotional, behavioral, academic, criminal, and other social problems [80, 101]. They tend to be lower on protective factors and higher on risk factors [97], increasing their risk for depression, suicide, eating disorders, chemical dependency, and teen pregnancy.

They tend to have heightened levels of conduct problems in preschool [37], elementary school [130], and delinquency in adolescence [22, 100], particularly if their parents also show antisocial behavior [108]. Children of substance abusers also demonstrate elevations in impulsivity and activity level [37] as well as behavioral disinhibition [126], leading some researchers to view them as behaviorally undercontrolled. Children of alcoholics have been found in a longitudinal study to age 23 years to employ more of a cognitive coping style and less of a decision-making coping style than children of non-alcoholic parents [46]. Similarly, children of two parents with substance use disorders tend to use aggression as a major coping style, compared with children of only one or no parents with substance abuse disorders, who use a more problem-solving, decision-making style of coping [8]. Earlier studies described children of

substance abusers as higher in "difficult temperament", meaning a relatively stable trait, likely genetically linked, that led to increased emotional and behavioral liability and difficulty with behavioral control [13]. Parental alcoholism has also been linked to anxiety and depression in children [22, 113], and West and Prinz [133] have noted that children of alcoholics had higher levels of anxiety and depression than did controls in 10 of 11 published studies.

Children of substance abusers show lower academic achievement than do children whose parents are not substance abusers [89], even in comparison with depressed children or children of divorce [116], and they have poorer cognitive functioning in the preschool years than do children whose parents are not substance abusers [95]. Casas-Gil and Navarro-Guzman [18] have identified five variables on which school performance by children of alcoholics was poorer: intelligence, repeating a grade, low academic performance, skipping school days, and dropping out of school. Sons of male alcoholics who have many alcoholic relatives across generations have been reported to show deficits in verbal and abstract reasoning and verbal learning [44, 134]. For this subgroup, Pihl and associates [106] suggested that cognitive deficits may be caused by heritable dysfunctions of the prefrontal cortex and limbic systems. However, cognitive impairments may also stem from fetal alcohol exposure [124], high stress levels in pregnant mothers or a lack of environmental stimulation or conversely a chaotic home environment [95].

Genetic Risks

Family, adoption, and twin studies support the heritability of addictions estimated to contribute to about 40–60% of the overall risk for addiction. This heritable influence appears not to be substance specific. For instance, children of alcoholics today are also becoming abusers of illegal and prescription drugs. Children in families with many early-onset alcoholics (beginning use before 15 years of age) are at highest risk for later substance abuse or addiction because this is an indicator of Type II alcoholism. Type II alcoholism is the highly heritable type of alcoholism that appears to have a heavy genetic loading as compared with Type I alcoholism, which is more environmentally caused. Research suggests that about 60% of the variance in risk for an alcohol use disorder is related to genetic factors and the remaining 40% is due to environmental factors in this type of alcoholism in males [117]. However, twin and adoption studies suggest that girls are not at such a high risk. In females, only about 40% of the variance in risk for an alcohol use disorder is related to genetic factors and the remaining 40% is due to environmental factors. However, this risk increases if both biological parents are alcoholics from Type II alcoholism families. Luthar and associates [84] found that similar adverse circumstances are present for children whose parents abuse illegal drugs. They concluded, however, that maternal drug abuse per se is not as damaging to children's resilience as maternal stress, depression, and anxiety disorders [85].

Which Genes are Involved?

Since the completion of the human genome project, there has been considerable interest in the identification of genes involved in this complex disease. Research has identified many genes that contain allelic variants associated with heritable phenotypes or characteristics that enhance vulnerability to addiction [127]. Over 1,500 genes have been implicated in research to increase vulnerability to addiction. However, a meta-analysis of these studies by a Chinese research team found that only five gene pathways were involved in the four major types of drug dependency from a total of 18 statistically significant molecular pathways for single types of addiction [81]. These five pathways may underlie shared rewarding and addictive processes—i.e., neuroactive ligand-signaling interaction, long-term potentiation, and the mitogen-activated protein kinase

signaling pathway linked to memory and learning, and two new ones: (1) the gonadotrophin-releasing hormone signaling pathway involved in gonodrophine secretion, and (2) stress-induced drug seeking and gap junction. They connected the five pathways into one common hypothetical molecular network for addictions. According to Uhl and associates, "The overlapping genetic vulnerability for developing dependence on a variety of addictive substances suggests large roles for 'higher order' pharmacogenomics in addiction molecular genetics" [128]. Discovering the pharmacogenomics of addiction is likely to have broad implications for neurotherapeutics.

Characteristics or Phenotypes of Children of Alcoholics that Increase Their Risk

Because the specific genes for addiction are only now beginning to be discovered, research has focused on identification of the phenotypes or disorders these children could inherit that increase their rates of substance abuse. Actually, genotypes do not always translate directly into phenotypes; hence, predicting later substance abuse is enhanced by monitoring the behaviors of high-risk children with many relatives who began alcohol or drug use before the age of 15 years of age.

These phenotypes or characteristics of children of substance abusers with Type II alcoholism include higher rates of neuropsychological and limbic system deficits that include either: (1) behavioral and emotional self-regulation problems or (2) reduced executive functioning [23]. Research suggests that these two cognitive deficits are primary factors leading to reduced resilience and increase risk for addiction [40, 43].

Children of substance abusers have been reported to be genetically vulnerable to two major syndromes: (1) the overstressed youth syndrome (e.g., poor emotional regulation, difficult temperament, autonomic hyper-reactivity, and rapid brain waves) and (2) prefrontal cognitive deficits in verbal and abstract reasoning and verbal learning. These cognitive deficits reduce their ability to understand that their parents' erratic behaviors are caused by drugs and not by the child's own behaviors [87]. Schuckit [115] found that alcohol smoothes out the overactive autonomic nervous system stress response in children of alcoholics so that they report feeling normal for the first time in their lives. Alcohol and drugs also increase essential neurotransmitters such as dopamine, serotonin, and noradrenalin, which reduce their depression and anxiety.

Diversity of Outcomes in Children of Substance Abusers

Although having a substance-abusing parent affects many aspects of a child's life, the degree of impact on children of substance abusers varies considerably. Although they are at higher risk, most children of substance abusers manifest few developmental and psychological problems and do *not* develop substance use disorders [119]. The great difference in later substance use disorder rates among children of substance abusers appears related to the number of inherited phenotype risks from Type II alcoholism family history and the number of Type I alcoholism environmentally caused risks. Also, girls appear to have less genetic risk than boys, but girls can have higher sensitivity to family environmental risks.

The impact of parental addiction on children of substance abusers varies with degree of severity, developmental timing, and length of parental substance misuse. For example, children of active alcoholics have greater psychological distress than children of parents in recovery [91], particularly if the parents' abuse ended early in the child's development before 6 years of age [92]. A longitudinal study by Andreas and O'Farrell [5] suggested that periods of fathers' heavier drinking patterns lead to increased children's psychosocial problems. O'Farrell and

Feehan [102] found that remission after alcoholism treatment was associated with reduced family stressors, domestic violence and conflict, separation, and divorce, as well as improvement in family cohesion and caring. Also, children were less affected by parental substance abuse if their parents had no other mental disorders [48].

The Family

Environmental Impacts: Global Negative Impact of Childhood Adverse Experiences on Children of Substance Abusers

There has been considerable interest recently in the negative impact of early childhood adverse experiences on children's neurodevelopment and health outcomes leading to increased health care costs [3]. Parental drug abuse and alcoholism has been found, in a decade-long study by the Centers for Disease Control and Prevention of health management organization members, to be associated with multiple adverse early childhood circumstances [31]. This same research group found that parental alcoholism and multiple childhood adverse experiences increased the risk for later adult alcoholism [32]. However, multiple childhood adverse experiences increased the risk 2- to 4-fold for later self-reported alcoholism, heavy drinking, and marrying an alcoholic even without parental alcoholism. In this retrospective self-report study of over 8,500 individuals, those who grew up with *both* an alcohol-abusing mother and father had the highest likelihood of childhood adverse experiences. The mean number of childhood adverse experiences for persons with no parental alcohol abuse was only 1.4, compared with about twice as many for those with an alcohol-abusing father only (2.6) or mother only (3.2). Having both parents abusing alcohol increased the risk of childhood adverse experiences almost 3-fold for a mean of 3.8 childhood adverse experiences. Of interest is the lack of protection from adverse experiences in the family if the mother was an alcohol abuser.

Similar adverse circumstances are present for children whose parents abuse illegal drugs [84]. These childhood adverse experiences can include exposure to frequent stressful and traumatic experiences such as abuse (emotional, physical, and sexual), neglect (emotional and physical), witnessing family violence and criminal behavior, parental divorce and separation, and parental incarceration. Hence, parental substance abuse or a family history of early-onset alcoholism or drug abuse is a potent risk factor for later addiction in children.

Family Environmental Risk and Protective Factors

A number of family risk and protective factors contribute to the high rates in youth today. Worldwide, parents are spending less time parenting and supporting their children. Few parents in the United States still have a meal each day with their children, although two-thirds of children in other countries still have the main meal with their parents. However, fewer children than that talk with their parents on a regular basis [129]. Living with drug-addicted caretakers, who spend about half as much time with their children as the average parents spend, increases children's stress levels.

Other research suggests that positive family functioning can reduce genetic predispositions [49]. Having a mother who is an addict or two parents who are addicted increases their risk for later developmental problems [31]. Without extended family protection and family or agency support, many children of substance abusers live in disruptive family environments. These environments are frequently characterized by family conflict, disorganization or disrupted family rituals (meals together, bedtime rituals, holidays, etc.). The environment contributes to an already elevated sense of anxiety and stress in the children.

In families where alcohol or other drugs are being abused, behavior is frequently unpredictable and communication is unclear. Family

life is characterized by chaos and unpredictability. Behavior can range from loving to withdrawn to crazy. Structure and rules may be either nonexistent or inconsistent. Adult children of alcoholics report more parentification, instrumental caregiving, emotional caregiving, and past unfairness in their families of origin [56].

Not every family is affected identically. Research has shown that families that maintain certain "rituals", such as holiday traditions or a Friday night pizza and movie, can help mediate the chaos of addiction. Sober parents who are able to provide stability, support, and nurturing also help to minimize confusion and strengthen children. Sometimes family life is less damaging because children rely on "adaptive distancing", a technique in which the child separates from the "centrifugal pull" of family problems in order to maintain pursuits and seek fulfillment in life, school, and friendships [62].

Finally, in addition to adverse circumstances within the family, parental alcoholism is also associated with elevated levels of more general negative uncontrollable life events [22, 113, 120]. In particular, because alcoholics are likely to have less education and lower income [93], children of alcoholics may have fewer economic resources available to them. Consistent with their lowered socioeconomic status, children of alcoholics are more likely to report that a parent was fired from a job and that their families suffered from financial problems [120]. Although little is known about the exposure of children of alcoholics to adverse neighborhood or school environments, their lowered socioeconomic status raises the possibility that their broader social environments may also be less than ideal.

Substance Abuse Impact on Parenting

An important, yet poorly understood, feature of drug overuse is the potential impact on parenting capacity and child health outcomes. It is known that parents who are substance users become more aggressive and/or abusive toward their child when under the influence of drugs [137]. It is estimated that 40–80% of child abuse reports concern families with substance abuse issues [24, 99]. Parents who use alcohol and drugs tend to be poor role models for their children, often exposing them to drug use and illegal behaviors, which may increase the risk of the children being recruited into drug use as they get older [20]. Thus, parents who use alcohol or drugs have greater risk of influencing children's developmental outcomes.

Although not all children are negatively impacted by their parents' use of alcohol or drugs, the task of raising a child is undoubtedly made more difficult when a parent is regularly affected by alcohol or drug use [9]. Despite federal funding and Medicaid funding for mothers' and children's residential or outpatient treatment facilities, there are still not enough treatment facilities that accept children; when they do, programming for the children is frequently neglected. Unfortunately, there is a common notion among many treatment programs that the parent should focus on his or her own recovery; the children are kept separated from the treatment process. This ignores the fact that improving parenting significantly reduces the parent's guilt and depression and reduces relapse.

Child Abuse Potential

The comprehensive national survey conducted by the National Center on Child Abuse and Neglect [98] found that 80% of surveyed states reported that parental substance abuse and poverty are the two major problems among child protective caseloads. Children of substance-abusing parents are 3 times more likely to be abused and 4 times more likely to be neglected than children from families where parents do not abuse alcohol and/or other drugs [66]. Other national studies also support these findings; between 40% and 80% of all child maltreatment cases involve parental misuse of alcohol or drugs [24].

Compared with non-addicted parents, addicted parents tend to neglect their children, spend about half as much time with them, and use more of a punitive and authoritarian parenting style with higher levels of corporal punishment [67]. However, these children are more often neglected rather than emotionally or physically abused. Suomi's [125] research with peer-raised monkeys suggests that neglect may be more devastating to children's brain and social/emotional development than physical punishment because neglected children feel unprotected by caring adults. Their levels of stress and anxiety are raised, resulting in insecurity, lack of parental bonding, and stronger peer cluster bonding; in turn, exploratory behaviors are reduced. Exploratory behaviors are needed in the development of self-control and executive functioning, but since they are reduced in stressful and anxiety-producing environments, the developmental process is perturbed.

The less-than-optimal parenting and family environments that children of alcoholics experience extend beyond the relationship between the alcoholic parent and the child. Even in infancy, deficits in mother-infant attachment have been found in families with problem-drinking fathers [33]. Moreover, parental alcoholism is associated with higher levels of parent-adolescent conflict [12]. Parental alcoholism is also associated with higher levels of exposure to family conflict and violence [90, 120], although parents are not necessarily the perpetrators of the violence [90].

Protective and Resilience Factors in Children of Substance Abusers

Resilience has been defined as the achievement of competence or positive developmental outcomes under conditions that are adverse or that challenge adaptation [88]. The Resilience Framework [61] suggests that the development of resilience in high-risk children, such as children of substance abusers, is a complex transactional process between the child, his or her parents or caretakers, and their environment.

Not enough research has been conducted to understand these resilience processes. In contrast to the substantial literature on the relationship between parental alcoholism and children's psychological problems, studies have generally failed to examine the development of resilience and competent performance or positive outcomes in children of alcoholics, although some relevant work has been done on the absence of negative outcomes. Generally, these studies have sought to specify factors that protect children of alcoholics from the negative outcomes associated with parental alcoholism. For example, Werner [131] followed children of alcoholics from birth to age 18, and reported that those who did not develop serious problems had experienced fewer negative stress events, had more cuddly and affectionate infant temperaments, and had higher self-esteem and better communication skills. In a 32-year longitudinal study, Werner and Johnson [132] found that one caring adult in the child's life is a significant protective factor.

Several studies have focused on positive family environment factors and have discovered a few protective factors or processes. Wolin and colleagues [136] found that alcoholic families who maintained consistent rituals (e.g., vacations, birthday celebrations) had children who were less likely to develop alcohol problems. Similarly, children of alcoholics whose families had higher levels of organization were less likely to initiate illegal drug use [45].

Higher levels of family cohesion and support have also been shown to enhance outcomes for children of alcoholics. Farrell et al. [36] found that children of alcoholics showed high levels of adolescent deviance and distress when family cohesion was low, but that these effects were reduced when family cohesion was higher. Similarly, Barrera and associates [12] found that children of alcoholics in low-conflict families resembled children whose parents were not alcoholics, whereas children of alcoholics who experienced high levels of family conflict showed elevated levels of psychological distress. The notion that family cohesion and support are associated with better outcomes among children of

alcoholics is consistent with Moos and Billings' [91] finding that families in which paternal alcoholism had remitted after treatment had both higher levels of family cohesion and lower levels of psychological distress among their children. These data suggest that parental recovery may promote resilience for children of alcoholics, perhaps because the family environment also recovers. However, because these findings are from a sample of fathers who received alcohol treatment, they may not generalize to untreated families [21].

Research has also suggested that parental supervision is an important protective factor for children of alcoholics. Curran and Chassin [27] found that consistent discipline and monitoring of their adolescents' behavior by mothers were associated with better outcomes among both children of alcoholics and children whose parents were not alcoholics. However, consistency of discipline includes monitoring and positive reinforcement and should not be taken as synonymous with punishment, which has been associated with poorer outcomes among children of alcoholics [130].

Finally, some data point to the importance of extra-familial influences. Ohannessian and Hesselbrock [103] found that children of alcoholics with high levels of support from friends closely resembled children whose parents were not alcoholics, whereas children of alcoholics with less peer support consumed more alcohol and had more alcohol-related problems. Thus, a supportive relationship with someone outside of the family may be protective. Moreover, Jordan and Chassin [52] found that adolescent children of alcoholics who had greater involvement in positive activities outside the home were less likely to develop a substance use disorder in young adulthood. In the case of parental alcoholism, where adverse circumstances exist within the family environment, extra-familial influences may be particularly important.

A significant protective factor to build the resiliency of children is to bolster social support networks and to increase autonomy and sense of safety. For children growing up in an unpredictable environment with parental substance abuse, improving resilience and enhancing protective factors is valuable. It seems clear that educational health care interventions presented in a supportive social environment are a useful and effective strategy for improving outcomes and enhancing health behaviors.

In summary, although research has not focused specifically on positive outcomes and competent performance among children of alcoholics, some work has been done to identify factors that predict lower levels of negative outcomes. These studies suggest that parental support and control, and family environments that are characterized by stability, cohesion, organization, and preservation of routines and rituals are associated with better outcomes. These critical family protective processes (e.g., family attachment, parental supervision and monitoring, and organization and communication) were found to be the most important protective factors of later substance use in a major cross-site study of 8,500 high-risk youth funded by the Center for Substance Abuse Prevention [123]. In addition, high levels of friend support and involvement in positive activities outside the home reduce negative outcomes for children of alcoholics. Finally, it has been suggested that parental recovery from alcoholism is itself protective.

Prevention Programs Specifically for Children of Alcoholics

School-Based Primary Prevention Programs

Very few prevention programs have been developed specifically for children of alcoholics [59, 135]. Most prevention programs specifically for children of alcoholics are limited to school-based education programs that are relatively short in duration and conducted with small groups of students who self-identify as children of alcohol or drug abusers [107]. Although there may be many such school-based programs for children of alcoholics, according to Price and Emshoff [107], very few of them are

even described in the prevention literature and even fewer have outcome evaluations. Because of the positive research results for behavioral training models, programs for children of alcoholics are including more social competency skills training. In one of the few research-based models, Roosa and colleagues [112] found positive changes in knowledge, social support, and emotion-focused coping behavior in their 8-week, school-based program for children of alcoholics. Emshoff's [34] Students Together And Resourceful program teaches students social competency skills, and provides accurate information about alcoholism and its effects on the family. Participants reported more friends and stronger social relations, increased sense of control, and improved self-concept with less depression.

Family-Focused Prevention Programs for Children of Alcoholics and Substance Abusers

Several prevention programs for children of alcoholics and substance abusers that include a family-strengthening approach to increasing resiliency through family skills training have been developed and tested in federally funded prevention research—namely, the Strengthening Families Program [60, 72] and Focus on Families [19]. Positive results have been found for the Strengthening Families Program in improving social competencies and family relationships and in reducing later tobacco, alcohol, and drug use in children of addicted parents in treatment. Moreover, this program has been modified and evaluated for rural and urban African/American, Latino, Asian and Pacific Islander, and, recently, American Indian families.

Community-Based Prevention Programs for Children of Alcoholics

There are very few community-based programs for children of alcoholics, but one popular one is Alateen. This self-help support program for children of alcoholics is implemented in the community through Alcoholics Anonymous. This program provides a safe environment in which children can share their feelings, experiences, and tips for surviving their parents' addictions and negative behaviors. The Cambridge and Somerville Program for Alcoholism Rehabilitation program [28] offered junior-high-aged children of alcoholics or children whose parents were not alcoholics a range of after-school services at schools or in community settings. DiCicco et al. [30] found that mixing children of alcoholics and children whose parents were not alcoholics in alcohol education groups, compared with groups specifically for children of alcoholics, resulted in reduced drinking among children of alcoholics and reductions in the intention to drink in the future. Moreover, because of stigmatization issues, recruitment of children of alcoholics was easier for the basic education group than for the group that was specifically for children of alcoholics. These results suggest that prevention programs not specifically for children of alcoholics may be a valuable option for recruiting and delivering services to children of addicted or substance-abusing parents.

Family-Based Prevention and Treatment

Developmental theories support the critical role of families in child raising and suggest that supportive families are key to raising healthy children and preventing later adolescent problems. Our consumer-oriented, fast-paced society appears to have forgotten this important role for parents. Longitudinal research suggests that parents substantially impact their teens' health behaviors [111]. Although peer influence is a major reason why adolescents initiate negative behaviors, a positive family environment (e.g., family bonding, parental supervision, and communication of pro-social family values) protects youth from engaging in unhealthy behaviors, such as substance abuse, delinquency, and

early or unprotected sex. These protective family factors have even a stronger influence on girls [71].

What can be done to reduce unacceptably high levels of harmful behaviors in adolescents? Evidence-based family intervention approaches that have been found to be effective include [65]: (1) behavioral parent training (primarily cognitive/behavioral parent training); (2) family skills training (including parent training, children's skills training, and family practice time together); (3) family therapy (structural, functional, or behavioral family therapy), and (4) in-home family support. The most recent review [2, 63] identified 35 family interventions. Information on these specific family interventions including program descriptions, Web sites, and contact information can be found at www.strengtheningfamilies.org.

Only seven family interventions of these 35 programs met the highest level of evidence of effectiveness, or Exemplary I, which required a minimum of two randomized controlled trials with positive results implemented by at least two independent research teams with different populations [70]. These Exemplary I family programs included: Helping the Noncompliant Child, The Incredible Years, the Strengthening Families Program, Functional Family Therapy, Multisystemic Family Therapy, Preparing for the Drug Free Years, and Treatment Foster Care. Seven programs were classified into the Exemplary II Level because they had at least one randomized controlled trial with positive prevention results. The other programs were classified primarily into the Model Level because they had only quasi-experimental research results. Some Promising Level programs were added to the list because they were programs that were based on existing proven programs, but did not yet have outcome results. Since the last expert review in 1999, additional randomized controlled trials have been conducted on existing and new family interventions; hence, this list is not complete.

The senior author is currently developing a Web site for the United Nations Office of Drugs and Crime with program descriptions and contact information of all the best parenting and family programs in the world for dissemination to developing countries. So far, at least 50 high level evidence-based programs have been identified, with over 500 programs located. A protocol for culturally adapting evidence-based family strengthening interventions has already been published from this United Nations Expert Group's work [77].

Family-Focused Prevention Programs for Children of Alcoholics and Substance Abusers

While a number of effective family-based approaches to substance abuse prevention have been found through expert reviews of the literature [71, 83], only a few were designed specifically for children of substance abusers and only two have been tested in randomized controlled trials—The Strengthening Families Program and Focus on Families.

The Strengthening Families Program [29, 67, 69] was designed by Kumpfer and colleagues in 1982 and tested specifically for children of substance abusers in outpatient methadone maintenance and mental health drug treatment centers in a National Institute on Drug Abuse randomized controlled trial testing the three different components. The resulting Strengthening Families Program includes three 14-week sessions in parent training, children's social skills, and family relationship enhancement, followed by booster sessions every 6 months. Specific program results included improved parenting skills, confidence, and parenting efficacy, which led to a reduction in children's overt and covert aggression, hyperactivity, depression, conduct disorders, and improved social competencies. Family relationships (organization, cohesion, communication, conflict) were significantly improved. Decreases in substance use in both the parents and older children were also revealed. Moreover, this program has been modified and evaluated by independent researchers for rural and urban African/American, Latino, Asian and

Pacific Islander, and American Indian families with positive program outcomes that include a 40% improvement in recruitment and retention for culturally tailored programs [74]. Other randomized controlled trials have reported positive program results in elementary school-aged rural children [75, 76], junior high school rural children [122], and inner-city 7–11 year olds [41]. One 10-year study followed participants to the age of 22 and found a 2- to 3-fold reduction in lifetime diagnosis of anxiety, social phobia, depression, and personality disorders when compared with their no-treatment controls [122].

Recently, a Cochrane Collaboration and World Health Organization meta-analysis of universal alcohol prevention programs in schools [39] found that a 7-session Strengthening Families Program for 10–14 Year Olds [72] was twice as effective in reducing alcohol use as any other school-based intervention having at least 2 years of follow-up data. A cost-benefit analysis showed a return of $9.60 for every dollar spent by the school when they implemented the Strengthening Families Program for 10–14 Year Olds [121]. Because of these positive results, the Strengthening Families Program has been adopted for replication and evaluation in seven countries in Europe, including four that have 1–2 years of pre- to post-test outcome results—Spain [105], Netherlands [104], Sweden [57], and the United Kingdom [38].

The second program, Focus on Families [19], was also developed for children of parents in methadone maintenance treatment. This program found reductions in relapse for the parents but no significant improvement in the children [20]. Zucker and associates [86] found positive results on children's prosocial skills at a 6-month follow-up after the fathers or both parents participated in a 12-session behavioral parenting program tested with fathers arrested for drunk driving.

Two other programs have been designed for children of substance abusers and show promising preliminary non-experimental research results—Celebrating Families and Nurturing Program for Families in Substance Abuse Treatment and Recovery. Designed to prevent child maltreatment in children of alcoholics, the 15-session Celebrating Families has been found to improve family reunification rates from 37 to 72% for children of alcoholics removed by child protective services [109] as well as to reduce the number of days to reunification. Positive changes in knowledge, coping skills, decision-making, and feelings expression were also reported for the program [53]. Using the same evaluation instruments as those used for the Strengthening Families Program, Celebrating Families reported similarly positive effects at post-test on several outcome measures: improving parenting skills, family organization, communication, and cohesion. The child outcomes were mixed, however, and only two positive child outcomes were reported (reduced depression and concentration problems). The study also reported a non-significant positive trend for social skills, and three negative iatrogenic effects, namely for overt and covert aggression, and hyperactivity [64]. A longitudinal study is necessary, as children of substance abusers have been observed to increase their negative acting-out behaviors when their parents enter treatment. Some suggest that these children act out because they feel safer to do so. Finally, research on 170 mothers participating in the Nurturing Program [16] suggested improved parenting attitudes at post-test on the Adult-Adolescent Parenting Inventory and reduced relapse [96].

Prevention programs not specifically designed for children of substance abusers may also be effective if they have core content demonstrated to be effective in reducing mediating factors for later substance abuse in children of substance abusers. For example, Chassin and associates [23] have discussed necessary core content for children of alcoholics that includes content that increases children's alcohol and drug awareness, social competencies, awareness of feelings, emotional and behavioral control, and reducing depression. With the exception of Zucker's intervention [86], most family-based programs for children of substance abusers are family skills training programs that typically include the parent training component and not

children's skills training or family skills training utilizing a standard dosage between 14 and 17 sessions. Shorter programs are not as effective in attaining behavioral changes in addicted families.

Reviews of prevention programs for children of alcoholics and substance abusers [23, 25, 107] have expressed the need for additional research on etiology and effective prevention programming as available outcome studies are dated. Ethical and practical issues in designing, implementing, and evaluating programs for children of substance users are discussed in several publications [25, 35, 50, 55, 61, 87, 107].

Core Content of Effective Family Programs

Effective family programs involve the whole family (rather than just the parents or children) in interactive, skills, or behavior change processes, rather than involving them in didactic educational lessons. The underlying psychological theories include behavioral psychology and/or family systems theory [82] which stress the importance of the engagement process and reducing barriers to attendance through relationship building, personal invitations, provision of meals, childcare and transportation, and sometimes, paying families for their time. Most effective programs begin with sessions designed to improve positive feelings in the family through positive reframing or skills exercises stressing family strengths. Engagement in structured methods for communication and discipline techniques are also practiced once positive family feelings are increased. O'Farrell and Fals-Stewart [101] have found that behavioral couples therapy reduces domestic violence, which indirectly benefits the couple's children. Hence, behavioral couples therapy should be expanded to include children of substance abusers to improve outcomes. An affectionate parent-child bond has a protective effect on later drug use [15]; hence, therapeutic interventions that strengthen parent and child bonding are recommended, particularly when there is already stress from the "generation gap" or differential generational acculturation in immigrant families.

Kaminski and associates [54] at the Centers for Disease Control and Prevention have analyzed the critical core components of evidence-based family intervention programs from 77 studies of programs for 0–7 year olds. Since the presence of conduct disorders in early life often precedes later delinquent, aggressive, and risky behaviors in adolescence, they reasoned that effective parenting could reverse this trend. The core components of effective parenting and family interventions are: (1) the format should include practice time for the parents with their children in the sessions with the therapists or group leaders available for coaching; (2) during family sessions, parents should be taught to interact positively with children (such as showing enthusiasm and attention for good behavior and letting the child take the lead in play activities); (3) parenting content should include increasing attention and praise for positive children's behaviors, children's normal development to make expectations realistic for children's behaviors, positive family communication including active listening and reducing criticism and sarcasm, and effective and consistent discipline including time-outs; (4) children's content should include teaching children social skills for how to get along better with parents, peers, and teachers in a more respectful manner, and (5) home practice assignments should be assigned and encouraged in order to improve generalization of new behaviors at home. Additional reviews of the literature on effective family strengthening approaches have also supported these findings [65, 77] (Office of Juvenile Justice & Delinquency Prevention, Strengthening America's Families Web site, www.strengtheningfamilies.org; United Nations Office of Drugs and Crime Web site, www.unodc.org/unodc/en/prevention/index.html).

Effective Prevention Programs

Kumpfer and Hopkins [68] have stressed preventive approaches for prevention programs for

children of alcoholics and substance abusers that include: emphasizing the negative consequences of alcohol; developing in youth an increased sense of responsibility for their own success; helping them to identify their talents; motivating them to dedicate their lives to helping society rather than feeling that their only purpose in life is to be consumers; providing realistic appraisals and feedback for youth rather than graciously building up their self-esteem; stressing multicultural competence in an ever-shrinking world; encouraging and valuing education and skills training; increasing cooperative solutions to problems rather than competitive or aggressive solutions, and increasing a sense of responsibility for others and caring for others.

Research-based prevention interventions developed for other high-risk youth can also be very effective for children of alcoholics if they address risk factors for children of alcoholics (described earlier) including externalizing problems, internalizing problems, and cognitive deficits or delays. Here we summarize prevention interventions not specifically for children of alcoholics that may be capable of strengthening resilience to later alcohol and drug use among children of alcoholics, organized by their targeted risk factors.

Programs that Increase Behavioral Control and Social Competency

A number of preventive interventions have been developed that are helpful in increasing social competencies, emotional management, and behavioral control, and these may be useful for children of alcoholics who manifest conduct disorders and aggression. When applied universally in classrooms [14, 47], these programs can reduce conduct problems, promote healthier friendships with prosocial children, and hence prevent substance abuse and violence. They are effective without the children having to be identified as children of alcoholics or drug abusers. Some of the indicated prevention programs, however, do require that the teacher refer children with aggressive tendencies and conduct disorders to a pull-out group. Because of possible negative contagion and labeling effects, it is best also to include socially skilled youth in the group.

Programs to Increase Emotional Resilience, Happiness, Self-Esteem, and Humor

Research on resilience in children of alcoholics [131, 132, 136] suggests that hopefulness, happiness, and emotional management increase positive outcomes in children of alcoholics. Universal prevention programs that support improved mental health and resilience also help children of alcoholics. One universal, school-based resilience program is the Strengthening Families Program for 10–14 Year Olds [72], which was first developed in Iowa with National Institute on Drug Abuse and National Institute of Mental Health funds. It is a 7-session parent, child, and family intervention for middle school students. Because resilience studies with adult children of alcoholics (Walker R, Kumpfer K, Neiger B, Richardson G (1997) Resilience in adult children of alcoholics, Department of Health Promotion and Education, University of Utah, "Unpublished doctoral dissertation") have found that meaning or purpose in life is the most critical resilience factor in positive life adaptation, this new Strengthening Families Program focused the first sessions on parents supporting children in developing dreams and goals. Depression is reduced by having children and their parents focus on hopefulness and positive dreams for the future. Youth are encouraged to think about their talents and ways they can use these talents to help others through kind acts and a productive and successful career. Positive psychology [118] suggests that feelings of well-being are more enhanced by doing kindness to others than by doing nice things for oneself. Children of alcoholics who are resilient are youth who have meaningful roles in

their families to help others, or the characteristic of required helpfulness, found in resilience research. Hence, parenting and family skills training programs that teach parents to negotiate chores, create chore charts, and monitor and reward completion of chores help to increase positive self-concept and increase happiness.

Programs for Emotional Management and the Awareness of Feelings

Because children of alcoholics have a higher likelihood of having alexithymia, an inability to identify feelings, most programs for children of alcoholics focus on feelings identification training and on training parents to label feelings that the child appears to be having. This intervention may also help to promote stronger parent-child attachments [33]. Anxiety in children of alcoholics can be reduced through increased predictability of the family environment as well as the school and community environment through family strengthening prevention programs that increase family organization, family management, and expression of supportiveness and love. Children of alcoholics often do have realistic reasons to be worried about their parents' welfare, their welfare, and the stability of the family, because child abuse and neglect [66], job loss and poverty, divorce, and parent deaths are more common [120]. Emotion-focused and problem-focused coping skills training within prevention programs for children of alcoholics [94] can help children to talk through feelings, reframe the negative aspects of the situations, create emotional distance from their fears, and develop other emotional supportive relationships with other adults. Mentoring and after-school programs can be very helpful to children of alcoholics in developing these needed supportive relationships with other caring adults. As found by Jordan and Chassin [52], involvement in positive activities outside the home by young children of alcoholics tends to reduce the likelihood of a substance use disorder in young adults.

Programs to Increase Cognitive Resilience Characteristics

Research with children of alcoholics [131, 50] found that cognitive resilience characteristics include a conceptual understanding of the parents' disease and relationships, the capability to distance oneself from the alcoholic parents in terms of identification, humor, and academic skills and mastery. Both traditional educational programs for children of alcoholics and community media campaigns can be used to promote these resilience factors.

Programs for Educational Interventions, Screening, and Referral

Children of substance abusers, as well as their parents, should know the results of the risk and resilience research on children of alcoholics. They need to know what signs and symptoms to watch for that might indicate that they or their children are high or low in resilience or in risk factors. Research demonstrates that children of substance abusers who are aware of their risk status drink significantly less than those who are unaware of their risk status [59]. Public media and education campaigns could be developed that will disseminate this research and allow children of substance abusers to conduct risk and resilience assessments for themselves. They need to know that a high tolerance for alcohol and being able "to drink others under the table" is not a good sign. Public education campaigns are also needed to reduce stigma and provide additional legal, social, educational, and academic supports for children of alcoholics in a non-stigmatizing environment. Parents and youth should be informed that living with an alcoholic parent can, in fact, lead to increased cognitive, behavioral, and emotional management. Increased stress-coping competencies can improve the ability of children of alcoholics to function in very stressful careers and in

times of distress, thereby improving pride and self-confidence and reducing the fear of a self-fulfilling prophecy.

Summary of Recommendations for Future Research and Policy Improvements

The most obvious implication from this review points toward the need for better longitudinal research. Most studies on children of alcoholics or other drug abusers are not longitudinal; that is, they examine behavior at one point in time. From these studies, it is unclear whether we see true deficits or merely developmental delay. Longitudinal studies allow us to predict when early disorders and behavioral deviations will be transient or when they will be precursors to more severe types of maladaptive behavior. Longitudinal research would also enable us to explain specific childhood outcomes. Differences in outcome could be studied simultaneously to understand whether antecedents discovered for one outcome are specific to it or are general antecedents leading to a broad variety of outcomes. The second implication from this review is the need also to understand the characteristics of resilient children in order to apply these protective factors in our campaign messages. Researchers and helping professionals have long identified a subgroup of children who grow up in homes with alcoholic parents and who seem to grow up relatively "invulnerable" to the detrimental effects of familial alcoholism. The research focusing on this subgroup is scarce. Anthony [6] suggested that there may be subgroups of children of substance abusers who, despite all odds, do, in fact, enjoy good health from birth, experience a positive environment at home, and develop rather normally into socialized, competent, and self-confident individuals. Certain individuals may be more competent in adapting to stressful living environments than others. These children are somehow able to compensate and cope with the various negative biological or environmental influences in their lives. Certain individuals may be able to manipulate their environment by choosing roles and goals in life that stabilize their developmental process and bring them the positive reinforcement they need to develop a positive self-image and, eventually, a relatively healthy life. Other individuals may be able to master the processing of incoming data and to conceptualize these data in such a way as to choose positive behaviors in life that compensate for whatever problems present. Finally, a list of policy recommendations, modified from a more extensive discussion by Chassin and associates [23], point the way toward future social responsibility:

1. International and local national agencies and institutes should develop research programs and support the implementation of evidence-based and family-focused prevention programs for children of substance abusers.
2. Policy makers within international, federal, state, and local governments should provide adequate funds for research, field tests, and wide-scale dissemination of effective prevention approaches for children of alcohol and drug abusers.
3. National surveys should include information that assesses and evaluates precursors of substance abuse such as risk and protective factors including strength-based behaviors.
4. Legislation affecting agencies providing services to children of substance abusers should include language that specifically stipulates the importance of funding effective and evidence-based prevention approaches that include parenting and family skills training programs.
5. Future research should maintain the privacy and confidentiality of children of addicted parents enrolled in prevention, education, and intervention programs.
6. Interagency collaboration is essential if public policy related to children of substance abusers is going to shift.

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Vulnerability to Addictive Disorders and Substance Abuse in Adolescence and Emerging Adulthood

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Overview of the Chapter

Adolescents and young adults make choices that set the course for much of their adult lives. While adolescence is not as chaotic as some may believe, substance use and abuse occurring during this critical period may have a continuing influence on emerging adulthood and beyond. For some, early experimentation with drug and alcohol use leads to a series of increasingly aberrant behaviors with social, legal, and educational consequences. Following experimentation, others age out of problems with the onset of adult responsibilities such as full time employment, marriage, and parenthood. In this chapter, we explore the scope of addictive disorders and substance abuse in adolescents and emerging adults, consider the impact of substance use and disorders on later development of addictive and other life problems, and review the potential for prevention or early intervention to reduce the consequences, including lifelong harm, of drug and alcohol use during these vulnerable periods.

Adolescence: Epidemiology and Risk Factors

Exploration and development of identity, autonomy, sexuality, academic functioning, and peer relationships are important age-appropriate tasks of adolescence [6, 15, 41]. Specifically, this developmental stage may manifest as adolescents question prior beliefs and assumptions and

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_66,

explore new philosophies and behaviors [96]. In addition, during this stage, adolescents are likely to try out behaviors that they believe characterize different facets of adult life. Some of this exploration and experimentation may include substance use and related risk-behavior, including normative and non-pathological experimentation with alcohol, cigarettes, and marijuana [4–6]. For those who are curious, high school provides many opportunities to experiment, as social events often include alcohol and other substances.

Across the nation, experimentation with substances has been starting progressively earlier; by age 13th (8th grade), 26% of surveyed students reported trying alcohol, 16% had smoked a cigarette and 9% had tried marijuana [10]. The rate of substance use and abuse increases throughout the high school years, with high school seniors showing the highest rates of alcohol and other substance abuse [10, 17, 63]. Throughout adolescence, many factors, including environmental characteristics, such as the availability of substances, the level of actual and perceived parental monitoring, and peer group behavior, play a strong role in determining level of substance experimentation and abuse [17].

Risk Behaviors During Adolescence

Binge Drinking During Adolescence

In a recent survey, 74% of adolescents reported having at least one drink in their lifetime [10]. Just under half of these students (43%) stated that they currently use alcohol (defined as at least one time of use during the past month), with that number rising to 51% for high school seniors [10]. More concerning, however, is the rate of binge drinking among adolescents. Specifically, approximately a quarter of adolescents (26%), and 32% of high school seniors reported recently engage in binge drinking [10]. For adolescents, binge drinking is defined more conservatively than for adults; the current definition is three drinks or more per drinking episode for adolescent girls and four drinks or more per drinking episode for adolescent boys. Binge drinking is considered one of the more problematic consumption styles [43].

Rather than causing harm through consistent, steady rates of excess, these single occasions of excessive consumption are harmful because binge drinkers may make poor choices that can lead to sadly irrevocable outcomes, such as the accidents, injuries, and fatalities that may result from drinking and driving [18]. The focus on the harms related to binge drinking are salient, as the current rates of alcohol-related risk behavior that occur among today's high school students is stunning. For example, 30% of American high school seniors reported having ridden in a car driven by a drunk driver, parallel to the percentage of high school seniors who smoke cigarettes [10]. In addition, just a slightly lower percentage (17%) stated that they had driven a car while intoxicated [10].

The demographic factors correlated with binge drinking have been consistent over the last few decades [9]. Specifically, being male, Caucasian, doing poorly in school (in terms of low grade point average and high truancy), having disposable income, and frequently socializing in the evenings correlate with higher levels of binge drinking.

Manifestations of Alcohol Abuse and Dependence in Adolescents Versus Adults

While alcohol use disorders (abuse and dependence) are relatively rare during early or middle adolescence, toward late adolescence, the rates begin to approximate those of adults [17]. Yet, distinct differences remain between adolescent and adult drinking [17, 22]. In a comparison of a adolescent drinkers and adults with alcohol dependence, it was found that while adolescents drink less frequently than adults (adolescents = 13.8 days per month; adults = 21.0 days

per month), the quantity of alcohol consumed per occasion was equivalent between the age groups [29]. Once adolescents commenced regular drinking, defined as drinking at least once a month for 6 months or more, adolescents displayed dependence symptoms including tolerance, withdrawal, and continued alcohol use despite related problems around month seven, while adults did not show these symptoms until year three [22]. After the first year and a half of drinking, many of the adolescent drinkers met criteria for a diagnosis of alcohol dependence whereas the adults did not meet criteria for dependence until year eight [22], indicating the possibility of a "telescoped" progression [62] for adolescents. Together, these data suggest that adolescents with alcohol use disorders may display an absence of traditional dependence symptoms [54].

Marijuana Use During Adolescence

Almost paralleling rates of binge drinking, 38% of American high school students have used marijuana in their lifetime, and 20% report current use [10]. Similar to the predictors of alcohol use, adolescents who use marijuana tend to be male, Anglo, performing poorly in school (in terms of low grade point average and high truancy), have higher income, and frequently socialize during weeknights [18]. While some posit that adolescent marijuana use is not risky and is potentially adaptive for adolescents [98], current concerns about the potential harms of marijuana use have resulted in several National Institutes of Health-based initiatives to intervene with adolescent marijuana use and related risk behavior. Specifically, the literature indicates that adolescent marijuana use has been linked to academic difficulties, other risk taking behavior, delinquency, legal consequences, and health consequences, particularly as related to sexual risk-taking [12]. Moreover, 40% of an adolescent sample identified their marijuana use as contributing to problems involving interactions with others [75]. In addition, this sample of adolescent marijuana users were so dissatisfied with the effects that marijuana had been having upon their lives, that 55% indicated having made a past decision to decrease their marijuana use and 20% stated that they intended to stop using marijuana within the following year.

Tobacco Use During Adolescence

Approximately one quarter (23%) of high school students currently smoke tobacco [10]. The prevalence of tobacco use has been found to vary by several factors, including educational level, income, gender, and culture [118]. Among adolescents, across cultures, Caucasian adolescents evidence the highest rates of current smoking and tobacco use [10]. Also, in terms of gender, smoking has been found to be greater among boys than girls [10]. The most notable aspect about adolescent tobacco use, however, is the high proportion of adolescents who are currently dissatisfied with their smoking. Specifically, over half (55%) of the current adolescent smokers report that they are actively trying to quit smoking [10]. However, tobacco use has been found to be fairly intractable, and reducing use has been found to be quite difficult [58, 59]. There are serious health implications for failed cessation attempts. Specifically, cigarette smoke contains thousands of substances, of which a substantial proportion is carcinogenic [111]. In addition, annually, the number of deaths caused by smoking surpasses the sum of deaths caused by HIV, alcohol and other drug use, motor vehicle accidents, suicides, and murders combined [29, 80]. Smoking has been linked to cancer, cardiovascular disease, pulmonary disease, reproductive health problems, and a number of health problems in nonsmokers [111]. In the United States, smoking peaks around late adolescence (ages 18–24; 24%), and decreases with age, with only 10% of people aged 65 and older smoking [11], highlighting the importance of determining and conducting efficacious tobacco prevention interventions for adolescents.

Alcohol- and Other Substance-Related Sexual Risk Behavior

Like substance use, sexual experimentation during adolescence is normative and has been argued to be developmentally appropriate [97]. While not inherently dangerous, high risk sexual behaviors, such as sexual intercourse without the use of a condom, or sexual intercourse with multiple partners, increase an adolescent's risk of unplanned pregnancy, contraction of sexually transmitted infections including HIV. Among adolescents, alcohol, marijuana, and tobacco use have been highly correlated with sexual activity [90, 104]. Specifically, 23% of sexually active adolescents have used alcohol or drugs before their sexual intercourse [10]. Unfortunately, the relationship between sexual activity and substance abuse is quite risky, as for many adolescents, adverse sexual consequences occur while using alcohol and marijuana, including unplanned sexual intercourse, intercourse with multiple partners, and inconsistent condom use [8, 90]. These risks are heightened for adolescents with comorbid psychopathology, who are two to four times more likely to engage in high-risk sexual behavior while drinking [8].

Adolescence as a Salient Developmental Period for Prevention/Intervention Efforts

Adolescent substance abuse patterns, particularly adolescent drinking behaviors, do not often predict later life patterns of use [25]. In fact, regardless of their substance use patterns, many adolescents continue into their adult lives without experiencing adverse effects [96]. However, the substance use and related risk behavior of some adolescents will interfere with their health and development [96]. The inherently transitional nature of adolescence presents a natural turning point for adolescents [94]. Specifically, the flux inherent in the adolescent lifestyle offers an outstanding opportunity to intercept maladaptive lifestyle choices, such as unhealthy drinking patterns and substance use, and re-route adolescents toward healthy life choices and skills [96].

Alcohol abuse and addiction in adulthood typically originate in drinking problems that begin in the adolescent and early adult years, a period termed "emerging adulthood." Patterns of drinking during this period may influence the onset or avoidance of alcohol abuse or dependence, and associated health, legal, and social problems related to excessive drinking.

Emerging Adulthood

Emerging adulthood is a developmental stage occurring in the late teens into the late twenties distinct from adolescence and young adulthood that is common in industrialized nations, during which individuals' demographics, subjective perceptions, and identity explorations are highly volatile [2, 3]. Emerging adulthood is characterized by a prolonged period of volitional activities, identity formation, seeking novel experiences, taking risks, and ultimately, achieving a defined sense of the self as an adult [41]. Attainment of adulthood is related to young people's subjective sense of attaining adult competencies, such as accepting responsibility for themselves, making independent decisions, becoming financially independent, and becoming a parent, and less related to status markers such as stable residence, school completion, career selection, or marriage/romantic commitment [21]. Emerging adults between the ages of 17 and 27 as a group show changes consistent with increasingly adult status markers; part time employment declines, full time employment increases, living with family declines, and being financially supported by family declines each year. However, status markers are highly volatile during this age period. Emerging adults show reversibility in status regarding residence, romantic attachments, and work life, and make

frequent transitions from one status to another, with periods of great independence sometimes followed by childlike levels of functioning in at least two domains [21]. Gender differences are strong during this period, with women achieving a stable residence status earlier, but achieving financial independence from families later [21]. Participation in higher education does not mediate demographic differences in the trajectories from childlike to adult status, with patterns similar among emerging adults who are in college and those who are not; thus, emerging adulthood is now viewed as a true developmental stage with distinct developmental challenges [12, 21, 41, 99].

Risk Behaviors Peak in Emerging Adulthood

Several types of risk behaviors peak between the ages of 18 and 25, indicating a strong relationship between risk behaviors and emerging adulthood [61]. While drinking, smoking, drug use, and sexual behavior are often initiated in adolescence, these behaviors increase in frequency and risk level during the emerging adulthood developmental phase, with risk behaviors such as binge drinking peaking at ages 21–22 according to the Monitoring the Future Survey [5]. The risk behaviors that peak during emerging adulthood and are of great public health concern include unprotected sex, substance use, and risky driving including high speeds and driving while intoxicated [5, 15]. Increased drinking is associated with leaving the parental home after high school and reduced adult supervision, and declining drinking is associated with marriage and parenthood [5]. Because of the strong relationship between age and substance abuse, problem drinking and other substance abuse has been labeled as a developmental disorder by some researchers [107, 108]. These increases in risk taking may be reflections of identity exploration, the desire for novelty and sensation seeking that is common among this age group, and the relative freedom from parental and role constraints [2]. Unfortunately, alcohol use can result in serious consequences, including injuries and death, most often from driving while intoxicated. College students are more likely to delay marriage and parenthood than other emerging adults and may drink at higher levels of risk for a prolonged period during emerging adulthood [2]. Binge drinking is particularly prevalent among college students with heavy episodic drinking higher among college than non-college youth ages 18–29 [28].

There may be long-term negative health consequences of binge drinking even among those who avoid injuries. Those who increase binge drinking between ages 18 and 24 are more likely to progress to alcohol abuse or dependence diagnoses [87, 120]. Although college students may be at particularly high risk, they did not differ from non-college students on criteria for alcohol dependence [28, 101]. While some researchers found a higher rate of clinically significant alcohol-related problems in the past year among college students vs. non-college peers [101], along with a higher rate of alcohol abuse and higher overall rate of drinking, others found no difference between college and non-college youth in rates of alcohol abuse [28]. Because heavy episodic drinking and alcohol use disorders are common among emerging adults and college students, research on college students may generalize to other emerging adults. However, residence status does relate to risk for diagnosis, with more alcohol abuse occurring among students living off campus, and the highest prevalence of alcohol dependence occurring among students living on campus [28].

Binge Drinking and Health Risks in Emerging Adults

Alcohol use in emerging adulthood is prevalent [63], and much of the drinking that occurs during this age period occurs in a binge pattern. Binge drinking is currently defined as drinking

that results in a peak blood alcohol concentration of .08 or greater, typically means consuming 5 (for males) or 4 (for females) standard drinks in about 2 h [88]. Binge drinking is persistently frequent among college students despite increased prevention efforts over the past decade [115]. Forty percent of college students have binged in the past two weeks, according to the College Alcohol Survey [115].

There are distinct developmental trajectories of binge drinking and associated health risks among emerging adults. In a prospective study of binge drinking trajectories and their correlates, investigators identified 4 distinct groups among a sample of high risk (children of alcoholics) and unknown risk (general sample) adolescents, with a college attendance rate of about 75% [12]. Nearly 40% of the sample was classified as non-bingers, having no evidence of binge drinking over a 5–7 year period with observations typically beginning at age 13. Those with an early onset of binge drinking (at 13–14 years old) reached a peak of binge drinking (weekly or more) at ages 19–20, had the greatest risk of short-term negative consequences of drinking, and were at the highest risk to develop alcohol abuse and dependence; this group represented 21% of the sample. A late-moderate group had an onset of binge drinking at ages 16–17, but binged less than monthly and represented 30% of the sample. The infrequent group had an early age of onset, but binged only a few times per year, and represented 9.6% of the sample. Consistent with other studies, this study found gender differences and negative health consequences of binge drinking. Males in any binge group showed increased risk for alcohol use disorder diagnoses by age 23, with 44% of the late-moderate group, 69% of the infrequent, and 84% of the early-heavy group carrying an alcohol abuse or dependence diagnosis by age 23. Females in the early-heavy group were at higher risk than those in other categories, with 73% becoming diagnosed with alcohol abuse or dependence by age 23. However, girls in the infrequent group were at the highest risk for elevated depression and were more likely to be children of alcoholics. Across genders, those in any of the binge drinking trajectory groups compared with non-bingers were more likely to be diagnosed with drug abuse and dependence. Across genders, non-bingers were more likely to be in college full time than those in any binge group. This study provided a promising roadmap for further examination of the impact of binge drinking on subsequent alcohol problems. While the authors found that the age on onset of binge drinking and the severity of drinking could generate risk trajectories, there are many possible factors that may determine the impact of risk drinking during emerging adulthood. These may include developmental processes such as individuation and identity formation and milestones such as coupling, educational achievement, and other risk behaviors such as smoking, drug use, unprotected sex, driving while intoxicated, etc.

Other Drug Use Among Emerging Adults

New evidence shows that marijuana use, binge drinking, and smoking often co-occur for college students. The Robert Wood Johnson foundation funded the Tobacco Etiology Research Network, tasked with identifying the trajectory of use of nicotine to dependence among college freshmen. The University Project Tobacco Etiology Research Network was a year-long study of freshmen at Purdue University and included screening assessment, baseline assessment, and weekly assessments, as well as twice-yearly cotinine and body weight measurements, on 912 university freshmen who had smoked 1 or more cigarettes in their lifetimes or had smoked 1 puff or more within the past year. Forty-six percent were female, 45% had smoked in the last month, and most had smoked fewer than 100 lifetime cigarettes. The University Project Tobacco Etiology Research Network utilized a Web-based application into which students entered weekly data. One advantage of the Web-based weekly survey methodology was the generation of a continuous stream of data that

could be queried for a large number of research questions, and that can identify patterns of risk and lower risk periods. For example, in the University Project Tobacco Etiology Research Network, most students smoked an average of 4 cigarettes per day, but this average could obscure the finding that cigarettes per day varied by day of the week, with most smoking occurring on the Thursday/Friday/Saturday weekend. Smoking occurred in a pattern consistent with weekend social events. Moreover, alcohol consumption, especially binge drinking, showed the same pattern, as did marijuana use [110]. These data clearly show that smoking, binge drinking, and marijuana use co-occur among large groups of college students, and that college students are willing and able to provide usable weekly data on their risk behaviors through a Web-based survey method. Unfortunately, because Tobacco Etiology Research Network studies are highly focused on smoking, the data they generated on drinking was relatively limited.

Consequences of Binge Drinking in Emerging Adulthood

Approximately 1500–1700 deaths and 599,000 injuries, and 200,000 serious injuries occur in the United States each year among college students [43, 44]. While some students may escape any problems related to binge drinking during college, others experience negative short-term problems and long-term health problems from drinking. Drinking among emerging adults can cause a range of health risks and psychosocial consequences including motor vehicle accidents, legal problems, personal injuries including date rape or other types of violence, blackouts, missing classes, unwanted or unprotected sex, and sexually transmitted diseases [56, 66]. Rates of these problems are high. Nearly 700,000 students are assaulted by another college student who has been drinking [56]. The 400,000 students ages 18–24 had unprotected sex and 100,000 students reported being too intoxicated to know if they consented to sex [56]. In the short term, other problems associated with drug and alcohol use in emerging adulthood include violence, depression, unprotected sex with risk for pregnancy and sexually transmitted diseases [9, 48, 49]. Twenty-five percent of college students report academic problems related to drinking such as missing classes, falling behind, doing poorly on exams and papers, or getting lower grades [48, 49, 91, 120]. Consequences are most likely among those students classified as frequent binge drinkers (defined in these older studies as 5+ drinks per occasion) vs. less frequent binge drinking [52].

While a minority of students becomes addicted to alcohol, 31% endorsed criteria for an alcohol abuse diagnosis and 6% met criteria for alcohol dependence during college [65]. When an adolescent or emerging adult evidences an alcohol use disorder, they generally have additional problems. Alcohol-related blackouts, craving, and risky sexual behavior are common among adolescents with alcohol use disorders [74]. Rates of disorders vary by gender and by binge drinking. Among household survey respondents ages 18–23, rates for men who had not binged (had not had 5 or more standard drinks on one occasion) in the past month for alcohol abuse were 13.3% and for dependence were 6.7% [116]. Among men who had binged, rates were much higher, 23.8 for alcohol abuse, and 13.0 for alcohol dependence. Among women 18–23 without recent binge drinking, 6.5% met criteria for alcohol abuse and 3.8% met criteria for alcohol dependence. Among women who had binged, the rates were 15.5% for alcohol abuse and 10.6% for alcohol dependence. Long-term effects can be quite serious; heavy drinking during the college years predicts alcohol-use disorders up to 10 years later [89, 120]. Binge drinking during college was also related to academic attrition, early departure from college, and less favorable job outcomes [60]. The use of illicit drugs in adolescence and emerging adulthood is the strongest predictor of life-time dependence [46].

Binge drinking is a prominent correlate of sexual risk among emerging adults, and this relationship is found across diverse studies.

A study using the 1993–1999 Youth Risk Behavior Survey found that binge drinking was a better predictor of adolescent sexual activity than lifetime and current use of alcohol [36]. Early binge drinkers had significantly more sex partners, while later onset binge drinkers and marijuana users had more sexual partners and were less likely to use condoms [47]. Binge drinkers were twice as likely as non-binge drinkers to have participated in unplanned or regretted sex. The use of other drugs in adolescence did not predict risky sexual behavior at age 21, suggesting a unique role for binge drinking and marijuana. Gender differences exist in risk-taking; for women, there is a risk profile with both high alcohol use and sexual activity, while for men, marijuana may be a marker for other risk behaviors [60].

Other Health Risk Behaviors and Consequences in Emerging Adults

Emerging adults are at risk for sexually transmitted diseases/HIV transmission due to multiple sex partners, unprotected sex, and substance use combined with sexual activity, and that these health risk behaviors were particularly problematic during "spring break" [1]. During spring break, prior casual sex, alcohol use prior to sex, and impulsivity significantly predicted casual sex, while condom availability and impulsivity predicted whether students used condoms. Unsafe sex could lead sexually transmitted diseases including HIV/AIDS or pregnancy. The consequences of infection with some sexually transmitted diseases include lifetime chronic illness in the case of herpes and a progressive fatal illness in the case of HIV/AIDS. The Youth Risk Behavior Surveillance System is an annual survey of health risk behaviors that contribute either to unintentional injury, illness, or death, and is administered in school to 9th–12th graders in the United States. The Youth Risk Behavior Surveillance System collects demographic information and covers a broad range of health risk behaviors including bicycle helmet use, seatbelt use, weapon carrying, school safety concerns, theft, property damage, fighting, date violence, depression, suicidal feelings, tobacco use, alcohol and drug use, sexual behaviors, weight, diet, exercise, riding with an intoxicated driver, driving while intoxicated, HIV knowledge, and asthma. The most recent analyses of the Youth Risk Behavior Surveillance System show that during the past 30 days, many high school students engaged in behaviors dangerous enough to increase their likelihood of death, including driving after drinking, drinking, and using marijuana. More than a third of the high school students who were sexually active reported using no condom during the last intercourse. The implications of the survey are that priority health risk behaviors such as drinking, unprotected sexual intercourse, and drug use are well established during adolescence, extend into adulthood, are interrelated, and are preventable [37].

Summary of the Literature on Drinking and Drug Use in the Emerging Adult Period

Data on emerging adulthood clearly points to a constellation of risk-taking behaviors centered around binge drinking, with an increasing risk of severe consequences with more frequent drinking. Emerging adults in college are at particular risk for frequent binge drinking and associated risk behaviors, including other drug use, smoking, unprotected sex, driving while intoxicated, and academic problems. The consequences of binge drinking and other risk behaviors are potentially lethal or lifelong, in the cases of motor vehicle accidents and sexually transmitted disease exposure including exposure to HIV. Most studies to date have provided a snapshot of emerging adults' behavior at one time point. Such studies do not allow a characterization of how binge drinking and other risk behaviors change as the emerging adult moves from adolescence to adulthood, how drinking may covary with other risk behaviors, and the likelihood of

alcohol use disorders and other alcohol problems due to patterns of risk drinking. What is needed is a longitudinal, real-time approach that could capture the ongoing drinking and other risk behaviors of a cohort of college students whose outcomes can be studied over time. That type of study would lead to the identification of students at greater risk of problematic outcomes and thereby identify the most fruitful targets for preventive interventions.

Prevention

Delay of Drinking and Substance Use

Preventing the initiation of substance use behaviors clearly has beneficial outcomes, in terms of adolescents' mental and physical health and development. Generally, the literature indicates that the earlier substance use begins, the more likely it is that the person will have problems such as a greater risk of substance use disorders, and other health problems [38]. Additionally, some adolescent boys who exhibit harmful drinking at younger ages have been found to persist in harmful drinking into their early 30s, while a percentage of both adolescent boys and girls who binge drink continue to binge drink into their early 30s [78]. As such, this has been an area of much interest, but research in this area has been more controversial, as many common educational approaches have not gained much empirical support for effectively preventing alcohol and other substance use [100]. However, while there is still much work to be done in this area, recent research has indicated that certain approaches may be better able to delay the onset of substance use and related risk behaviors.

Settings for Prevention Efforts

Media-Based Programs

Adolescents are reliable media consumers; 37% of adolescents watch more than 3 h of television a day [10]. Studies from the tobacco and alcohol advertising literature have indicated that adolescents' decisions to use tobacco and alcohol are influenced by media messages promoting their use [39]. Following these findings, several alcohol and substance abuse prevention programs have organized around helping adolescents develop media resistance and substance refusal skills (e.g., [40, 53]). Specifically, research has supported that the development of skills in these areas has predicted with lower levels of alcohol abuse up to two years following the prevention program [40].

School-Based Programs

Several school-based prevention programs have gained empirical support in intervening with substance use behaviors. Three of these approaches, while slightly different in content or construction, occur in school settings. When compared with control groups who receive education only or no intervention, many of these programs evidence support for interrupting the trajectory toward increased substance use. First, Project ALERT [73] and Project CHOICE [27], two relatively brief prevention programs that included several components common to many effective intervention strategies. Examples of those components include the provision of normative feedback, evaluating substance use expectancies, substance refusal skills, developing alternative coping strategies, planning, and problem solving options for potential settings where there is likely to be substance use. Second, although containing a slightly longer curriculum (18 sessions), the Positive Youth Development Program [109] was developed with a focus on strengthening adolescents' skills in problem solving and decision making. This prevention program has also gained support for interrupting the increasing progression of substance use among participating adolescents. Third, with components that integrate both effective prevention as well as effective family intervention strategies, Spoth and colleagues have found empirical support for their prevention approach [102, 103], which actively involves family members in their substance abuse prevention programs. After provision of this brief family-based prevention

intervention, this program significantly interrupted the rate of adolescents' substance use initiation [103].

Prevention for Emerging Adults

Much less has been published about prevention of substance use sequelae among emerging adults with the exception of interventions delivered in college settings. College prevention and intervention programs have included social marketing campaigns that attempt to set a new (more accurate) norm of lower levels of drinking or rates of binge drinking, or of drug use [16, 22, 69]. In addition, a variety of interventions for college drinkers have been tested, and generally include a non-confrontational approach, provision of personalized feedback of risk, raising awareness of potential negative consequences, education about specific dangers such as health risks of very high blood alcohol content, and referral to treatment when needed [22, 67, 82]. In addition, innovations such as Web-based programming are now gaining popularity; these interventions are generally based on evidence and can be completed in private at the student's convenience [34, 92, 93]. These interventions can be cost-effective and may reduce any potential for aberrant renorming by peers as might occur in an assessment plus feedback group [113, 114].

Early work settings have been overlooked as potential forums for dissemination of substance misuse prevention programming for emerging adults. The early work setting has been targeted for health behavior improvements for diet and exercise, thought to reduce later costs associated with heart disease and diabetes [92]. One study evaluated the effect of a Web-based normative feedback program designed for the prevention of high risk drinking among emerging adults in the workplace [35]. Compared with controls, intervention participants drank significantly less at the 30 day follow-up. Such studies, while rare, point to innovative solutions that may hold special appeal for today's emerging adults.

Treatment

The majority of adolescents and emerging adults who use substances do not face future substance dependence during their lives [4, 19, 96, 98]. For many, substance abuse and related problems naturally remit [9], leaving only a minority, who tend to be heavier or binge users, on the trajectory toward chronic and severe substance dependence [13, 14, 17, 20, 30, 89]. While treatment goals for adolescent interventions vary (i.e. some emphasize the importance of abstinence, while others strive for harm reduction), it is clear that most of the interventions aimed at adolescents do not result in long-term sustained abstinence [17, 55, 119]. The same is true for emerging adults, where most intervention programs target reducing harm related to drinking and drug use, rather than achieving abstinence [22]. The data suggest that interventions based on information and awareness models do not decrease substance use, while skills-based and cognitive-behavioral interventions show greater promise in decreasing substance use or related harms [69]. The interventions that have gained empirical support with adolescent substance abuse primarily fall between two categories: individual interventions and family-based interventions. Because many emerging adults no longer live with their families of origin, most treatment interventions for them have focused on them as individuals or as members of a specific peer group, such as college students who violated underage drinking policies.

Treatment for Substance Use Problems Among Adolescents and Emerging Adults

While the social nature of adolescent behavior, and the predominance of peer-based settings (i.e., schools, after school programs) make group interventions for adolescents appear to be a natural (as well as cost-effective) fit, the use

of group approaches to intervene with adolescent substance use has been quite contentious. Specifically, many argue that group-based interventions pose a high risk for iatrogenic effects with substance abusing adolescents [33]. Others posit that adolescent group-interventions lead to improved substance use and related health outcomes [64], and some group interventions for college emerging adults with drinking problems have been successful [68, 73, 82, 109].

In terms of individual interventions, two intervention approaches have gained substantial empirical support for reducing adolescent substance abuse: cognitive-behavior therapy [117] and motivational interviewing [83]/motivational enhancement therapy [84]. The skills-based and behavioral nature of individual cognitive-behavior therapy may assist adolescents in specifically developing skills and actively implementing strategies to reduce adolescent substance use [31, 96]. Often used in conjunction with cognitive-behavior therapy, the non-judgmental, open, and guiding approach of motivational interviewing and motivational enhancement therapy, focus on adolescents' ambivalence around their substance use and related risk behaviors. Both motivational interviewing and motivational enhancement therapy have led to reductions in alcohol use, related risk behaviors [17, 42, 85, 86], marijuana use [54, 112], and poly-substance use [76, 77]. However, the efficacy of motivational interviewing and motivational enhancement therapy with adolescent tobacco use has yielded mixed results [23, 24, 100].

One intervention finds itself between individual and family interventions: the adolescent community reinforcement approach [45]. Drawing on the community reinforcement approach [81] and effective parent-training programs, this intervention style includes both individual and family sessions dedicated to components including skill building, relapse prevention, increasing prosocial behaviors, positive communication, and effective parenting. The adolescent community reinforcement approach has gained empirical support in intervening with adolescent marijuana abuse [31].

As adolescents function within multiple systems, several empirically supported interventions have indicated that effective interventions for adolescent substance use should include a systems or multiple-level approach [7, 79]. Three types of family interventions have gained support in reducing adolescent substance abuse behavior [103]: brief strategic family therapy [105], multidimensional family therapy [70, 71], and multisystemic therapy [49, 50].

Developed for Hispanic and African-American youth with unremitting conduct, substance abuse, and related problems, brief strategic family therapy focuses on the behaviors and interactions of the family, culture, and critical social systems [106]. Notably, this intervention was one of the first to emphasize and integrate the role of culture into an adolescent substance abuse intervention. During the last two decades, Szapocznik and colleagues have found that families receiving brief strategic family therapy evidenced reduced adolescent substance use and improved family functioning [106]. In addition, when compared with adolescents who received group therapy, adolescents who received brief strategic family therapy demonstrated significantly reduced conduct problems, delinquency, substance use, and significantly improved family cohesion and interactions [95].

Like brief strategic family therapy, multidimensional family therapy was created as a developmentally-conscious intervention for adolescent substance abuse [103]. Like brief strategic family therapy, multidimensional family therapy is focused on enhancing positive family interactions [71, 71]. In addition, multidimensional family therapy also operates at a larger systems level to enhance the relationships between the family and relevant social systems [71]. Adolescents receiving multidimensional family therapy have displayed sustained reductions in substance use at 6 and 12 month follow-ups as well as improvements in externalizing symptoms, family cohesion, and school behavior [70, 72].

Like brief strategic family therapy, multisystemic therapy is a strength-based approach, aiming to empower families of adolescents engaged

in substance use and delinquency [26]. Like multidimensional family therapy, multisystemic therapy focuses on the interface between the adolescent, family, peer, school, and social networks [51]. Across evaluations, multisystemic therapy has gained support with adolescent offenders, showing improved caregiver functioning, family cohesion, caregiver supervision of the adolescent [26], reduced adolescent criminality [52], and more mixed outcomes for substance abuse, likely due to confounds in study design and treatment fidelity [52].

Many questions remain regarding driving factors behind efficacious interventions [32, 57]. Also, research is only beginning to explore the factors that moderate and mediate the efficacy of adolescent and emerging adult substance abuse interventions. However, it appears that some common factors, such as the emphasis on alliance, strength-based, and non- confrontational approaches may play an important role in the positive outcomes in these adolescent interventions. Medication-based interventions for addiction have yet to be widely tested in adolescents or emerging adults. The possibility of using a combination of psychotherapeutic and pharmacologic treatments to interrupt progression to dependence among early heavy drinkers or drug users remains intriguing and understudied.

Conclusions

Many factors lead to adolescent and emerging adult experimentation with alcohol and drugs, and for the majority of people, experimentation is a rite of passage that does not lead to irrevocable harm. Increasingly, preventive interventions strive to delay the initiation of use, and then to minimize any consequences or harms of drinking or drug use. For a minority with heavier patterns of drinking, binge drinking, or early onset of drug use, more selected interventions may be needed to alter a course toward aberrant, hazardous, and health-harming substance use. Studies that have examined the trajectory of risk over long periods of time have begun to identify those adolescents and young adults who may be at greatest risk. New directions that will further develop our understanding of adolescent and emerging adult substance abuse risks will include genetic evaluation of those with heavier patterns of use and abuse that may lead to highly specific pharmacotherapy treatment for those with highest risk and highest potential treatment response. In addition, new behavioral interventions that include delivery in non-traditional formats such as over the internet or via cell phones may have enhanced, specific appeal to adolescents and young adults.

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Alcohol and Substance Abuse in African Americans

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Contents

Introduction

The problem of health disparities for Africans Americans is well documented. The Surgeon General's Report noted that mental health and substance abuse disorders were common, and contributed significantly to morbidity and mortality [57]. In a subsequent supplement, it was concluded that racial and ethnic disparities existed in mental health and substance abuse for racial and ethnic minorities. The report found that mental disorders, including substance abuse, were not more common in African Americans than in other ethnic groups [58]. The problem was not one of differing prevalence. Rather, ethnic minorities had a greater illness burden. Clearly, socioeconomic factors are important. African–American families are more likely to have incomes below the poverty level, and they are more likely to be uninsured. Moreover, they are often the first or second generation able to accumulate wealth. As a result, family wealth among African Americans is only a fraction of that of their White counterparts [38]. However, the Surgeon General's Report showed that disparities in outcome persisted even when income or insurance status was controlled.

The reason for concern about substance abuse is its pervasive impact. The direct effects of substance abuse cost the country over $100 billion per year [55]. The African–American community probably is affected differentially because their median income is lower than that of Caucasians and their family wealth is substantially lower. Drug abuse contributes to the health disparities seen in ethnic minorities, and these disparities persist even when income is controlled [58].

Epidemiology

Although African Americans are often stigmatized as being at greater risk of becoming substance abusers, the evidence shows otherwise. Prevalence of overall substance abuse disorders is indeed greater [31]. However, these global statistics often hide trends that suggest the opposite, depending on age of use, gender, and type of

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_67,

drug. For example, among teenagers, Caucasians are more likely to drink or use some drugs than African–American youth [27, 63]. African Americans tend to begin drinking at an older age than other ethnic groups. African Americans have lower levels of alcohol use in both adolescence and young adulthood, develop fewer alcohol-related problems, and are less likely to smoke. Crack cocaine, on the other hand, is more commonly used than powdered cocaine and may be related to income since it is much cheaper [59]. Marijuana use may be greater later in life, but African Americans start using at a later age [31]. Compared with other ethnic groups, however, African–American youth are significantly more likely to initiate marijuana use before cigarette use [60].

The peak age for injected heroin use is higher for African Americans than for Caucasians [10]. This is a consequence of African Americans resisting the use of injected heroin and preferring non-injected heroin. Such a finding has obvious implications for the AIDS epidemic and mode of the spread of HIV. Overall, these findings show the importance of examining the patterns of usage rather than the volume or quantity of use to better understand ethnic differences.

Preventive and Risk Factors

Multiple factors contribute to the ethnic differences in use patterns. As noted above, socioeconomic factors are important, not only because the cost of a drug may determine use but also because income can determine where one resides. Drugs of abuse may be more easily accessible in inner-city and marginalized areas [25]. Also, residents in many of these areas consider themselves trapped and unable to move due to poverty and other social factors such as redlining [66].

Dealing drugs of abuse, while risky, is also potentially lucrative. For a low-income individual, the benefits may outweigh the risks and have the added value of giving the dealer status [19]. Such an individual would have the power to distribute wealth and paradoxically appear altruistic to the community as one who has the resources to make things better for everyone.

Place of residence is also important. African Americans who live in the same locations as Caucasians and who, therefore, have the same access to drugs tend to show the same abuse pattern in both the type of drug used and the prevalence of abuse [58]. The type of neighborhood clearly impacts use. However, geographical location is important as well [35].

The type of neighborhood also can determine the risk of exposure to trauma. Traumatic experiences are a risk factor for substance abuse even when it does not lead to post-traumatic stress disorder [48]. It is well documented that individuals in inner-city neighborhoods are more likely to be exposed to traumatic events [3]. African Americans are especially at risk given their residence pattern, which is often not because of choice [66].

Media exposure and advertisement also are factors. Advertisement, either directly or indirectly, can certainly influence drug use. Some in the African–American community have contended that their drug use is a result of targeted advertisement [58]. However, other ethnic differences probably contribute to differential exposure. African Americans spend more time watching television than do other groups. Recent studies have shown that African–American women exposed to alcohol ads are more likely to drink [34]. Manipulation of this factor could both explain use and provide a way of reducing abuse.

Education and positive role models are associated with drug use. Academic achievement and peer drug use have consistently been shown to have protective effects. In a recent study, they were shown to be significant predictors of alcohol and marijuana use among high-risk African–American youth [17]. Religiosity and spirituality have been proposed as protective factors [63]. One way in which these factors may work in inner-city youth may be through preventing post-traumatic stress disorder or other complications of trauma exposure [4].

It has been reported that African–American youth are significantly more religious than White and Hispanic youth, which could explain the lower rates of drug use for this group [64]. However, more recent studies have found that religion does, in fact, "protect" Black and Hispanic youth from substance abuse, but the strength of this relationship is greater for White than for non-White youth. The reasons for racial and ethnic differences in the strength of the relationship between religiosity and substance abuse are not clear. One possibility is that religiosity may be more of a cultural or group phenomenon among non-White youth, while among White youth it may be more of an individual factor affecting individual behavior such as substance use. Understanding the mechanisms by which religion might influence substance use and the reasons why these mechanisms may vary by race and ethnicity may provide clues to implementing effective prevention programs.

Impact on the Individual

Alcohol- or substance-abusing African Americans compared with other ethnic groups have worse mental health outcomes, physical health outcomes, and social outcomes when socioeconomic factors are controlled [58]. These agents adversely affect health outcome irrespective of race. African Americans, however, seem to be more adversely affected.

In one report in a cross-sectional study among mostly African–American alcohol-, heroin-, or cocaine-dependent persons without primary medical care admitted to an urban inpatient detoxification unit, 45% reported being diagnosed with a chronic illness, and 80% had prior medical hospitalizations. The mean age-adjusted SF-36 Physical Component Summary score was significantly lower than in the general United States population [21]. The impact of drug abuse is, therefore, pervasive and can be shown to impact broad measures of health outcomes.

In yet another study of substance abusers, African Americans averaged more emergency department visits than Whites and higher average yearly emergency department charges than Hispanics ($1,991 vs. $1,603). Charges over 2 years totaled $6,111,660. The high charges were no surprise since Blacks were most likely to be diagnosed with injury, hypertension, cardiac disease, alcohol abuse/dependency, and sexually transmitted diseases. Only 34% of this group of drug users was identified with a diagnosis of drug abuse or dependency [7]. These findings emphasize the high cost of substance dependence to a community that can ill afford it, as well as the problem of lack of access to services, since emergency department visits can be considered a proxy for limited access to treatment programs.

Substance abuse also contributes to mortality. The Surgeon General's Report and other previous reports have noted the consistently lower life expectancy in African Americans in comparison with other racial and ethnic groups. While there have been improvements, the trend has been a maintenance of that gap [57]. The lesser use of alcohol has, however, meant lower rates of death from alcohol-related diseases [45].

General medical conditions show poorer outcomes in substance abusers, which may help explain the mortality gap. One of the most important is HIV/AIDS, which the National Institute on Drug Abuse has concluded has now become a pandemic. The National Institute on Drug Abuse has established that drug abuse treatment is essential to HIV prevention [43]. Due to a number of complex and interacting biological, social, and economic factors, there are some populations that are at increased risk for HIV/AIDS. African Americans experience striking disparities in HIV-infection rates compared with other populations, and they are at particularly high risk for developing AIDS. African Americans make up just 13% of the U.S. population but more than half of the total AIDS cases diagnosed in 2004. Moreover, African–American females accounted for 68% of the female HIV/AIDS diagnoses from 2001 to 2004 while White females accounted for 16% and Hispanic females 15%. Although African Americans aged 13–19 represent only 15% of

U.S. teenagers, they accounted for 66% of new AIDS cases reported among teens in 2003 [14]. Not only is AIDS more common in African Americans, but African Americans tend to seek treatment later and do not survive as long after diagnosis. As a result, HIV infection has become the leading cause of death for African–American women aged 25–34 and for African–American men of all ages [43].

Drug abuse and addiction have been inextricably linked with HIV/AIDS since the start of the epidemic. While intravenous drug use is well known in this regard, less recognized is the role that drug abuse plays more generally in the spread of HIV by increasing the likelihood of high-risk sex with infected partners [49]. As a consequence, while the use of illicit substances by injecting abused drugs has featured prominently in the epidemic, the recent tendency to use agents such as opiates intranasally has not diminished the risk. Non-injected abused drugs such as cocaine, marijuana, methamphetamine, and even alcohol are also significant cofactors that affect HIV transmission as well as the course and outcome of the disease. Continued drug use contributes to the poor outcome seen in African Americans. These findings are consistent with others in showing that drug abuse is a major contributor to the health disparities and higher mortality rate in African Americans.

Drug abuse is known to be associated with family and personal violence. Adults who were abused were often abused by an intoxicated parent, leading to increased risk of drug abuse and abusive behavior [67]. The increased risk of child abuse in African–American communities can be attributed to the interaction of drug abuse with other risk factors in inner-city settings. Drug abuse contributes to behaviors such as personal conflicts, poverty, poor maternal care, and other factors that increase the risk of abusive behavior. Minority women are more likely to be assaulted or raped [1]. Additional to factors such as poverty and living in the inner city, drug abuse carries an increased risk of being victimized. Incapacitated/drug-alcohol-facilitated sexual assault is rapidly gaining recognition as a distinct form of assault with unique public health implications. Incapacitated/drug-alcohol-facilitated sexual assault accounted for 18% of all reported sexual assaults, with a prevalence of 4.0% among girls 15–17 years of age and 0.7% among girls 12–14 years of age. Girls with a history of incapacitated/drug-alcohol-facilitated sexual assault were significantly more likely than girls with other sexual assault histories to report past-year substance abuse [40].

The problem of gang violence is well known as a risk factor for the high rate of adolescent assaults and the extremely high homicide rate in African Americans, making communities unsafe and worsening poverty by making such areas unattractive to businesses. Drug abuse is clearly a factor. Drug abuse provides economic benefit for crime, but it also can lead to violent turf wars and be a justification for violent crime [8]. Even illicit but less lucrative drugs such as marijuana can contribute to gang formation and criminal activity in African–American youth. In fact, alcohol and marijuana are often the most commonly used drugs [39].

One of the consequences of drug abuse is involvement with the criminal justice system. African–American substance abusers are far more likely to be referred to the correctional system rather than for treatment. Moreover, African Americans arrested for possession are more likely to be incarcerated than their White counterparts [29]. These observations are significant because 40% of those in the correctional system have alcohol abuse and 20% have substance abuse at the time of offense, with two-thirds actively involved with drugs prior to admission to jail [22]. Incarceration means that as many as 14% of African–American males can no longer vote as a result of criminal conviction. Those who have served time can be excluded from public assistance, subsidized housing programs, and college financial aid. Many are also barred from employment in certain professions, including education, childcare, and nursing home service provision [15]. As a consequence, factors that contribute to drug abuse are exacerbated. In an effort to remedy the negative consequences of drug abuse, legislatures across the country passed harsh penalties including mandatory

minimum sentences targeting the derivative crack cocaine drug while users and distributors of the parent drug cocaine were able to escape with less punishment. This legislation had the consequence of further exacerbating the disparity in incarceration seen for African Americans since they and others in poverty settings were far more likely to use crack cocaine [23].

Thus, while many drugs of abuse are used less by African Americans compared with other ethnic groups, drug use itself interacts with other risk factors that contribute to violence and other risky behaviors. African Americans are more likely to be exposed to factors that contribute to drug abuse. African Americans may, in fact, be at lower risk of drug abuse if all other factors are kept equal [24]. Nevertheless, a legacy of discrimination, poverty, and social adversity contribute to a drug abuse problem that, in turn, worsens the impact of the drug use.

Comorbidity

Substance abuse is often comorbid with mental disorders. People diagnosed with mood or anxiety disorders are about twice as likely to suffer also from a drug use disorder (abuse or dependence) compared with respondents in general. Similarly, people diagnosed with drug disorders are roughly twice as likely to suffer also from mood and anxiety disorders [18]. This observation has important implications for African Americans.

First, comorbidity may contribute to the misdiagnosis of mental disorders. It has been established in multiple studies that African Americans with mental disorders are often misdiagnosed or never diagnosed [2, 53]. As a consequence, they are often never treated, overmedicated, or not offered treatment by mental health professionals [36, 46].

Because drugs of abuse affect similar brain circuits or receptor mechanisms proposed for mental disorders, drugs of abuse can cause abusers to experience one or more symptoms of mental illness. The result is misdiagnosis and inappropriate treatment of those without a mental disorder. Second, mental illnesses can lead to drug abuse [18, 32]. Additionally, individuals with overt, mild, or even subclinical mental disorders may abuse drugs as a form of self-medication. As a result, the mental disorder is ignored or considered yet another symptom of substance abuse. Treatment for the mental disorder is delayed or never provided. This treatment deferral or delay is often seen in African Americans with mental disorders [58]. Drug use disorders and other mental illnesses are caused by overlapping factors such as underlying brain deficits, genetic vulnerabilities, and/or early exposure to stress or trauma [12, 20]. The very factors that we described earlier as risk factors for substance abuse also increase the risk of mental disorders. To the extent that African Americans may be exposed to risks for substance abuse, similar factors may contribute to mental disorders. Finally, the combination of substance abuse and mental disorders adds greatly to the burden of illness [47, 62]. Treatment is more difficult. Services are less available, and the burden on the individual, family, and community is far greater. The increased burden of disease in African Americans is exacerbated.

Often African Americans face a triple burden as both disorders are important risk factors for general medical conditions such as HIV. In a recent study, individuals were assessed for psychiatric diagnoses, substance abuse, and HIV risk behavior using structured clinical interviews and self-report questionnaires. The majority (75%) were sexually active in the past 6 months and reported high rates of sexual risk behaviors, including unprotected intercourse (69%), multiple partners (39%), sex with prostitutes (24%, men only), and sex trading (10%). Recent manic episodes and greater drug severity were independent predictors of total HIV risk. Cocaine dependence was associated with increased risk of sex trading [42]. Mental disorders and substance abuse can, therefore, interact to increase the risk for HIV.

To conclude, comorbidity is yet another complication of substance abuse in African Americans. The co-occurrence may be yet

another factor that contributes to health disparities. In addition to the problem of misdiagnosis and undertreatment, the co-occurring disorders may further increase the risk of suicide, homicide, and chronic diseases.

Prevention

As noted above, protective and risk factors can be identified that may impact on drug use. Such a strategy can be used to develop prevention interventions for high-risk youth. Prevention strategies work. These can include parental monitoring and supervision [33]. They also may include drug education and information for parents or caregivers [6]. Additionally, brief family-focused interventions for the general population can positively change specific parenting behavior and reduce later risks of drug abuse [50]. These programs are particularly effective when culture is taken into account [26, 44]. Often, however, prevention programs to the African–American community are limited in scope or given low priority in funding compared with interdiction and law enforcement programs [46, 68].

Treatment

There is now little doubt that treatment can work, and it works for a variety of substances, across ethnicity groups, and in a variety of settings [28, 41]. Treatment programs, especially if they address cultural needs, are effective and have strong participation by ethnic minorities [51]. Effective treatment also can mean reductions in behaviors that increase the risk of HIV [52].

Racial disparities in treatment participation and access are well documented [58, 65]. Income and poverty are certainly a factor. As a result, African Americans have to depend on the availability of public facilities, which are sensitive to the political climate and willingness to provide funding for treatment versus the correctional system. However, differences persist even when income is controlled [65]. Part of the disparity may be related to the unwillingness of African Americans to accept treatment. In fact, African Americans may discontinue treatment sooner, leading to a poorer outcome [30]. This finding is complicated by the fact that African Americans are less likely to receive outpatient care. When access to outpatient care was controlled for statistically, racial differences in residential care and overall treatment retention disappeared [9].

The problem of access to service is complicated further by the type of services available. In one study, a city's racial composition was found to influence treatment center characteristics and services available, but the pattern is complex in that there are inequalities in treatment for certain types of services but not others. For instance, cities with high percentages of Latino Americans and African Americans provide more treatment options, such as employment and domestic violence counseling or programs for gay/lesbian clients. However, such cities have fewer integrated treatment centers that provide comprehensive assessment for substance abuse and mental health problems [61]. Thus, the problem is not simply the quantity of services but the quality of services that may greatly impact the poor and the underserved.

African Americans with substance abuse problems are more likely to be incarcerated [29]. However, many substance abusers in jail have received treatment or participated in a substance abuse program [22]. Correctional settings for African Americans are more likely to be punitive rather than rehabilitative. Moreover, the limitations in personal freedom after incarceration further limit access to treatment [15].

African Americans have been found to have less access to newer, more effective treatment approaches in mental health services [37]. Similar findings have been made in substance abuse. For example, buprenorphine is a long-acting partial agonist that acts on the same receptors as heroin and morphine, relieving drug cravings without producing the same intense "high"

or dangerous side effects. Congress passed the Drug Addiction Treatment Act, permitting qualified physicians to prescribe Schedule III–V narcotic medications for the treatment of opioid addiction. This legislation created a major paradigm shift by allowing access to opiate treatment in a medical setting rather than limiting it to federally approved opioid treatment programs. Buprenorphine was found to be effective in reducing opiate abuse and is an effective tool in AIDS prevention [54]. Moreover, African Americans were as accepting of this treatment as other ethnic groups [5]. Yet the vast majority of those who have access to buprenorphine are non-White males [16].

Clearly a number of socio-cultural factors exist that would prevent access to treatment and reduce disparities. However, some approaches have worked very well. As noted above, African Americans are more likely to be incarcerated. Untreated substance-abusing offenders are more likely to relapse to drug abuse and return to criminal behavior. This can bring about re-arrest and re-incarceration, jeopardizing public health and public safety and taxing criminal justice system resources. Successful drug abuse treatment in the criminal justice system can help reduce crime as well as the spread of HIV/AIDS, hepatitis, and other infectious diseases. Recent findings show that drug treatment works very effectively in the correctional system [11, 56]. Studies show that treatment can cut drug abuse in half, reduce criminal activity up to 80%, and reduce arrests up to 64% [13]. The result has been that more Africans Americans can have treatment available and avoid the revolving door of re-incarceration. Moreover, such treatment also reduces the spread of HIV, which has been associated with individuals in corrections returning to the community. Additional efforts, such as drug courts to avoid incarceration and legislative changes making it easier for inmates to expunge a criminal record if substance use or possession is the only crime, would go a long way to reduce the factors that contribute to involvement in the correctional system. Most importantly, it would move the focus of African–American drug users from punishment to treatment.

Conclusion

Addressing the problem of drug use and abuse in the African–American community has special challenges. Yet the problem must be addressed if there is going to be a genuine effort to reduce racial disparities in health. Drug abuse is clearly a problem that exacerbates the consequences of discrimination and poverty. The good news is that advances have been made in understanding the behavior and neurobiology of addiction, which has led to effective methods of detection, prevention, and treatment. These interventions work for African Americans. The challenge is to create the public and political will to shift the addiction focus to prevention and treatment, and to reduce disparities and improve treatment accessibility.

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Gays, Lesbians, and Bisexuals

Connie R. Matthews

Contents

Sexual Orientation: An Overview

Often the expression "sexual orientation" is used as though it were a simple concept with a clear meaning. To the contrary, "sexual orientation" is a complex concept that is often misunderstood. As an umbrella term, it replaced "sexual preference," which was more or less discarded as the ongoing discussion escalated regarding whether one's sexual orientation is really a choice, or "preference," or whether it is innate, something we are born with. We still do not have an answer to that question [104] nor do we need one to address the issues covered in this chapter. Sexual orientation has been defined as "the preponderance of erotic feelings, thoughts, and fantasies one has for members of a particular sex, both sexes, or neither sex" ([104], p. 28). Everyone has a sexual orientation.

The expression is sometimes used interchangeably with "sexual identity" although they are not the same. Sexual identity generally refers to a label one uses to describe oneself, usually incorporating a number of elements, including behavior, feelings, attractions, and fantasies [104]. Sometimes others, such as clinicians or researchers, might apply a sexual identity label that is incongruent with how the individual labels himself or herself. Likewise, the meaning of a label may change depending on who is applying it. For example, the young college student who proudly proclaims herself or himself to be "queer" likely has a different frame of reference for the term compared with the bully who calls a classmate "queer" in an attempt to intimidate.

It is also important to distinguish sexual behavior from sexual orientation or sexual identity [104]. Sexual behavior can be more confusing than it sounds as we debate about which acts constitute sexual behavior. A person's self-labeling and the behavior in which he or she engages often are consistent but sometimes are not. This distinction can become critical as we make assessments in both research and clinical practice.

Despite these complexities, it is helpful to have some sense of what terms generally mean (while being open to the possibility that any given client or research participant might have

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_68,

a different perspective). "Gay" can mean a man or woman whose sexual and affectional involvements are exclusively, or almost exclusively, with someone of the same sex, although "lesbian" is often used when referring to women. People who are "bisexual" are sexually and affectionally drawn to both women and men, sometimes sequentially and sometimes simultaneously, more often the former [63]. It is important not to confuse bisexuality with promiscuity because one does not imply the other. "Heterosexual" generally refers to someone whose sexual and affectional interest is exclusively, or almost exclusively, with persons of the opposite sex. Historically, we have tended to view sexual orientation and sexual identity as static, something we have for life. Recent research has shown that this is not always accurate, especially among young people [32, 33, 104]. Sexual identity in particular and sometimes sexual orientation can be quite fluid over time. Also, many people are reluctant to label themselves at all when it comes to sexual orientation. Thus, simple questions on research surveys or intake forms might not always be sufficient to gather the complex information needed to understand fully a person's experience.

Importantly, society does not, on the whole, portray a range of options when it comes to sexual orientation or sexual identity. Rather, heterosexuality is considered the norm, with anything else portrayed as some sort of lesser option if it is portrayed at all. As a result, most people are raised believing that they are heterosexual unless and until they realize that this does not fit with their experience and identity. If and when this occurs, there is often a transition process as one becomes more aware of oneself and of new ways of understanding and defining oneself. There are currently more models of lesbian and gay identity development (e.g., [15–17, 28, 42, 84, 107, 113] than there are of bisexual identity development (e.g., [11]), although work continues in both areas. Part of the process of developing a gay, lesbian, or bisexual identity involves moving away from a majority identity toward a minority identity [75], which is critical in fully understanding the scope of what occurs. It is important for researchers and clinicians to have a working knowledge of gay, lesbian, and/or bisexual identity development or the coming-out process.

Part of moving from a majority identity to a minority identity involves facing the stigma and oppression that confront minorities in a culture that values conformity. The victimization that gay, lesbian, and bisexual people face through harassment, verbal, sexual, and physical assaults, including murder, and continuing discrimination in housing, employment, and custody rights has been well-documented [7, 51, 55–57, 59, 60, 66, 67]. In addition, lesbian, gay, and bisexual people face less overt but still serious social experiences wherein they are marginalized or stigmatized as "other" [34, 44, 99]. A discussion about the mental health consequences of this minority stress follows later in this chapter.

"Heterosexism," defined by Herek ([58], p. 158) as "an ideological system that casts homosexuality as inferior to heterosexuality," is present whenever heterosexuality is seen as the standard and any other sexual orientation or identity is seen as "something else" or "other" rather than simply having a range of options—for example, when intake forms provide options related to marital status that do not include one pertaining to a same-sex life partner. Heterosexism also applies to the privileges that one enjoys when one is part of the majority—for example, the right to inherit jointly owned property without being taxed or to bring a partner to a company social event without fear of being fired. Likewise, heterosexism is present when we assume that all clients or research participants are heterosexual unless they make a point of telling us otherwise. Heterosexism also can pertain to bisexuality or any other non-heterosexual orientation besides homosexuality, although one's experience of it might look different depending on whether one is currently with a same-sex or other-sex partner.

A related expression is "internalized heterosexism," which refers to "the internalization by lesbian, gay, and bisexual ... individuals of negative attitudes and assumptions about

homosexuality that are prevalent in society" ([111], p. 510). Simply put, it is difficult to live in a heterosexist society without coming to believe some of what one hears and observes, or at least wonder what is true and what is not true. Thus, it is not uncommon for gay, lesbian, and bisexual individuals to develop self-hatred or self-questioning to accompany the social negativity that they experience on a regular basis. "Internalized heterosexism" has tended to replace the expression "internalized homophobia" in the literature as a more accurate description [111]; however, the expression "internalized homophobia" still continues to appear. Those familiar with addiction know that alcoholics and addicts often must overcome the stigma and accompanying shame that can arise from society's attitudes toward alcoholism and addiction. Hopefully that awareness can be helpful in understanding the complexities of heterosexism and internalized heterosexism. People who are gay, lesbian, or bisexual and addicted must face both sets of struggles simultaneously.

Prevalence of Substance Use and Abuse and Related Problems

The gay, lesbian, and bisexual population has long been considered an at-risk population with respect to alcohol and other drug addiction; however, it is difficult to assess exactly what this means. Early studies suggested rates of addiction, particularly alcoholism, that were far greater than those among the general population, with perhaps as much as 30% of the gay and lesbian population experiencing problems (bisexual men and women were not considered in these earlier studies) (e.g., [43, 71, 103]). Although these studies were important in bringing attention to the issue of substance abuse in the gay, lesbian, and bisexual population, they have since been criticized for their methodological problems (e.g., [6, 13, 95]), such as inconsistent definitions of both substance abuse and sexual orientation, convenience sampling drawn largely from gay bars, and lack of heterosexual comparison groups [23, 25, 30, 46, 63].

Despite the methodological concerns and resultant inflation of the problem, these early studies were helpful in bringing the gay, lesbian, and bisexual population to the attention of the addiction field and awareness of addiction to the gay, lesbian, and bisexual community. A number of studies followed in the late 1980s and early 1990s that attempted to address some of the concerns in the earlier studies, especially by recruiting larger, more representative populations from sources other than bars and making some attempt at having comparison groups of heterosexuals. Stall and Wiley [108] conducted a prospective study of single men living in and around the Castro district of San Francisco, which is known for having a heavy concentration of gay males. This allowed them to draw not only a pool of gay men, but also a comparison group, which had been lacking in previous studies. Bloomfield [8] studied lesbian/bisexual women and heterosexual women living in San Francisco using a random sample from a household directory. McKirnan and Peterson [86, 87] examined gay men and lesbians in and around Chicago, recruited through a variety of connections with the Chicago gay and lesbian community; they used results from a 1979 national survey as a comparison group. Skinner [105] and Skinner and Otis [106] conducted a longitudinal study of lesbian and gay men in two unidentified small cities in a southern state, recruited through mailing lists of gay and lesbian organizations, through snowball sampling, and at a gay pride celebration. They used the 1988 National Household Survey on Drug Abuse as a comparison group.

These studies helped to enhance our understanding of substance use in the gay, lesbian, and bisexual population although there were still methodological problems. They provided a more complex look at the issue, or at least helped point out the complexities that needed to be explored further. They did not offer consistent results; indeed, they sometimes contradicted each other. They were, however, consistent in suggesting that the early research likely

presented an exaggerated picture of substance use and abuse, especially alcohol use, in the gay and lesbian community. Nonetheless, this did not mean that the community should no longer be considered an at-risk population.

Contrary to the earlier studies, several of these studies found few differences in overall alcohol use between gay, lesbian, and bisexual populations and heterosexual comparison groups [8, 86, 108]. Still, they all found differences in patterns and outcomes of use that were important at the time and helped to shape future research. Among the more consistent results with respect to alcohol were fewer declines in use with age among the gay, lesbian, and bisexual samples compared with the heterosexual comparison groups [86, 106, 108]. Although Bloomfield [8] found very few differences between lesbian or bisexual women and heterosexual women in her study, those looking at both men and women [86, 106] found gender differences in results such that lesbians showed patterns of alcohol use more similar to their gay male counterparts than to heterosexual women. McKirnan and Peterson [86] and Skinner and Otis [106] found gay men and/or lesbians to be less likely to abstain from alcohol use; however, Stall and Wiley [108] found gay men to be more likely to abstain. McKirnan and Peterson [86] observed that their gay, lesbian, and bisexual sample was more likely to experience a variety of problems related to alcohol use than their comparison group despite a lack of differences in heavy use. Bloomfield [8] found that a larger percentage of lesbians than heterosexual women in her study were in recovery from alcoholism.

Another advance during this period was the examination of drug use beyond alcohol [86, 106, 108]. Patterns of other drug use for gay men and lesbians did show significant and sometimes substantial differences from comparison groups, although there are variations between studies in terms of which drugs are more prevalent and how this is broken down in terms of frequency, timeline, and demographics. Marijuana use was consistently found to be higher among the gay, lesbian, and bisexual samples [86, 106, 108]. McKirnan and Peterson [86] also found cocaine use to be higher among the gay, lesbian, and bisexual sample, although neither Stall and Wiley [108] nor Skinner and Otis [106] observed this to the same extent. Gender differences were also apparent with drug use, as with alcohol use, with lesbians tending to use at rates more comparable to gay men than to heterosexual women, although there were variations by drug and by study. Skinner and Otis [106] looked at cigarette use as well and found that lesbians were smoking at rates not only higher than those reported in national studies, but also higher than gay men in their own study. Another drug found to be related to both sexual orientation and gender was "poppers," the inhalants amyl nitrate and butyl nitrate sometimes used during sexual activity, especially among gay men [86, 106, 108]. Indeed, the use of poppers was so strongly associated with gay men that Stall and Wiley ([106], p. 68) commented, "If there is a distinctive 'gay drug,' that drug is poppers." Stall and Wiley [108] also found that gay men used a larger number of different drugs than their heterosexual comparison group, although this was not associated with the use of particular drugs more frequently.

Although these studies were an improvement over the very early ones and they did help to advance the field, there were nonetheless still numerous methodological problems. Some of the comparison groups were not true comparison groups, but rather attempts to compare data collected in a study narrowly defined by population and location with national data [86, 105, 106]. All of the studies were done in urban areas with a definable gay, lesbian, and bisexual community, which is not always the case in many areas. Having the availability of an identifiable community, even if somewhat hidden from the general population, has the potential to make the experience of being gay, lesbian, or bisexual different from that in locations lacking such a community. Likewise, recruiting from gay, lesbian, and bisexual organizations and gay pride events likely attracts a particular segment of the community that might not be representative of other segments of the community. Furthermore, although an improvement over recruiting

from gay bars, they are still convenience samples.

The reliance on local samples, whether prospective or convenience, was necessary due to the fact that none of the larger national studies asked questions about sexual orientation. By the late 1990s, some of these larger, national, random studies did add a question or questions that attempted to tap into sexual orientation. This change allowed researchers not only to assess gay, lesbian, and bisexual people's patterns of use with more confidence in the methodology, but also to get better comparisons with the heterosexual population.

Several large population-based studies asked participants about the sex of their sexual partners in the past year, over their lifetime, or both. This question was used to examine differences between heterosexual participants and participants with any same-sex sexual activity during the time period being considered. National surveys used have included the 1996 National Household Survey on Drug Abuse [23, 24] and the National Comorbidity Survey [47]. Although a detailed description of each study is beyond the scope of this chapter, there were some themes worth noting. No differences were found among men with respect to consumption of alcohol or meeting criteria for alcohol or drug disorders, although there were some differences between exclusively heterosexual men and men with any same-sex experience with respect to mood or anxiety disorders, with the latter more likely to meet criteria for disorders. Among women, those with same-sex sexual experience had higher consumption rates than those who were exclusively heterosexual, and were more likely to meet criteria for an alcohol use disorder. Women with same-sex sexual experience were also more likely to report having received treatment related to their alcohol use. Unlike some studies that have found lesbian or bisexual women to have consumption patterns similar to gay and bisexual men, the National Household Survey on Drug Abuse found gender differences such that women's consumption patterns were lower than men's regardless of sexual behavior or orientation [23].

Regional studies have included The California Women's Health Survey [12], the Los Angeles County Health Survey [31], and a survey of members of a large health maintenance organization [49]. These studies have looked exclusively at women and focused primarily on alcohol. In these studies, which compared exclusively heterosexual women with women who either self-identified or behaviorally were identified as lesbian or bisexual, the non-exclusively heterosexual women reported higher rates of consumption than the exclusively heterosexual women for both tobacco and alcohol [12, 31, 49]. There were some interesting age-related patterns. Unlike other research that has suggested that lesbian and bisexual women's use does not tend to decline with age, as is the case with the general population, these studies did find decreases over time. One study [49] found that differences in heavy drinking at younger ages between lesbian or bisexual women and exclusively heterosexual women disappeared over time and were not present in older age groups. Another study [12] found that there were declines with age for all women, although the declines were not as large for the lesbian and bisexual women.

Several studies examined the 2000 National Alcohol Survey, a population-based survey of more than 7,000 adults in the United States [35, 36, 112]. Two questions addressed sexual orientation—one asking participants to self-identify and one that asked about sexual behavior—and were combined in the analyses differently from other studies. Four rather than two sexual orientation categories were determined, with self-identification and sexual behavior matched as homosexual, bisexual, heterosexual, or a fourth category for both males and females wherein participants self-identified as heterosexual but also had some same-sex behavior in the past five years.

Breaking out self-identification and behavior, as well as gender, allowed for examining some finer distinctions among non-heterosexual participants than had been done previously. For example, heterosexual men and women were significantly more likely to abstain from using

alcohol than any of the other groups; however, lesbians were more likely to abstain than bisexual women or women who identified as heterosexual but had some same-sex partners, although these latter differences were not significant. Controlling for other variables removed most of the differences among groups with respect to consumption, although there were a few significant differences that put bisexual women and heterosexual women reporting some same-sex sexual activity at higher levels than exclusively heterosexual women. The only significant difference among men was that homosexual men reported more incidents of drunkenness than exclusively heterosexual men. Lesbians and bisexual women were more likely to report problems related to alcohol and to report past treatment than exclusively heterosexual women. Lesbians were about eight times more likely and bisexual women were more than five times more likely than exclusively heterosexual women to have been in treatment. At the same time, they were less likely than heterosexual women to report being satisfied with their treatment experience. There were no significant differences among men with respect to having been in treatment. These higher rates of treatment involvement for lesbians are important to note as they suggest that treatment facilities are likely to have lesbian and bisexual women among their women clients, whether they publicly identify as such or not, and that they might not be adequately meeting their needs.

It has not been until very recently that researchers began considering bisexual individuals and/or people who self-identify as heterosexual but report same-sex sexual activity separately from gay men and lesbians. Early indications seem to suggest that bisexual people may experience greater and perhaps unique risks with respect to the use and misuse of addictive substances. When researchers using the California Women's Health Survey [12] broke out lesbian and bisexual participants, they found that, although exclusively homosexual women did report higher rates of alcohol consumption than exclusively heterosexual women, those differences were not significant. The most prevalent and significant differences were between bisexual women and exclusively heterosexual women, leading the authors to conclude that the bisexual women were most at risk. Other studies [36, 112] found bisexual women more likely to drink heavily in bar and party contexts, more likely to use tobacco, and more likely to use tetrahydrocannabinol. An Australian community survey found that bisexual participants displayed poorer mental health than either heterosexual or homosexual participants across a range of problem areas, including alcohol misuse [69]. In contrast to these results, one of the studies based on the National Household Survey on Drug Abuse [24] did not find differences in prevalence of psychiatric syndromes between gay/lesbian participants and bisexual participants. Clearly this is an area ripe for more extensive and sophisticated research. In the meantime, however, it does show the importance of recognizing differences in non-heterosexual sexual experiences rather than simply referring to "gay/lesbian/bisexual" as if it was one all-encompassing description. This is vital in both research and clinical work.

Unfortunately, there has not been much research examining the influences of race or ethnicity on substance use and misuse or recovery. One recent study that drew data from the National Latino and Asian American study [26] found that, as has been the case in general population studies, lesbian and bisexual women showed greater likelihood than heterosexual women of recent substance use disorders, although gay and bisexual men showed lower likelihood than heterosexual men. The authors also compared prevalence rates with published general population studies and suggested that rates among the Latino and Asian American population seem to be less than what is reported in the general population studies. In a couple of studies in which the samples included half to two-thirds ethnic minority participants [62, 65], the researchers found lesbians reporting high rates of problem drinking, having been treated for addiction, and being in recovery. These results are consistent with other research. The one study that looked at racial differences found very few [65]. Clearly, more work needs

to be done in this area before we can draw any conclusions. Such research needs to address not just prevalence rates but also the ways in which sexual orientation and race interact, as well as the ways in which both interact with substance use and misuse.

Much of the research pertaining to substance use and misuse in the gay, lesbian, and bisexual population has focused on alcohol, perhaps because the earliest studies showed such high rates of alcoholism and perhaps because the role of the gay bar suggests that this is an area of particular vulnerability. This has produced some valuable information that had been lacking, and as research methods improve we gain a better understanding of the role of alcohol in the gay, lesbian, and bisexual community, as well as some of the outcomes of alcohol use in this population. In addition, as in the general population, alcohol use is more prevalent, thus affecting more people, than the use of other drugs. At the same time, the limited research that has examined the use of other drugs in the gay, lesbian, and bisexual community has found rates to be higher in this population than in the general population [64]. The use of stimulants, especially methamphetamine, among gay men is particularly problematic, especially among those involved with circuit parties (see discussion below). In fact, the Gay and Lesbian Medical Association recently undertook a project to increase the understanding of the problem of methamphetamine use among gay and bisexual men with the aim of better addressing it [45]. They reported that 10–20% of gay men had used methamphetamine in the 6 months prior to the publication of their report, with considerably larger percentages among some subpopulations. These rates are quite a bit larger than rates in the general population. The report addressed challenges in terms of treatment and encouraged health care providers to take a proactive role in screening and referral to treatment. In addition to the problems that methamphetamine creates on its own, its use in conjunction with sexual activity can put users at increased risk of HIV [52]. Another recent study reported higher rates of tetrahydrocannabinol use (e.g., marijuana, hashish) among lesbian and bisexual women than among heterosexual women [36]. More research is needed to gain a better understanding of drug use as well as alcohol use in the gay, lesbian, and bisexual population.

The large population-based studies have primarily sampled adults; however, there is evidence that gay, lesbian, and bisexual youth are also at increased risk for substance use and misuse. A study in New York City found adolescent gay males and females using alcohol at higher rates than their heterosexual counterparts, with differences between lesbian/bisexual and heterosexual young women being greater than differences between gay/bisexual and heterosexual young men [100]. Another study that used behavioral indicators to determine sexual orientation found similar results [94]. Lesbian, gay, and bisexual adolescents have also been found to use illicit drugs, including marijuana and cocaine, at higher rates than heterosexual adolescents [4]. Thus, adolescent treatment programs also must be prepared to address the specific needs of gay, lesbian, and bisexual youth.

Why Might Gay, Lesbian, and Bisexual People be More at Risk?

Although there continue to be more questions than answers regarding the increased risk that gay men, lesbians, and bisexual individuals face with respect to substance abuse, there are two reasons that seem to be consistently offered, both linked to their sexual minority status. One has to do with gay culture and the role that alcohol and other drugs have played over time. The other pertains to the stress created by living constantly in a society that oppresses them.

Although there are a greater range of options available now, historically gay, lesbian, and bisexual people have had limited avenues available for finding each other and gathering where they could be open about and accepted for who they are. Traditionally, the gay bar has played a

central role in bringing gay, lesbian, and bisexual people together. These places were far from paradise, and patrons frequently faced raids by police and harassment as they entered or left, but nonetheless they were all that was available that provided any type of refuge or sense of community. Indeed, the modern gay rights movement is generally traced to a police raid on a bar in New York City when patrons fought back rather than passively submitting to being rounded up and harassed. The pride celebrations that many communities still hold in the month of June originally began to commemorate the riots at the Stonewall Inn.

It is difficult to have a bar be a central gathering place without having alcohol (and often tobacco and other drugs) come to be a large part of social interactions. This raises the question of whether greater prevalence of drinking, heavy drinking, or problem drinking might be a function of contextual factors that create greater access [25]. The research on this is extremely limited. One early study found that the use of alcohol in recreational settings by homosexual men and women correlated significantly with alcohol problems, although this was mediated considerably by consumption [87]. A more recent study found that gay men, lesbians, and bisexual individuals do seem to frequent bars more often than their heterosexual counterparts, but do not uniformly drink more when they are there [112]. There were no significant differences in number of drinks among men or between lesbians and exclusively heterosexual women; however, bisexual women and women who identified as heterosexual but had same-sex partners did drink more in bars than other women. There is a need for more research in this area before any conclusions can be drawn about the role of bars in contributing to prevalence rates for the gay, lesbian, and/or bisexual population.

Still, for the gay, lesbian, and bisexual population, the bar has always represented more than a place to go for a drink; it has represented community [18, 115]. This has implications when attempting to intervene in problem drinking. The traditional approach of urging recovering alcoholics to refrain from going to bars might be less realistic when working with this population. Many will continue to go anyway [115]. Thus, harm reduction approaches may, where appropriate, be more pragmatic than abstinence-only approaches. In addition, relapse prevention work might need to focus more on abstaining in situations where alcohol is present than on avoiding alcohol-related events. With a wider variety of options now available for the gay, lesbian, and bisexual community, it is also vital that treatment providers familiarize themselves with what is available locally to help clients make connections with activities and groups in the gay, lesbian, and bisexual community that are less alcohol and drug oriented.

Another more recent cultural phenomenon that pertains primarily, although not exclusively, to gay men is the circuit party. These are dance parties, often private, but sometimes sponsored by commercial establishments, that can last for several days and attract large numbers of men [85]. They tend to occur in larger cities, with various cities holding annual events. Many participants make the circuit of numerous such parties—hence the name "circuit party" [82]. Men who attend these parties tend to be well educated and financially well off [82]. Circuit parties can sometimes be fundraisers for services in the gay community, frequently related to HIV/AIDS, although often they are not. They involve dancing, music, and light shows, as well as extensive drug use and sexual activity. Although a variety of drugs, including alcohol, are used heavily, the most popular drugs used at these events tend to be stimulants, including methamphetamine, gamma-hydroxybutyric acid, ecstasy, ketamine, cocaine, and amyl nitrite or poppers, with many participants using multiple drugs [74, 82, 85]. Some of these drugs are particularly risky for potential overdose. In a study of men who had attended at least one circuit party in the past year, 25% of the sample indicated at least one instance of overuse during that time [74].

Gay men attend circuit parties for a variety of reasons. For the majority, the reasons are primarily social. As with the gay bar, these

parties provide an opportunity for socializing and meeting people in a gay-friendly environment. For some, however, the reasons are primarily sensation-seeking [82, 101]. Not surprisingly, there is greater risk for problematic substance use and/or sexual behavior among those who attend for sensation-seeking reasons. Likewise, drug use, especially the use of multiple drugs, increases the likelihood of risky sexual behavior [74, 82, 101]. For those seeking the sensation of combined drug, especially stimulant, use and intense sexual activity, the two behaviors can become associated in ways that must be considered in treatment [50]. Just as the drug use can enhance the sexual experience, so too can the sexual activity become a trigger for relapse. Although it is not uncommon to include sexual abstinence as part of a treatment plan, this must be done in ways that do not exacerbate any psychological struggles with minority sexual orientation.

Another reason often associated with the gay, lesbian, and bisexual population's special risk with respect to substance use and abuse is the stress of living in a society in which they are marginalized as "other" and face prejudice, discrimination, and oppression. Minority stress has been defined as "a state intervening between sequential antecedent stressors of culturally sanctioned, categorically ascribed inferior status, resultant prejudice and discrimination, the impact of these forces on the cognitive structure of the individual, and consequent readjustment or adaptational failure" ([10], p. 84). It has been used to describe the physical and psychological fallout of discrimination and oppression related to racism, sexism, and classism. More recently, the concept of minority stress has been applied to the mental health consequences of heterosexism experienced by lesbians and gay men [10, 34, 88, 89]. We are beginning to see consistent evidence that lesbian, gay, and bisexual people are experiencing harmful effects that go beyond the harassment—even violence—that they experience because they violate society's norms of heterosexuality. Further, research is also beginning to show that such experiences have negative ramifications for both physical and mental health, even if one is not open about one's sexual orientation (e.g., [34, 44, 102]).

Some researchers have operationalized minority stress as it pertains to sexual orientation through measures assessing such things as internalized homophobia, stigma or stigma-consciousness, and experiences of prejudice and/or discrimination related to sexual orientation [27, 60, 72, 73, 83, 88, 92]. They have found that these factors contribute to elevated levels of psychological problems such as demoralization, guilt, thoughts of suicide, depressive symptoms, depressive disorder, traumatic stress symptoms, anxiety, anger, panic disorder, and meeting criteria for more than one disorder, as well as physical problems.

To date, the empirical research examining substance abuse in conjunction with minority stress has been quite limited, most of it not addressing minority stress theory per se. The results have been mixed and somewhat weak. An early study [87] found the use of alcohol to reduce tension to be related to the prevalence of alcohol use and alcohol problems among gay men and lesbians. The same study found that external stress due to discrimination had a greater influence than internal turmoil related to sexual orientation, although this effect was more pronounced among men than among women. Another study [83] that examined the relationship of perceived discrimination to a variety of mental health problems, including alcohol and drug abuse, found that gay men, lesbians, and bisexual individuals experienced more discrimination than their heterosexual counterparts and that those experiences correlated with greater psychiatric morbidity, even when controlling for other factors. A more recent study [114] also found that gay, lesbian, and bisexual individuals whose responses indicated a substance use disorder had significantly higher scores on a measure of discrimination due to sexual orientation; however, the effect size was small. Studies looking at internalized homophobia in relation to substance use and misuse have found less consistent and weaker relationships with indicators of excessive or problematic use of substances, as well as some inconsistent gender differences

[1, 2, 114]. One study even found a negative relationship between internalized homophobia and lifetime use of tobacco, alcohol, and marijuana, as well as past-month use of marijuana, among lesbian and bisexual women. There is a need for more research in this area, perhaps enhanced by stronger measures of internalized homophobia [2], which is a concept still being refined empirically, as is sexual orientation-based discrimination. The existing literature suggests that minority stress might contribute to increased levels and more problematic use of substances among the gay, lesbian, and bisexual population; however, that relationship is likely more complex than our current understanding reveals. It is also worth remembering that, given the high rates at which substance use disorders coexist with other mental health disorders [40], the effects of minority stress as evidenced in other psychiatric problems will likely have ramifications for many individuals in treatment for addiction.

It is important to keep in mind several things when considering explanations for elevated and sometimes unique risks for substance use and misuse among the gay, lesbian, and bisexual population. Perhaps the most important is the fact that, even though there might be particular risks for gay, lesbian, and bisexual individuals, the majority of them do not experience substance abuse or other psychiatric disorders [25]. Thus, it would be wrong to operate on the premise that addiction is rampant in the gay, lesbian, and bisexual population or that this population is somehow sicker than the heterosexual population. Recognizing some potential aspects of gay, lesbian, and bisexual culture or experience that might put them at risk does not mean pathologizing them as a group, especially since some of those factors are socially imposed. Likewise, it would be short-sighted not to consider the elements that help the majority of gay, lesbian, and bisexual people to be resilient in the face of these unique risk factors [25]. It is important not just that we affirmatively treat those who do misuse substances, but that we work to strengthen the resiliency factors in those who do not but might eventually misuse them without intervention. It is likewise critical that we as a profession work to reduce the risk factors that come from social structures that oppress minority groups, including those who are gay, lesbian, or bisexual.

Affirmative Treatment with Gay, Lesbian, and Bisexual Clients

The State of the Field

Despite the fact that earlier methodological problems might have accentuated the risk for addiction among the gay, lesbian, and bisexual community, this population nonetheless continues to be considered a high-risk group. Furthermore, there are particular issues facing gay, lesbian, and bisexual people, which seem to influence how they use addictive substances and what they must face in recovery. Likewise, there is evidence to suggest that gay, lesbian, and bisexual clients are less likely to be compliant with medical and therapeutic recommendations when providers behave in ways that are insensitive or hostile with respect to sexual orientation [92, 95, 97]. Thus, treatment services that recognize and address these concerns are essential (e.g., [5, 29, 37, 61, 70, 109]). This includes programs that target gay, lesbian, and bisexual clients or have specific components geared for them, as well as counselors in all treatment facilities who are culturally competent in working with this population. Although only a few studies to date have directly queried gay, lesbian, and bisexual people in recovery about their treatment experiences, their message is consistent regarding the importance of counselors, programs, and 12-step meetings that are affirmative [9, 70, 78, 79, 80].

Unfortunately, such cultural competence with respect to the treatment and recovery needs of lesbians, gay men, and bisexual individuals who misuse alcohol and other drugs may be hard to find, especially in less urban areas. Each year, the Substance Abuse and Mental Health Services Administration collects self-reported

information about specialized services offered by substance abuse treatment facilities through the National Survey of Substance Abuse Treatment Services. Although 854 of 7,691 treatment facilities responding in a recent year indicated that they provided specialized services for gay, lesbian, and bisexual clients, when researchers [22] followed up to determine what services these facilities provided, almost three-quarters of them indicated that they did not provide any specialized services. For some facilities, specialized services were described simply as not discriminating against or being accepting of gay, lesbian, bisexual, and transgender clients, although it was not clear exactly what this meant. Only 62 agencies actually provided services specifically directed to gay, lesbian, and bisexual clients, and half of those were located in California and New York. Not only did these researchers find a serious lack of services for an at-risk population, but they also found a considerable amount of inaccurate information that could lead clients to facilities that profess expertise they do not have.

Studies of addiction counselors have likewise found many of them to be insufficiently prepared to work with gay, lesbian, and bisexual clients. Although the research is scant, the results consistently show a lack of knowledge and understanding of both gay, lesbian, and bisexual culture and the particular challenges facing this population in treatment and recovery [29, 38, 39, 54, 68, 80]. Attitudes among addiction counselors toward gay, lesbian, and bisexual clients seem mixed, with some counselors showing fairly positive attitudes, even if they lack the knowledge and skills to be fully effective, while many others display insensitivity and bias that is likely detrimental to clients [38, 39, 79–81]. Interestingly, both attitudes and knowledge seem to be lower, or more negative, with respect to bisexual and transgender clients than to lesbian and gay clients [38, 39]. Given that the limited research considering bisexual individuals separately from gay men and lesbians suggests that bisexuals might be at greater risk, this finding is particularly concerning.

There is some evidence to suggest that counselors who are themselves gay, lesbian, or bisexual are more likely to engage in affirmative practice [39, 78–80]. Caution must be used here because this does not mean that any given gay, lesbian, or bisexual counselor will be more affirmative or more skilled in working with sexual minority clients than any given heterosexual counselor. Nor does it suggest that only sexual minority counselors can be effective with sexual minority clients. Still, addiction treatment facilities would likely benefit from having counselors who are openly gay, lesbian, or bisexual on staff. Such facilities have long recognized the value of having staff members who are in healthy recovery themselves to serve as role models. It seems possible that openly gay, lesbian, and bisexual counselors who are comfortable with their sexual orientation could similarly serve as role models for clients who might be struggling with this aspect of their lives.

There is a need for both systemic and individual efforts in providing affirmative treatment for gay, lesbian, and bisexual substance users and abusers. In the National Survey of Substance Abuse Treatment Services study, some of the agencies reported previously having specialized services that were no longer available after a particular counselor left [26]. Affirmative treatment for gay, lesbian, and bisexual clients cannot be dependent on one counselor. A commitment to sensitive programming must go beyond the term of employment of particular counselors or the length of a grant. Although counselors may specialize, it is important that all counselors have a basic level of attitudes, knowledge, and skills that allows them to work affirmatively and effectively with lesbian, gay, and bisexual clients. Agencies can and must establish a climate that is non-heterosexist. When such a climate exists, individual counselors are more likely to have affirmative attitudes and behavior toward lesbian, gay, and bisexual clients [78]. Such a climate includes, but is not limited to, adding sexual orientation and gender identity to the agency's non-discrimination policy. This lets clients know up front that the agency has

considered their needs [79]. At the same time, such a statement must be backed up by practice.

Affirmative Practice

Because acknowledging one's sexual orientation can often lead to negative or even harsh ramifications, many gay, lesbian, and bisexual people are reluctant to offer this information until they have assessed the climate. Gay, lesbian, and bisexual clients often watch for signs that a facility or a counselor will be affirmative, or at least not discriminatory [79, 81, 109]. Including sexual orientation and gender identity in an agency's non-discrimination policy and publishing it in promotional material is an important way to let potential clients know that an agency has thought about gay, lesbian, and bisexual clients and taken a position that such clients will not face bias or discrimination in treatment. Such a statement must be supported by mechanisms to ensure that it is unequivocally enforced, not only by staff but by other clients as well [109].

Although they provide a critical foundation, non-discrimination policies are not sufficient for creating an affirmative climate. It is important to provide other visible indications that agencies and counselors are aware that some of their clients are likely to be gay, lesbian, or bisexual and actively seek to be inclusive [79–81, 109]. Periodicals and other information in waiting rooms or resource rooms ought to include materials that specifically address the gay, lesbian, and bisexual population. Videos or other materials used in educational programming should be screened to ensure that they are not heterosexist and that gay men, lesbians, and bisexual individuals see themselves portrayed as well as others. Likewise, to the extent that there is artwork or other decorative displays, it should be reflective of the diversity of clients the agency serves. It is also important to remember that the gay, lesbian, and bisexual population reflects the diversity of the general population and is not all White, young, able-bodied, or middle-class.

Another critical piece of affirmative practice involves recognizing that gay men, lesbians, and bisexual individuals represent a hidden minority (e.g., [41]). Thus, a client's status as a sexual minority is not immediately evident. We cannot simply assume that all clients are heterosexual unless they tell us otherwise; we must ask [6, 21, 37, 75, 78]. Likewise, we cannot draw conclusions based on other demographic information. For example, someone who reports being married might be heterosexual, but he or she could be bisexual or even gay or lesbian (married in a state where same-sex marriage is legal, or coming out later in life). Making assumptions can mean missing vital information about a client. Furthermore, making assumptions about heterosexuality can communicate to clients, correctly or incorrectly, that a treatment facility or counselor has not considered their needs. Putting the burden of disclosing sexual orientation on clients serves to marginalize them [98], forcing them into a role of someone who is different from what is expected. Asking all clients about sexual orientation helps to normalize all potential responses. It is important to remember from the discussion earlier that sexual orientation can be fluid and multidimensional, so inquiries must reflect the complexity of the concept. Such questioning also helps counselors to get a clearer understanding of individual clients, regardless of how they identify themselves.

Proper assessment goes beyond just adding a few questions about sexual orientation. Most treatment facilities have extensive assessment procedures that address a wide range of biopsychosocial issues. It is important to ensure that such assessment takes into account concerns related to sexual orientation. There are a number of ways in which assessment procedures might be biased [19]. Omission bias occurs when instruments assume heterosexuality. As important as it is to ask questions about sexual orientation during intake, it is also important to use assessment tools that take a range of sexualities into account. It is especially important to avoid using instruments that pathologize non-heterosexual orientations. Connotation bias occurs when negative concepts are associated

with being gay, lesbian, or bisexual. Likewise, it is important when selecting and interpreting testing instruments to be careful with instruments that have not been normed on the lesbian, gay, and bisexual population [37]. It would be preferable to use only instruments that have been properly standardized with this group, but since so few exist, it is critical to consider whether sexual orientation might influence responses and take this into account when making interpretations. Also important to remember when making interpretations is that scores considered "normal" usually fall within a range. Thus, when gay, lesbian, and bisexual clients score lower than heterosexual clients, but still within the normal range, they are not less psychologically healthy [48].

It is also vital during assessment to examine the interplay between sexual orientation and addiction in a sensitive and informed way [5, 6, 14, 37]. Both addiction and sexual minority status have a history of being linked through shame and pathology in ways that have been inaccurate at best and often more destructive than helpful [9, 14]. Being a sexual minority does not make one a sicker addict; nor does being an addict provide support for pathologizing sexual minorities. Nonetheless, internal struggles around accepting one's sexuality can exacerbate an addiction, and problematic use of substances can make it more difficult to work through conflicts related to sexual orientation. It is important to assess how the two concerns interact with each other in an individual client [5, 6, 14] in ways that empower rather than diminish the client. Included in such an assessment is evaluating a client's stage of development in terms of both addiction and sexual orientation [6, 14, 37, 109]. Assessing the level of addiction and readiness for change is a standard element in treatment facilities and, thus, is familiar to most addiction professionals. Assessing development with respect to sexual orientation is more difficult because theory and research regarding gay, lesbian, and especially bisexual identity development are still considered works in progress; hence, standardized instruments appropriate for clinical use have yet to be developed. Thus, such exploration is best accomplished through the clinical interview, and there are some informal protocols available for guidance in doing this affirmatively (e.g., [76, 109]).

Treatment Issues Specific to Gay, Lesbian, and Bisexual Clients

In addition to the general guidelines for affirmative practice, there are some specific issues that are important to address in addictions work with gay, lesbian, and bisexual clients. Perhaps the most critical issue involves self-acceptance. This was the overarching theme expressed in a qualitative study of lesbians in recovery [79] and is repeated throughout the literature in both empirical and anecdotal work (e.g., [5, 6, 14, 61, 78, 90, 97]). Shame has long been recognized as an element of addiction to be addressed in treatment [96]. Gay, lesbian, and bisexual clients experience this as well. At the same time, they often experience internalized heterosexism, which can interact with the shame around addiction. Participants in qualitative studies stress that both of these issues must be addressed [78, 79] and that the interaction can be tricky. Consistent with common practice in the addiction field, they report that being clean and sober must come first. Without that, it is difficult to tackle the issues related to sexual orientation. At the same time, self-acceptance as a gay man, lesbian, or bisexual person is critical to long-term sobriety. Thus, programs that address only the addiction might help gay, lesbian, and bisexual clients initially to get clean and sober, but are likely to fail them in terms of long-term success. Indeed, one inpatient treatment center specifically for gay men and lesbians has found that over half of the clients who entered had been through inpatient treatment at least once prior to entering that facility, often without ever addressing sexual orientation [97].

Helping lesbian, gay, and bisexual clients develop self-acceptance involves two critical elements for counselors. In keeping with standards for multicultural practice, the first step is an

assessment of the practitioner's own attitudes and beliefs about non-heterosexual orientations [21, 37, 110]. It is a challenge to help a client accept an aspect of himself or herself that the counselor or physician finds unacceptable. Even for the practitioner who wishes to be accepting and affirmative, the effects of societal heterosexism can easily creep into treatment. This applies to practitioners who are themselves gay, lesbian, or bisexual as well as to those who are heterosexual. The next step involves being knowledgeable enough about sexual orientation identity development and the coming-out process to be able to recognize where a client is in that process [5, 6, 14, 18, 61]. Responses that can be very facilitative at one phase of the process can be limiting or even frightening at other points. Just as addiction counselors must assess and work with alcoholics and addicts at their current stage of readiness for change, so too must they assess and work with gay, lesbian, and bisexual clients at their current stage of identity development. This can be further complicated if the gay, lesbian, or bisexual client also happens to be a racial or ethnic minority because that involves negotiating at least two interacting trajectories, sexual orientation and racial identity development [20, 93], along with the addiction.

The coming-out process has some unique implications for gay, lesbian, and bisexual people with respect to recovery from addiction [3, 5, 6, 61, 79]. Although the expression "coming out" can sometimes mean recognizing one's minority sexual orientation and coming to terms with it, "coming out" also means acknowledging this status to other people. Hence, it is an ongoing and lifelong process. Coming out can often bring positive results as one shares important aspects of oneself with important people in one's life. Sometimes, however, the results can be devastating and can include being fired from a job, kicked out of a home, or ostracized by friends or family. Thus, the gay, lesbian, or bisexual person must constantly assess the environment, and interpersonal relationships, to determine whether or not it feels safe to come out in a given context. There are very real reasons for choosing not to do so. This need for caution can sometimes conflict with treatment prescriptions about the importance of honesty over keeping secrets. Because denial and secrecy are often considered unhealthy remnants of addiction, clients are taught the importance of honesty.

Counselors and health care providers must be able to help clients learn to negotiate this tricky process. This begins by creating an environment where clients can feel free to be open with the counselor. It also involves establishing parameters that make it clear that discrimination, bias, or harmful comments from other clients will not be tolerated, thus making it safer for gay, lesbian, and bisexual clients to be open throughout the treatment program. At the same time, it is important to leave decisions about when and to whom to come out up to the client. Confidentiality is a hallmark of most addiction treatment programs; it is even more vital when it comes to disclosing a client's sexual orientation. This should never be done without the client's consent, and clients should never be coerced into giving consent against their better judgment, even if their judgment in many other areas might be questionable, as it often is for people early in recovery. Part of the treatment plan might include learning to distinguish between healthy caution about coming out and unhealthy denial that can threaten long-term sobriety. Some clients might also need help in learning how to assess situations to determine safety for coming out, as this is not a skill that people inherently have. This is an area where it can be very helpful to have gay, lesbian, or bisexual counselors and others who can serve as role models.

Closely related to self-acceptance is helping clients address both heterosexism in society and internalized heterosexism [3, 5, 37]. The stigma, oppression, and perhaps even victimization that existed before a gay, lesbian, or bisexual client entered treatment will not disappear just because he or she gets clean and sober. It is critical that treatment programs help their gay, lesbian, and bisexual clients learn first how to understand the concept of heterosexism and how it works and then how to confront it without using substances to escape it. Intentionally creating a non-heterosexist program helps clients to

experience a healthier environment and also hopefully to better realize that heterosexism is socially created and can be changed. This in turn can help clients to address internalized heterosexism. As they learn new messages about sexual orientation, they can replace the old messages that condemned them for being who they are. Finally, it is sometimes important to act as an advocate in working to change some of the social structures that victimize clients. This does not take responsibility for addiction away from the client but can help facilitate recovery for all gay, lesbian, and bisexual clients. Indeed, part of the process of addressing heterosexism and internalized heterosexism is helping the client to better recognize those forces that are operating from without and those that are operating from within.

In recognizing and addressing heterosexism, it is critical that addiction treatment programs be very familiar with all of the people and places to which they refer clients. This, of course, should be standard procedure across a range of issues, but it has a particular function with respect to gay, lesbian, and bisexual clients. Helping clients to address heterosexism and internalized heterosexism can be undone by referring to programs or people who are likely to further stigmatize or victimize clients. It is critical that treatment staff become familiar with 12-step programs that are affirming of their gay, lesbian, and bisexual members. Some communities have gay meetings, but many do not. Sometimes women's meetings can be helpful to lesbians, although sometimes particular meetings can promote traditional gender roles in ways that might not be a good fit for all lesbians. Gay people have a mixed history with Alcoholics Anonymous, some of it incredibly helpful and some of it dangerously destructive [9]. Treatment programs must know which is which locally. Likewise, just as treatment programs develop a familiarity with respect to which health care providers understand addiction and which ones are likely to feed an addiction through over-prescribing, so too must they become familiar with those who understand the needs of their lesbian, gay, and bisexual clients and are affirming.

Spirituality is another issue that is often a mainstay of addiction treatment and has particular relevance for gay, lesbian, and bisexual clients [61, 78]. Because many of society's views about homosexuality and bisexuality stem from religious teachings, many gay, lesbian, and bisexual people have an understandably ambivalent view toward traditional religion. This can then create a delicate balancing act in treatment programs and especially in 12-step programs that promote dependence on a higher power as a means to ongoing sobriety. Participants in a qualitative study about lesbians' recovery from addiction [78] reported that finding ways to renew a sense of faith while letting go of the aspects of religion that they found hurtful was an important piece of their ongoing sobriety. In general, participants suggested that counselors, sponsors, and others who were less tied to traditional Christianity and more open to faith and spirituality that was not necessarily linked to a particular religious tradition were more helpful. This then becomes another factor when referring clients to 12-step programs. Those that have a more open understanding of "higher power" might be a better fit for some gay, lesbian, and bisexual clients than those that connect "higher power" more directly to religion or religious teachings. Other clients might need assistance in maintaining a church community that is important to them while letting go of the messages that oppress them.

Family programs have become an important piece of many treatment programs. This might involve working through family-of-origin issues or working with current family members to address problems that might have developed due to addiction. Family issues are critical for gay, lesbian, and bisexual people to address as well; however, there are some specific concerns that must be kept in mind [5, 37, 78, 79]. First and foremost, it is important to recognize gay, lesbian, and bisexual people's families [77, 79], which might not always look like traditional families. Same-sex couples are not allowed to marry in most states, but they do nonetheless have long-term relationships, many of which include children. These families must

be included in family programs just as are families recognized through marriage. In addition, many gay, lesbian, and bisexual people form kinship networks among friends, which become families of choice. There might be times when it is important to include members of these kinship networks as extended family in the same way that aunts, uncles, or cousins might be included. Gay, lesbian, and bisexual people are likely to have family-of-origin issues around addiction, just as other clients do; however, they might also have concerns or tensions around sexual orientation. Treatment providers need to be prepared to help clients deal with these issues. They also have to be able to help gay, lesbian, and sometimes bisexual clients address relationship issues in ways that recognize and are sensitive to the fact that the client's primary relationship is with someone of the same sex. Thus, knowledge of same-sex relationships is important so that nuances that might be reflective of a different type of relationship are not pathologized.

All of the above issues that are unique and specific concerns for gay, lesbian, and bisexual clients must be addressed in an atmosphere of safety from oppression, marginalization, and discrimination. This was one of the themes that gay men and lesbians in recovery presented in a qualitative study [79]. Treatment worked better when it was free from the heterosexism that pervades society. When clients felt safe in addressing sexual orientation, they were better able to attend to the tasks of recovery, some of which involved sexual orientation and sexual identity. With this in mind, treatment approaches that are more client-centered or developmentally oriented might work better with this population than more confrontational approaches [37, 53]. To date, there has been very little empirical work on treatment outcomes with gay, lesbian, and bisexual clients. One randomized controlled study did find that motivational interviewing alone had significantly better drinking outcomes than motivational interviewing with a cognitive behavioral component added [91], but this was just one study. There is a need for more such studies examining different approaches specifically with the gay, lesbian, and bisexual population. Given the variety of issues that this population faces, in addition to the concerns common to all clients struggling with addiction, we cannot assume that approaches that are successful with a general population will be successful with this population.

In addressing some of the particular challenges facing them, it is important to remember that gay men, lesbians, and bisexual individuals *do* recover from addiction and experience long-term sobriety. In the United States, gay men, lesbians, and bisexual individuals gather in about 1,800 gay Alcoholics Anonymous meetings per week [9], and that likely taps into a small fraction of the recovering gay, lesbian, and bisexual community. They struggle with many of the same issues with which all recovering people struggle, and some additional ones besides, yet like others they find ways to be successful. It is important to be aware of some of the particular challenges facing this community, but it is equally important to remember that there are strengths as well. Despite living in a culture where heterosexism is pervasive and where oppression is real, the large majority of gay, lesbian, and bisexual people do not fall into addiction [25]. We must learn from their resiliency and find ways to help our gay, lesbian, and bisexual clients develop it as well. Openness and affirmation are a place to start.

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Substance Use Disorders in Health Care Professionals

George A. Kenna, Jeffrey N. Baldwin, Alison M. Trinkoff, and David C. Lewis

Contents

Introduction

The impact of licit (i.e., alcohol and nicotine used legally) and illicit (including non-medical prescription) drug use, abuse, and dependence in the United States is well documented in the general population. Overall, a 2006 survey reported that an estimated 20.4 million Americans aged 12 or older were current illicit drug users, meaning they had used an illicit drug—defined as "marijuana/hashish, cocaine (all forms), heroin, methamphetamine, hallucinogens, inhalants or psychotherapeutics used nonmedically"—during the month prior to the survey interview [86]. This estimate represents 8.3% of the population aged 12 years old or older. More specifically, an estimated 5.2 million persons were current non-medical users of prescription pain relievers, up from an estimated 4.7 million in 2005.

A recent report of abuse of prescription medication in the United States reported that many health care professionals are poorly trained to deal with alcohol or drug abuse [84]. A substantial number of patients served daily by health care professionals in various health care facilities are abusing or dependent on alcohol and or other drugs. On the other hand, the public expects health care professionals to understand the proper use of the medicines they prescribe, dispense or administer to their patients. Just as in their patients, though, alcohol or drug use also affects the lives of a number of health care professionals [23].

Starting in college, some health care students develop an attitude of invulnerability and immunity to addiction, fueled by their advanced understanding of the mechanisms of drug action. What begins as recreational college alcohol or drug use [73] may, for some, develop into a

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_69,

complicated pattern of alcohol or drug abuse or dependence intended to attain a "sense of well-being" ([77] p. 17) without an overt manifestation of intoxication or side effects. This concept of balancing drug effects, also called "titration", or "walking a chemical tightrope" [23] refers to a practice whereby students or health care professionals use their pharmacological knowledge to balance positive and negative drug actions and reactions by "enhancing, neutralizing or counteracting specific drug effects through ingesting multiple types of drugs" [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"].

Health care professionals have a significant responsibility that comes with the privilege of using medications to treat patients [11, 56, 59, 71]. While most health care professionals engage in appropriate prescribing, dispensing and administration of medication, reports of exceptional cases often receive public attention. A North Hollywood, California physician, for example, was charged with conspiring to distribute 406 prescriptions of hydrocodone and oxycodone over two months after he surrendered his license to the Drug Enforcement Administration in May 2008. This pain management specialist was also being investigated regarding a role that his prescriptions might have played in the deaths of six patients over the past 3 years [121]. A Virginia pharmacist was caught with hundreds of phentermine capsules when apprehended by law enforcement authorities [90], and a Maryland pharmacist was trading sex for drugs [90]. Medication errors caused by substance-impaired pharmacists have been cited as posing a direct and serious threat to the public [78]. Moreover, nurses were reported to be alcohol or drug impaired while committing "dozens of errors leading to patient deaths in Illinois" ([9], p. A1).

Whether by virtue of their drug access [72] or socioeconomic status [48], most evidence supports the notion that a small but significant proportion of health care professionals do experience personal problems with the use of alcohol and other drugs which can result in serious consequences to themselves and to the public [Valentine N (1991) Stress, alcohol and psychoactive drug use among nurses in Massachusetts. Brandeis University, Boston, MA, "An Unpublished Dissertation"] [73, 83]. Not only can the economic costs of substance use disorders [27] in health care professionals be considerable [67], early identification is essential as patient and provider well-being may be at risk [23]. Given the increasingly stressful environment due to manpower shortages in the health care system in general [91], alcohol or drug use and misuse among health care professionals has been projected to grow [89]. Treatment of alcohol or drug disorders by health care workers was a policy issue recognized years ago by the professional organizations [2, 5], and the Joint Commission requires hospitals to monitor and identify matters of health [52] including substance use and abuse by physicians and other health care professionals.

The aim of this chapter is to provide perhaps the most comprehensive review of the problem of drug abuse by health care professionals to date. Additionally, while covered in greater detail in other chapters in this book, we will also briefly discuss the behavioral signs and symptoms of addiction in health care professionals, the treatment of substance use disorders in this special subpopulation and the prognosis of sustained recovery and efforts needed to enlighten the various health care professional programs and groups.

Epidemiology of Alcohol and Other Drug Use by Health Care Professionals

The current literature regarding the prevalence of substance use and dependence in health care professionals is limited in both its scope of generalizability and methodological rigor [13, 60]. Lack of empirical data have contributed to an air of skepticism regarding the actual prevalence of substance abuse (abuse as referred to

colloquially, not *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [27] diagnosis) and dependence by health care professionals. In fact, evidence of the extent of medication diversion, considered to be the major source of non-prescribed drug abuse by health care professionals is based primarily on retrospective accounts [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] [10, 70, 111], though the actual size of the diversion problem is largely unknown [36]. As a result, the prevalence of inappropriate substance abuse and chemical dependency among health care professionals is inconclusive [16, 72] and, like the extent of prescription opioid drug diversion in the United States, for example, is impossible to estimate at the present time [54]. The fact that the behaviors being measured represent illegal or inappropriate behaviors compounds the problem, as it is difficult to obtain accurate estimates of sensitive variables such as substance use [117].

Providing a glimpse of the lack of epidemiological knowledge in the field is best illustrated by contradictory prevalence estimates found in the literature. For example, reports [20, 107] suggested that narcotic addiction in United States physicians was as much as 30–100 times the rate found in the general population, but these data were based on data from Germany in the 1950s [13, 31]. Additionally, the lifetime estimate of combined substance abuse and dependence among health care professionals was reported by Kessler et al. [65] to be at a rate nearly equal to that of the general population, or 26%. Similarly, estimates from other studies of health care professionals have reported a lifetime prevalence of substance dependence ranging from 3 to 20% [11, 42, 95, 114, 116]. While the literature provides limited studies of substance use by dentists, Hedge [46] estimated that as many as 15–18% of dentists could be addicted to drugs and alcohol. In contrast to these rates, however, another report concluded that physicians were at a "greater lifetime probability of developing a substance-related disorder than the general population" ([30], p. 7).

Such statements clearly demonstrate the confusion and misinformation surrounding a meaningful discussion of alcohol or drug use by health care professionals. These generalizations have not only contributed to the uncertainty about the prevalence of substance use, but also to the confusion with regard to risk factors that contribute to substance use among health care professionals [13]. For example, while referring to pharmacists as "drugged experts" ([26] p. 102), Dabney [24] used a measure of questionable reliability and validity to assess substance use in a nationwide sample of pharmacists. Specifically, the measure assessed redundant drug use items, categorized unauthorized use of non-narcotic medications as addictive drug use and provided no directions to participants regarding exactly which drugs were included in each drug category [55]. Moreover, as also noted by Baldwin [7], the frequency data reported by Dabney [24] contained no time frame for reported substance use and were, therefore, not useful in estimating the prevalence of substance use. Though Dabney [24] claimed that the onset of potentially addictive drug use in pharmacists occurred upon becoming a professional, such a conclusion was essentially impossible without longitudinal data or some specific items assessing age of onset of regular use. Though the methods were strongly defended by the author [25], these issues contribute to a suspect interpretation of the data.

Overgeneralizations from methodologically questionable data also exist in the limited amount of literature describing substance use by the dental profession. Except for reporting the number of disciplinary actions taken against Oregon dentists from 1979 to 1984 [18], no known empirical prevalence data for substance use had ever been reported for practicing dentists until recently [62]. However, Chiodo and Tolle [17], drawing on non-representative disciplinary action data, inaccurately concluded that dentists, like physicians, were at higher risk for substance use and abuse than the general population, and also concluded the literature had consistently reported higher rates of chemical dependency in health care professionals, a notion unsupported by quantitative self-reported data [62].

In a series of important analyses, McAuliffe et al. [71–75] assessed alcohol or drug use by both physicians and pharmacists, and Valentine [Valentine N (1991) Stress, alcohol and psychoactive drug use among nurses in Massachusetts. Brandeis University, Boston, MA, "An Unpublished Dissertation"] assessed alcohol or drug use by nurses. Lack of generalizability to other practitioners outside these two disciplines was a major limitation of these studies. Additionally, these studies were conducted in the northeast where past-year alcohol or drug use has been reported to be higher than in other areas of the United States [86]. Subsequently, to address some of the "methodological shortcomings" of these studies, Hughes and colleagues ([48], p. 2333) compared a national sample of physician use of alcohol or drugs with the general population. They reported that when compared with the general population, physicians were more likely to use alcohol, benzodiazepines and minor opioids but less likely to use street drugs such as marijuana and cocaine. Furthermore, contrary to the suggestion made by Chiodo and Tolle [17] that the literature consistently reported disproportionately higher rates of chemical dependency in health care professionals, Hughes et al. reported that only 7.9% of physicians identified themselves as substance abusers, while the corresponding rate for the general population at that time was 15–18% [98]. Hughes et al. also noted, however, that physicians were as likely as their age and gender peers to have experimented with illicit substances in their lifetime, an observation also affirmed more recently [59]. Although methodologically rigorous, Hughes et al. acknowledged the narrow focus of their study to physicians alone that subsequently limited their findings due to the lack of comparable national data across other similar professions. In recognition of this limitation, the authors concluded that any comparisons between physicians and other health care professionals in "similar socioeconomic strata may have yielded different results" ([48], p. 2337). Complicating these issues is stigma that accompanies alcohol or drug use in any population, which leads to underestimates of problem use [88].

Etiology of Substance Use Disorders in Health Care Professionals

Many etiologic factors have been reported to contribute to substance use in health care professionals such as a family history for drug or alcohol use [21, 76, 104], college substance use [6, 19] or age at first alcohol or drug use [66], psychological factors such as "pharmacological optimism" [23, 34, 42, 119], access to prescription medications [42, 69], self-prescribing [19, 48, 72], socioeconomic status [48] and additional factors such as gender (male), lack of religious practices [72, 123] and social influences [66, 92].

Drug Access

Drug access, and in particular easy drug access [118], is generally recognized as a principal factor contributing to substance use by health care professionals. Certainly, studies show, access to prescription medications would explain the higher rates of use of these drugs than the general population [48, 60]. While research on drug use in the working population in general has been inconclusive, Mensch and Kandel [81] suggested that drug use by workers was due less to the workplace than to the workers themselves. Clearly, however a substantial foundation of research indicates that health care professionals are at considerable risk due to their working environment [23, 114, 118]. Drug access is directly related to the job of being a health care professional. As such, the working condition related to medical practice is an important contributing factor enhancing one's exposure to addicting drugs.

To illustrate this point, dentists have historically had easy access to nitrous oxide, an inhalant commonly kept in dental offices, and a known drug of abuse for dentists. Though the data are now dated (1979–1984), 7.1% of 109 impaired dentists in a study that took place in Oregon were sanctioned for abusing nitrous oxide [18]. The authors concluded that nitrous

oxide in particular posed a serious hazard for dentists. While dentists have access to nitrous oxide for procedures, access to other drugs such as minor opioids and anxiolytic drugs is limited. For example, dentists were the only health care professional group who did not report personal use of samples; the study, nonetheless, indicated that they found other sources for addicting prescription medications [63].

Different researchers have developed measures to assess the impact of drug access by health care professionals on drug use [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] [75, 118]. A pilot study by Trinkoff and Storr [117] suggested that easy access to drugs contributed to misuse. This was more firmly supported in a later, more extensive study of nurses (n=3,917) wherein the ease of access positively correlated with past-year misuse [118]. Three workplace dimensions were measured (availability, frequency of administration and workplace controls), and, summed as an index, nurses with easy access on all dimensions were most likely to have misused prescription-type drugs (odds ratio = 4.18; 95% CI: 1.70–10.30). Furthermore, access continued to show the same correlation to misuse, when knowledge of substances was also controlled in the analysis, showing that access was not explained by nurses' knowledge of substances used.

In a survey study performed comparing alcohol or drug use by pharmacy and nursing students and with pharmacists and nurses, predictors of lifetime illicit drug use by pharmacists and nurses included having a family history of drug problems, greater amount of past-month alcohol use, lack of religious affiliation and notably greater access to drugs [60]. Predictors for use of an illicit drug (any Schedule I or unprescribed drug use) by pharmacy and nursing students included a family history of drug problems, less drug access and cigarette use in the past year. Interestingly enough, lower drug access was a significant predictor for lifetime illicit substance use by pharmacy and nursing students, suggesting that when substances were unavailable in the workplace, students were more likely to obtain them elsewhere. Despite a reassurance of anonymity, students may also have been reluctant to admit to such behavior due to the fear of being discovered. In support of this notion, none of the students in the study reported diverting any medications from where they work, yet a greater number of pharmacy and nursing students in the same sample reported use of prescription medications than among the general population [60]. We know that various sources for drug use include the home [108] and friends [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"], but we also know that sources include the workplace as well [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"].

Where pharmacy students worked did not appear to be related to disproportionate drug use; however, a greater number of retail pharmacists reported illicit drug use than pharmacists in other pharmacy practice areas [60]. When parsing out comparisons of individual drugs, except for marijuana, consistent with the Hughes et al. [48] data, a higher proportion of the general population reported use of street drugs such as cocaine, hallucinogens and inhalants. A greater number of health care professionals and students, however reported use of drugs to which they typically had access such as opioids and anxiolytics [60]. In sum, quantitative and qualitative studies have all demonstrated that increased drug access in an unrestrictive environment provides an important substrate permissive of drug use by health care professionals. The available studies are consistent for studies of nurses [118], pharmacists [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] [72], certain types of physicians [114] and health care professionals in general [23, 83] that report drug access to be a key element leading to drug misuse and abuse in health care professionals. Efforts to restrict

drug access in every setting, as well as increased vigilance to monitor drug procurement and drug disposition by clinicians who dispense from their offices should be considered a priority.

Family History of Alcohol and Drug Use

Without a doubt, the greatest concern for health care professionals, as it is for the public, are alcohol use disorders [87]. Lifetime prevalence of alcohol abuse in the United States is 17.8% and alcohol dependence is 12.5%. Past 12-month prevalence of alcohol abuse is 4.7%, while alcohol dependence over the same period is 3.8% [44]. Alcohol dependence is significantly more prevalent among men, whites and younger unmarried adults, and lifetime alcohol abuse is highest among middle-aged Americans [44].

Twin studies of alcoholics have highlighted the possibility of genetic components of alcoholism [94] while other researchers [105] have also sought genetic markers for individuals with a positive family history for alcoholism. Studies have demonstrated that first degree relatives (parent, sibling or offspring) are more likely to use alcohol, become alcohol dependent and are at substantially higher risk to develop problems with alcohol sometime during their lives [88]. Family history of alcoholism has been estimated to be approximately 38% in the United States [43].

A retrospective review of substance use and addiction in medical students, residents and physicians [33], suggested that the most predictive factor for alcoholism in physicians was a positive family history for alcoholism. Kenna and Wood [62] reported that significant bivariate correlations between positive family history and pattern of alcohol use ($r = 0.31$), as well as positive family history for drug problems and current drug use ($r = 0.55$), existed for physicians alone. There is the possibility that there were genuine relationships between those physicians reporting a positive family history for alcoholism and their alcohol use and between a positive family history for drug problems and drug use. Physicians are trained diagnosticians and can putatively accurately assess the presence or lack of alcohol and drug use problems by family members. These diagnoses may have led to a more accurate assessment of family members, thereby reducing measurement error in this particular group.

Numerous studies also demonstrate that first degree relatives are at substantially higher risk to develop problems with alcohol sometime during their lives [88]. Coombs [23] proposed that the health care professions attract "people vulnerable to drug abuse because of emotional impairment due to alcoholic and emotionally abusive parents" ([23], p. 192). Several studies of dental students [12, 100–102] previously speculated that many dentists perhaps come from dysfunctional families or families with a history of alcoholism or chemical dependency. Sammon et al. [100], for example, reported that 35–39% of students at two dental schools had an alcoholic parent or grandparent, and Sandoval et al. [101] reported that 15% of all dental students at the University of Texas had a family history of alcoholism and 17% of illicit drug use. In a more recent study, however, dentists reported the fewest family members with alcohol problems of any health care professional group [62], suggesting there is little evidence that dentists are at greater risk than other health care professionals to report a family history of alcohol problems.

Several other studies have also reported high rates of positive family history for alcoholism for health care students and health care professionals as well. For example, in a comparison of chemically dependent and nondependent nurses, Sullivan [110] reported that 62% of chemically dependent nurses reported an alcoholic family member compared with 28% for non-chemically dependent nurses. Additionally, in a sample of recovering pharmacists, Bissell et al. [10] reported a positive family history for alcoholism rate of 55–58% in recovering pharmacists, slightly higher than the 47.4% prevalence estimate reported by Kenna and Wood [59] in a survey. What of course must be considered between the two rates are the differences

between the two study populations: one clinical [10] and the other population based. In college students, Tucker et al. [120] reported a positive family history for alcoholism in 28.1% in a sample of pharmacy students, and Kriegler et al. [66] established that a positive family history for alcoholism was reported by 38.3% of nursing student respondents. In a measure including eight close relatives (other studies typically included parents, grandparents and siblings), Kenna and Wood [58] reported a positive family history for alcoholism in 46% of pharmacy students and 74.5% of nursing students surveyed.

In a follow-up study of 479 licensed health care professionals (68.7% response), researchers sought to ascertain whether positive family history for alcoholism and positive family history for drug problems were more prevalent among nurses than among dentists, pharmacists and physicians and if an association between positive family history for alcoholism or positive family history for drug problems and current alcohol or drug use, respectively, existed [62]. Nurses reported a significantly higher prevalence of positive family history for alcoholism than other groups of health care professionals, ($P<0.001$) (see Fig. 1), and nurses also reported significantly higher prevalence of positive family history for drug problems than dentists and physicians ($P<0.01$), but not pharmacists (see Fig. 2). The study also demonstrated that positive family history for alcoholism in nursing was not associated with either amount of current alcohol use or abstinence. On the other hand, as previously noted, among physicians alone, relationships between alcohol use and positive family history for alcoholism as well as between drug use and positive family history for drug problems were significant. The results of this study support the notion that positive family history for alcoholism and positive family history for drug problems differ across groups of health care professionals.

While speculated, no one truly understands why a significant number of people with a positive family history for alcoholism appear to select nursing as a profession. Some have suggested that the desire to go into nursing emanates from the family of origin [66] and that nurses assume parental roles taken on in childhood [82]. For example, in a study of the characteristics of chemically dependent nurses [110], 48% indicated that while growing up, they had

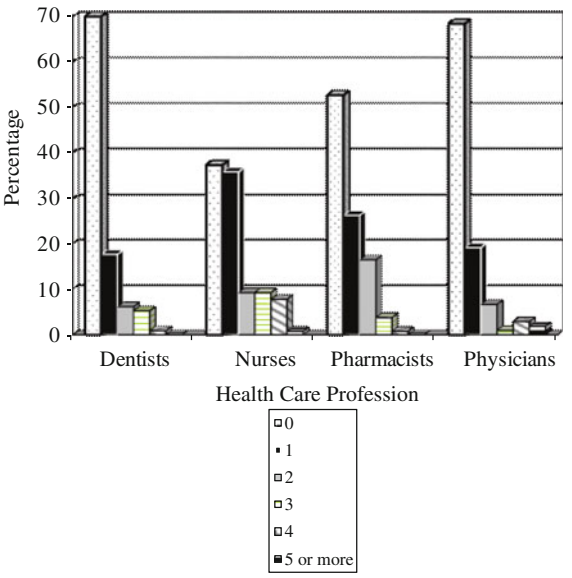

Fig. 1 Family history of alcoholism among health care professionals ($n = 479$)

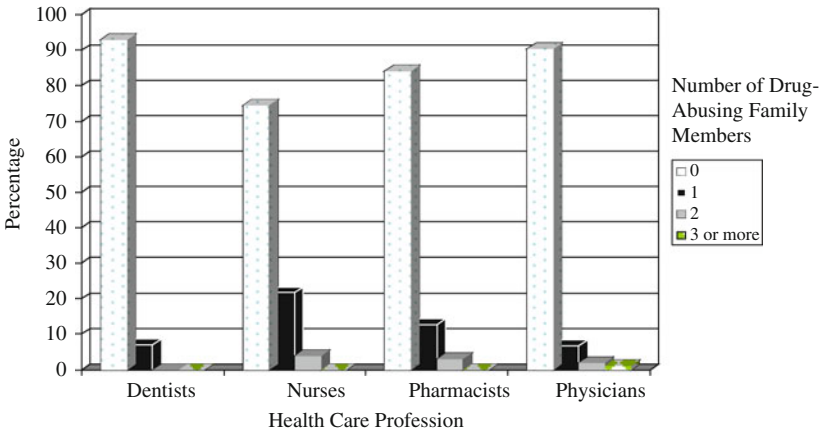

Fig. 2 Family history of drug abuse among health care professionals ($n = 479$)

acted in some type of parental role compared with only 22% of nondependent nurses. In order to delineate the association between nursing and family history of alcoholism, more research into the familial dynamics or individual differences of nurses and nursing students needs to be performed.

Professional Invincibility

Many health care professionals assume that their education, intelligence and knowledge of pharmacology will provide immunity from substance related impairment [23]. This self-deception of "professional invincibility" are attitudes of denial of impairment. More importantly, intervention is difficult in health care professionals as denial to the existence of a substance related problem contributes to continued substance use, abuse and dependence [106, 113]. Hankes and Bissell [42] referred to this air of invincibility in physicians as "MDeity" (p. 890). The attitude that health care professionals are selectively immune to the pharmacological actions of addictive medications—based primarily on their knowledge of drug action—has been the subject of retrospective accounts given by many health care professionals [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] [23]. The health care professionals may believe that their education particularly with respect to drug titration, makes them impervious to physical or psychological dependence, or the unconsidered equivalent, drug addict. Health care professionals are good at hiding their addiction by walking a "pharmacological tightrope" [23]; they tend to take greater amounts and a wider variety of drugs, making them more difficult to treat [115]. Perhaps, then, it is this attitude of pharmacologic invincibility that becomes the fundamental problem with substance use experimentation and addiction in health care professionals, particularly those who choose to treat themselves or who continue treatment beyond the period of illness or at dosages escalating beyond those required to circumvent tolerance.

Pharmacological Optimism

"Pharmacological optimism," or the anticipated benefits of medication use, has also been suggested to be a contributing factor in the development of chemical impairment by health care professionals. In 2000, pharmaceutical companies spent 15.7 billion dollars on drug promotion

that grew to almost 30 billion dollars by 2005 [29], with most of the expenditure aimed toward health care professionals [37]. Although pharmaceutical companies relentlessly directly target consumers, the impact does not compare to the decades-long indoctrination that health care professionals have received. Moreover, in view of a health care professional's training and education, familiarity with drugs is an important aspect of professional competency. Development of beliefs about the anticipated outcomes using drugs can be assumed to be a logical extension of knowledge of a drug's effect.

The literature has been inconsistent in defining "pharmacological optimism". For example, one researcher defined pharmacological optimism as "a generalized positive belief about the efficacy of drugs for managing symptoms as measured by an individual's willingness to use psychoactive drugs under varying circumstances" ([36], p. 48). Though reported to be based on alcohol expectancy literature [14], the measure developed did not assess specific beliefs about the effects of psychoactive drugs but misoperationalized the concept as a general willingness to use psychoactive drugs [34].

A qualitative study of health care professionals suggested that pharmacological optimism was synonymous with the concept of "better living through chemistry" ([23], p. 187), which suggests that all ills can be cured with a medication. While pharmacological optimism was one of several key factors considered to contribute to substance use and abuse by health care professionals, the author did not further define or quantitatively assess the construct [23]. Trinkoff and colleagues [119] suggested that pharmacological optimism may occur as a result of highly specialized knowledge about drugs. For example, self administration practices by health care professionals may occur as a result of the development of attitudes and or beliefs that drugs may be the quickest route to change one's feelings and mood. Trinkoff et al. measured pharmacological optimism with the combination of access to drugs and knowledge of drugs, reporting pharmacological optimism to be significantly associated with past-year substance use, but only when access was not included in the analysis [119].

Other researchers suggest that pharmacological optimism is more specifically based on beliefs of a drug's anticipated effect and conceptually similar to alcohol and other drug expectancies [64]. Alcohol [14, 96], marijuana and cocaine [50, 103] expectancies are beliefs about the effects of these specific drugs that develop prior to and as a result of their use and show significant variability across levels of use.

To test this theory related to prescription medications, Kenna and Wood [64] developed scales to measure pharmacological optimism and one's willingness to use drugs of abuse [34]. The authors administered a self-report cross-sectional survey to upperclassmen and graduate pharmacy and nursing students as well as comparable non-health care students ($n = 401$). The results demonstrated that while pharmacological optimism predicted unique variance in drug use over a person's willingness to use a drug, no differences were demonstrated between health care and non-health care students on pharmacological optimism, nor was pharmacological optimism associated with greater drug use by health care students. In sum, while the results support the existence of pharmacological optimism, these beliefs ultimately did not appear to facilitate drug use by health care students over and above experiential or occupational circumstances such as workplace access to substances.

Negative Proscriptions

Winick [122] proposed a theory that the incidence of substance abuse is highest in those groups in which easy drug access, role strain and disengagement from negative proscriptions exist. Disengagement from negative proscriptions regarding substance use may be an important correlate to one's level of association with conventional institutions and subsequent risk for substance use. While difficult to measure directly, both religiosity (internal factors) and social networks (external factors) have been

hypothesized to be important conjoined factors to measure negative proscriptions. Religiosity has been hypothesized to be an internal factor that may mitigate substance use [99]. One's social network has been found to be an important external factor, linked to one's reference group, norms and peer group choices that may promote drug use [51]. Trinkoff et al. [119] tested the utility of this theory in 3,600 nurses and reported that nurses were more likely to use drugs when drug access increased, social networks contained drug users and religiosity decreased. These data also suggest that weak attachments to negative proscriptions (low religiosity and social networks that promote drug use) and high drug access are influences related to one's drug use.

Social and Professional Influences

Social influences have been hypothesized to play a central role in models of substance initiation [39] and are considered among the strongest correlates of alcohol use and misuse [45]. Within the social influence framework, two types of social influences ("active" and "passive") are proposed [39]. "Active" social influences consist of explicit offers to use drugs or alcohol that require an immediate response from the individual offered the substance and are seen as important sources for substance use initiation. "Passive" social influences include both social modeling and perceived peer norms. Social modeling involves observing drug or alcohol use by one's family or friends. Perceived norms are beliefs surrounding what referents consider or perceive as normal drinking or drug use that may affect both behavior and attitudes about alcohol or drug consumption. In short, these social influences are the means by which a person may gain information simply by observing another's behavior or developing a sense or misperception of what level of substance use is ongoing and acceptable by peers. It is thought that this information may influence future behaviors. For example, social modeling by family members has been hypothesized to be a risk factor in nurses [110]. Significant differences were found when comparing drinking behaviors in the families of chemically dependent and non-chemically dependent nurses; 32% of the chemically dependent nurses reported heavy drinking at home during childhood as compared with only 10% of the non-chemically dependent nurses [110]. Moreover, Dabney [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] reported from the qualitative arm of his study of 50 recovering pharmacists that 30% of these health care professionals were encouraged by peers and supervisors that it was acceptable to use drugs to be able to function and perform at work. Kenna and Wood [59] demonstrated that social influences, primarily active offers of drugs and to a lesser degree social modeling of drug use, were strong predictors of current drug use in college students. These analyses suggest that peer groups and social networks play an important role in the use of drugs in this population.

As an occupational hazard, health care professionals frequently receive offers to attend dinners at which alcohol is served without cost. These dinners are intended to inform health care professionals about specific treatment protocols or new drugs that have recently become available. For example, Kenna and Wood [61] reported that physicians received significantly more offers to drink alcohol than other health care professionals offered alcohol by pharmaceutical companies ($P<0.001$). In the same study it was also found that dentists received significantly more offers to drink alcohol in social situations than other health care professionals ($P<0.01$). As for prescription medications, Clark and colleagues [20] reported that physicians wrote more prescriptions for family, friends and colleagues immediately upon receiving prescriptive authority. While not statistically significant, there results however do suggest that physicians, dentists and potentially other health care professionals are asked to provide prescriptions or medications to friends, family and other colleagues.

Age and Substance Use

The data from studies consistently demonstrate that older health care professionals drink significantly more alcohol than younger health care professionals, a finding that is supported by both quantitative and qualitative data in health care professionals. For example, McAuliffe et al. [71] first reported that among physicians, heavy alcohol use (five or more drinks at one time on five or more days during the past 30 days) increased with age. Moreover, heavy alcohol use by pharmacists declined only slightly after peaking at ages 31–40 years. Notably, each professional group in the McAuliffe et al. study had their own distinctive trend of heavy alcohol use across age. Drinking habits among doctors were not associated with medical specialty or type of practice, but were positively related to gender (men greater than women) and to age (older were more apt to qualify as heavy drinkers than younger doctors). Hughes et al. [48] reported that physicians were more likely to report past-year alcohol use than age and gender matched cohorts to the general population. On the contrary, after peaking at ages 21–25 years, past-year alcohol use, binge and heavy alcohol use, all decrease with age among United States adults [86].

Qualitative studies also report that older substance impaired health care professionals have a tendency to be more alcohol involved than younger ones. Retrospective studies with health care professionals [111, 114] suggest that younger health care professionals tend to use a greater variety of drugs in addition to alcohol than older health care professionals. For example, Talbott et al. [114] examined the substance abuse patterns and specialties in 1,000 substance impaired physicians referred for treatment in Georgia and reported that younger physicians tended to be more polydrug involved than older physicians, who tended to use alcohol alone. General population data would suggest that combined alcohol and illicit substance use peaks in the range of 18 to 25 years of age [86]. Similarly, in a study of nurses, Sullivan et al. [111] reported that alcohol was the most common drug of dependency and that women and older registered nurses tended to use alcohol alone while younger registered nurses tended to report narcotic dependency more frequently. In a study of recovering pharmacists, Bissell et al. [10] found that by the age of 49 years, the majority of pharmacists in their study abused alcohol alone.

Alcohol, Tobacco, and Other Drug Use in the Health Care Professions

Dentists

While there is no overwhelming evidence that dentists are at a higher risk to develop alcohol dependence than the general population, alcohol use and misuse appears to be the most notable substance use problem facing dentistry. As previously noted, dentists engage in other social interactions that promote their alcohol use [61]. Nearly every major alcohol use standard assessed indicated that dentists were significantly more likely than other health care professionals surveyed to self-report use and misuse of alcohol [62]. Compared with other health care professionals, dentists reported a higher lifetime prevalence of alcohol use, significantly greater past 30 day quantity and frequency of alcohol use, greater past-year and past-month binge drinking (5 or more drinks for men or 4 or more drinks for women at one time) as well as greater daily use. When compared with United States general population data for individuals 35 years of age and older at the time [85], dentists reported a greater prevalence of lifetime alcohol use and past-year binge drinking [62]. These data are consistent with retrospective treatment records of 2,015 health care professionals in Georgia's substance abuse treatment program in which dentists, in addition to physicians, were more likely to be exclusively alcohol dependent [35].

Information is limited as to why alcohol use, misuse and problems appear to be higher among dentists compared with other health care professionals. Hankes and Bissell [42] pointed out that good data regarding substance use for dentists were extremely limited; this has not changed. Putatively, causes could be linked to several risk factors previously noted in the general population such as gender, family history, income and social factors [44].

Certainly, one could assume that alcohol use differences may be related to the gender imbalance of more men in the dental profession, and men report more alcohol use than women [65]. More so than in any other health care professional group surveyed [62], more dentists were men (85%), which was consistent with American Dental Association [1] data reporting that almost 83% of dentists were men. However, it is important to note that 74% of the physicians in the Kenna and Wood [62] study were men, and physicians reported the least amount of alcohol use of any of the professions. Additionally, while there were no differences between men and women regarding regular alcohol use, analyses demonstrated there to be no gender difference on weekly quantity and frequency of alcohol use in health care professionals in general.

One potential explanation for the increased alcohol use by dentists may be related to higher income. In other words, the use of alcohol may increase with increased incomes [38]. Previously, Hughes et al. [48] noted that the prevalence of alcohol use was greater among physicians than in the general population by virtue of their socioeconomic class and not related to the profession of medicine. Consistent with Hughes et al. [48], lifetime prevalence and past-year binge drinking reported by physicians, was higher than reported for the general population [61, 85]. While dentists did report the highest mean income of all health care professional groups, they also reported income only slightly greater than physicians, who reported the least amount of alcohol use of all health care professional groups. In short, dentists drank significantly more alcohol than physicians, yet dentists and physicians reported essentially the same income. Furthermore, nurses and pharmacists reported a substantially lower income than dentists and physicians and still reported greater lifetime prevalence of alcohol use and past-year binge drinking than the general United States population and physicians. The results reported by Kenna and Wood [61] support the notion that alcohol use may, indeed, vary by virtue of health care profession and independent of socioeconomic status.

As noted, social factors might significantly impact alcohol use by dentists. An underlying social structure defines and shapes a relationship between alcohol use, alcohol involvement and group membership. One must consider that dentistry is also a business, and networking through memberships in various organizations is an important part of building a successful dental practice [68]. Kenna and Wood [61] reported that, during the past year, dentists were offered alcohol by friends and colleagues significantly more often than any of the other health care professional groups ($P<0.01$). In addition, while nurses knew significantly more heavy drinkers or alcoholics than pharmacists and physicians in their "social networks," there was no significant difference between dentists and nurses, perhaps suggesting that a strong social interaction component, more than any other risk factor, may contribute to alcohol use and misuse by dentists.

Nurses

In 1991, Nancy Valentine's study of Massachusetts nurses led her to conclude that alcohol use by her sample was low compared with use by the physicians, pharmacists and students in the McAuliffe et al. [72] study. More recently, however, alcohol use by nurses overall was surprisingly high given the overwhelming proportion of women compared with the other health care professional groups [61]. Nurses used less (mean use) alcohol than only dentists surveyed, but not significantly less. While nurses reported fewer mean drinks per day than dentists, they also reported more mean monthly

alcohol use than pharmacists and physicians. Moreover, while nurses reported less past-year "binge" drinking than the other three health care professional groups, they reported more past-year binge drinking than the general population aged 35 and over, despite the fact that they are largely female. Results from the Kenna and Wood [61] study report higher lifetime (67%) and past-year (22%) binge rates compared with rates reported by Trinkoff and Storr [117] in a comparably sized study (54.4 and 19.3%, respectively). In a larger study performed by Trinkoff and colleagues [118], 17% of nurses reported binge drinking during the past year (n=3,919). In the Kenna and Wood study [61], 55% of nurses reported they used alcohol on at least four days or more a month during the past year, and only 20.2% of nurses reported they were non-drinkers.

Surprisingly, one of the primary substance use concerns for nurses compared with other health care professionals continues to be cigarette use. Padula [93] previously suggested that the level of smoking in the nursing profession was unacceptably high, higher than other health care professionals, and should be cause for concern within the profession. Consistent with Padula's findings, more recent research reported that past-month cigarette use by nurses was significantly greater than any other health care professional group [59], though the past-month rate was less than half the rate reported by similarly aged peers in the general population [85].

A significant number of nurses also report use of illicit drugs. For example, Trinkoff and Storr [117] reported significant rates for lifetime (41%) and past-year (3%) marijuana use by nurses in their study. Lifetime marijuana use self-reported by nurses in the Kenna and Wood [57] study was 57.4%, and past-year use by 4.7%, which was less than the 61% lifetime use reported by experimenters in the Sullivan et al. [111] study of nurses, but consistent with the 37.3% lifetime use reported by nurses surveyed in New York [22] and by 37% of nurses surveyed in Massachusetts [Valentine N (1991) Stress, alcohol and psychoactive drug use among nurses in Massachusetts. Brandeis University, Boston, MA, "An Unpublished Dissertation"].

Nurses also report extensive non-prescribed prescription medication use. For example, 14% of the nurses in the Kenna and Wood [57] study reported ≥61 non-prescribed medication taking episodes, which was more than any of the other professions surveyed. Lifetime non-prescribed opioid use reported by nurses ranges from 52% [Valentine N (1991) Stress, alcohol and psychoactive drug use among nurses in Massachusetts. Brandeis University, Boston, MA, "An Unpublished Dissertation"] to 45.7 % [117] to 21% [57]. In addition, when combining one or more episodes of lifetime drug or medication use, 63.6% of nurses reported use of one or more drugs [57], which is less than rates reported by 68.6% of nurses surveyed by Trinkoff and Storr [117] and 73.7% surveyed by Valentine [Valentine N (1991) Stress, alcohol and psychoactive drug use among nurses in Massachusetts. Brandeis University, Boston, MA, "An Unpublished Dissertation"]. However, when compared with the general population, with a few exceptions (e.g., cigarettes consistently, minor differences with cocaine and hallucinogens), lifetime, past-year and past-month substance use rates were higher among nurses [57].

Though still high compared with the general population, one possibility for the reduced drug use among nurses over the last 20 years may be twofold. First, the mechanism for access to prescription medications in many facilities has changed a great deal. The link between access and drug use has been noted by many researchers [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] [23, 114, 117, 118]. In order to meet Joint Commission [53] requirements to maintain strict controls over medications to promote patient safety, most hospitals use automated machines that control and dispense medications to nurses for patients. One of the major advantages of these dispensing units is to maintain accurate counts of controlled drugs that must be verified at each shift change. Potential unauthorized access can be more readily detected. Though speculative, the automation of dispensing has probably reduced the access-prescription

medication use link for many nurses. Second, the steady decline of drug use in society in general [86] is also likely an important factor in this observation.

A number of nurses in the Kenna and Wood [57] study reported iatrogenic drug exposure as they had been prescribed medications such as minor (e.g., C-III–C-IV) and major (C-II) opioids by practitioners. This finding was consistent with Valentine's [Valentine N (1991) Stress, alcohol and psychoactive drug use among nurses in Massachusetts. Brandeis University, Boston, MA, "An Unpublished Dissertation"] study that reported prescribed drug use was much higher in nurses than other health care groups used for comparison, which led Valentine to conclude that "the path to dependence for nurses is use of drugs as a consequence of treatment under another provider's direction" [Valentine N (1991) Stress, alcohol and psychoactive drug use among nurses in Massachusetts. Brandeis University, Boston, MA, "An Unpublished Dissertation"; p. 651]. While the issue regarding gender has generally not been considered, data suggest there is an increased likelihood that more women than men will visit a physician and receive a prescription. In a report on the ambulatory care of patients in the United States [15], women were 33% more likely than men to visit a doctor, even after accounting for pregnancy associated visits. Moreover, the rate of physician's office visits for such reasons as annual exams and preventive services was 100% higher for women than men. Furthermore, prescriptive habits differed as well. Women were more likely to receive medications such as non-narcotic analgesics and antidepressants than men. The likelihood that a group such as nurses that is predominately female would report more iatrogenic contact with various addictive substances is consistent with this notion.

Pharmacists

The data suggest that pharmacists are not inclined to drink more alcohol than other groups of health care professionals. The mean drinks per month reported by pharmacists surveyed by Kenna and Wood [61] was 18.4 drinks, which was comparable to the rate of 21.2 drinks per month reported by McAuliffe et al. in 1991 for pharmacists [71]. One possible reason accounting for the slight difference might be attributed to the dominance of men (84%) in the McAuliffe et al. study compared with only 59% of men in the Kenna and Wood study. Twelve percent of pharmacists also reported past-month use of five or more drinks or "binge drinking" [61] which was comparable to 9.3% of physicians reporting binge drinking by Hughes et al. [48].

Based on qualitative studies [10, 23], alcohol remains one of the salient drugs of choice for substance impaired pharmacists, though it is important to note that alcohol was rarely the sole drug of choice. Bissell et al. [10] reported that only 21% of the pharmacists in their study were "addicted" to alcohol alone while 77% were addicted to a combination of alcohol and other drugs, most always prescription medications.

As noted by Bissell et al. [10], the combination of alcohol and prescription drugs presents a more formidable threat to pharmacists, and that the pathway to addiction for most pharmacists who may become impaired is probably through polydrug use [10]. That is, alcohol in combination with medications, most notably minor opioids and anxiolytics, comprise the bulk of current substance use by pharmacists. Seldom are pharmacists addicted to just a prescription medication [10].

Studies using varying designs suggest that pharmacists do use drugs and suffer the consequences of their use [8]. These include quantitative [74, 92] qualitative [10, 70], retrospective [35] and combination designs [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"]. There is currently no evidence that total lifetime or past-year drug use by pharmacists significantly exceeds that of other major groups of health care professionals or the general population [57]. Yet, pharmacists by virtue of their ease of access may be at greater risk to use prescription

medications than the general population. It appears that the greatest threat to pharmacists is non-medical opioid, stimulant and anti-anxiety drug use due to easy availability. McAuliffe [70] initially reported what he called "non-therapeutic" opioid use by health care professionals. The health care professionals interviewed described their progression of opioid use that led to becoming addicted. A high rate of self treatment with tranquilizers was also noted in the McAuliffe et al. [74] study that included pharmacists. Most non-prescribed opioid and anti-anxiety drug use seems to be for self-diagnosed ailments and most stimulant use is reported to be for facilitating performance, such as staying awake, performing better and studying [72].

As reported, lifetime stimulant use by pharmacists was 15.8% [57], and was greater than twice the general population rate. Access to drugs by pharmacists would most likely explain the differences in prescription medication use between the general population and pharmacists. Consistent with studies of resident physicians who gain access to prescriptive privileges at that stage of their medical career [20, 49], opioid and benzodiazepine self-treatment represented the bulk of prescription medication use by resident physicians. The majority of pharmacists who report the unauthorized use of prescription medications, not surprisingly, initially did so after leaving college [24]. Dabney reported that 40% of pharmacists surveyed had used prescription medications without a physician's authorization, and 20% reported they had done so five or more times in their lifetime. It was proposed that diversion was the primary source for obtaining these medications [8], and that access to medications is therefore a prerequisite to use for many pharmacists. However, as noted by Trinkoff and Storr [117], perhaps access alone is necessary but may not be sufficient to foster the conditions that promote drug use in health care professionals. Access in a permissive environment, coupled with drug use knowledge, the lack of education of the developmental dynamics of addiction [69] and peer, academic or occupational influences that don't dissuade substance use, appear to be the primary factors contributing to illicit prescription medication use [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] [23, 114, 117, 119]. Among other legal and ethical concerns for such behavior is the concern with pharmacists self-diagnosing their condition. A common theme with pharmacists who were interviewed for the Bissell et al. [10] study was that while pharmacists sought help, they often misdiagnosed their substance use problem and sought ineffectual or misplaced support and did not see, or were unable to correctly diagnose, their own addiction.

Physicians

With the exception of anxiolytics, physicians appear to be less likely to use alcohol, tobacco or other drugs than other health care professionals or the general population [57]. For example, McAuliffe et al. [71] reported that physicians drank 20.3 drinks per month in their study and concluded that there was no reason to suspect that alcohol use by physicians differed from other professionals. More recently [61], physicians reported consuming an average of only 17.9 drinks per month, which was also the lowest monthly mean total of any health care professional group. Not only was alcohol use lower than in other health care professional groups surveyed, alcohol use was lower compared with previous data reported by Hughes et al. [48] and McAuliffe et al. [71]. Physicians' lifetime prevalence (92.3%) was similar to the general population (85.8%) as was past-year binge drinking (22.1% vs. 18.6%, respectively), though past-month binge drinking was much lower (7.7% vs. 16.2%, respectively) [61].

As noted earlier, an important social-professional contributor to alcohol use includes alcohol served by pharmaceutical companies at education seminars. A Kaiser Family Foundation [3] study of physicians found that of 2,608 physicians polled, 61% received free meals, drinks, travel and tickets from pharmaceutical companies. Pharmaceutical companies

are providing alcohol at continuing education seminars as a part of a marketing approach targeting practitioners [97]. Some estimate that 12% of a pharmaceutical company's marketing budget (12.5–15 billion dollars a year) is targeted at physicians [4]. While the use of alcohol by physicians does not appear to be a problem, alcohol continues to be served by pharmaceutical companies to provide sales representatives the opportunity to engage health care professionals and facilitate conversations regarding the use of their particular medication. Kenna and Wood [61] reported that physicians were offered alcohol by pharmaceutical companies, significantly more often than all other health care professionals.

As for other drug use, Kenna and Wood [57] reported that the prevalence of lifetime street drug use among physicians exceeded rates reported by the general population, some other health care professional groups in the study, and rates reported previously by Hughes et al. [48]. For example, lifetime prevalence of marijuana use by physicians (51.9%) exceeded rates reported by the general population (31.6%), by physicians in the Hughes et al. study (35.6%), as well as rates reported by pharmacists (44.4%) and dentists (48.7%) in the Kenna and Wood [57] study. Furthermore, Kenna and Wood [57] reported that the lifetime prevalences of cocaine (17.3%) and hallucinogen (11.5%) use by physicians were the highest among health care professional groups used for comparison and higher than both the general population (11.8 and 10.1%, respectively) and the physicians surveyed (10.3 and 7.8%) by Hughes et al. [48]. Results regarding past-year use of street drugs by physicians from the Kenna and Wood [57] study, however, were consistent with data previously reported by McAuliffe et al. [72] and Hughes et al. [48], and self-prescribed minor opioid use among physicians was far lower in the Kenna and Wood study. In addition, past-year minor opioid use (1%) was only one-eighth the rate reported by pharmacists (8.3%). On the other hand, prevalences of anxiolytic use by physicians were the highest among health care professional groups and were much higher than rates reported for the general population [85]. Despite this, reported rates have been dropping. For example, past-year use by physicians was 4.8%, a rate higher than reported by pharmacists (4.5%), nurses (3.1%), dentists (2.7%) and the general population [57], whereas past-year use of benzodiazepines (anxiolytics) was 11.4% as reported by Hughes et al. and 9% in the McAuliffe et al. study.

In terms of onset of use, initiation of street drugs often begins in college, high school or earlier; only opioid and anxiolytic use began during residency [18, 49]. Hughes et al. [48] suggested that unsupervised opioid and anxiolytic use could contribute to substance abuse or dependence in physicians, particularly in light of the results in their study that found that physicians were more likely than age and gender peers to have used alcohol, minor opioids and anxiolytics.

Identifying Drug Problems in Health Care Professionals

Job performance issues such as excessive absenteeism, errors, frequently changing jobs, calling in sick or offering to work overtime, frequent wasting medication, sleeping on duty and always giving maximum doses of medications are a few of the important behavioral signs useful to identify substance abuse problems in health care professionals [95]. Additionally, there are several symptoms of alcohol or drug abuse that co-workers may experience such as memory blackouts, emotional lability, withdrawal from family or co-workers, depression, insomnia, slurred speech, disappearing frequently or the odor of mouthwash or mints on their breath (Table 1). In fact, some of these markers may hold the key to the type of impairment. For example, unexplained work absenteeism may indicate an alcohol abuse or dependence problem since, in addition to hangover, home is the more convenient place to store and access this drug of choice. By contrast, consistently volunteering to work overtime, or arriving at work when not scheduled, provides an impaired co-worker

Table 1 Signs and symptoms of potential chemical impairment in a co-worker

- The odor of alcohol on the breath or strong odor of mouthwash or mints to mask the alcohol.
- Hand tremor that occurs when in alcohol withdrawal (such as in the morning)
- Excessive perspiration
- Absence from work without notice, frequent absenteeism or late for work
- Unexplained disappearance during work for long periods of time
- Sleeping or dozing off while on duty or complaints of difficulty sleeping
- Frequent bathroom breaks
- Volunteering for overtime or being at work when not scheduled to be there.
- Deterioration in personal appearance
- Reports of illness, minor accidents and emergencies
- Confusion, memory loss and difficulty concentrating
- Heavy drug waste and or drug shortages
- Inappropriate prescriptions for large narcotic doses
- Increase in medication order entry errors or sloppy recordkeeping.
- Work performance that alternates between periods of high and low productivity.
- Unreliability in keeping appointments and meeting deadlines
- Personality changes and mood swings

the opportunity to access controlled substances not available at home. Unfortunately, such symptoms are more easily identified with hindsight than before a co-worker is identified with an alcohol or drug use disorder.

Governmental, state, local, corporate and hospital employers use statistical analysis to monitor worker access to specific drugs performed on a periodic basis. Subsequently, at the person level, if a particular health care professional appears to consistently access controlled drugs at higher rates than peers, a more formal investigation is begun, perhaps instituting use of investigators, covertly employing video cameras or auditing the site.

The Intervention of Health Care Professionals

Data suggests that denial is often greatest for those health care professionals who are the most addicted [42]. Health care professionals often use a greater amount of drugs for longer periods of time, for they can go undetected by their ability to use various drugs to cover drug side effects [23]. Often the only time health care professionals are caught is through a drug audit by supervisors or internal security measures.

Probably one of the most difficult professional decisions a health care professional can make is to intervene on behalf of a co-worker who has an alcohol or drug problem. Given the seriousness of dependence disease and its treatment, intervention can present problems at many levels for both individuals. Despite these difficulties, it is important to recognize that health care professionals with alcohol or drug problems in retrospect feel that an intervention probably saved their lives [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"]. Also, while at the time of their discovery these individuals were devastated, the reality is that after receiving treatment the majority do successfully return to work [80].

Interventions are different for health care professionals than are other interventions for others. The intervention is professionally based and focused on practice. The intervention team must recognize that the professional's identity is fused with the role they perform, and the intervention must focus on objective data from their investigation. There are potentially significant financial implications if the professional is unable to practice, so leverage during the intervention is focused on ability to practice and maintaining employment [112].

There are three major reasons why early intervention and treatment for health care professionals is desirable: (1) it should lower the risk of patient care errors due to substance impairment;

(2) it helps the health care professionals prevent overdose that could result in their own death, suicide or other problems from adverse drug reactions and (3) the health care professionals may have an easier experience with drug withdrawal and less resistance to treatment. There are also advantages for health care professionals who come in for treatment on their own as they are protected by confidentiality laws which protect their identity. In these cases, neither the employer nor the state are notified of treatment. This can protect the health care professionals from loss of privileges or licensure, vs. if their addiction were to become known to the Drug Enforcement Administration or state licensure boards, and is a powerful incentive to engage in the recovery process. Additionally, the health care professionals may be able to stay at work and not suffer economic hardships that accompany forced loss of licensure due to discovery. This is not necessarily the best treatment strategy, as treatment may require work modification to restrict access to substances. Finally, if treatment is successful, the health care professionals won't be subjected to stigma associated with loss of licensure.

Once an individual's alcohol or drug problem surfaces, treatment decisions are generally tailored to his or her needs. Although a thorough discussion of the diverse treatment options are better covered elsewhere in this book, certain basic goals of treatment include matching the patient to the correct level of care, such as deciding whether someone is better suited to inpatient versus outpatient treatment [83] are also relevant for health care professionals. Beyond placement, fundamental components of treatment include individual and group therapy, pharmacotherapy when appropriate, urine drug monitoring and 12-step facilitation. Twelve-step programs include Alcoholics Anonymous, Narcotics Anonymous as well as programs targeted toward health care professionals such as Caduceus, International Pharmacists Anonymous (a psychosocial support group specifically for pharmacists), International Doctors in Alcoholics Anonymous and many others.

There is relatively little research assessing risk factors for relapse or treatment success of recovering health care professionals. In a retrospective cohort study of 292 health care professionals enrolled in the state of Washington's Physicians Health Program, only about 25% of the study population had one or more relapses [28]. The risk of relapse was significantly increased in health care professionals who had used a major opioid, had a coexisting psychiatric illness or reported a family history of an alcohol or drug disorder. Co-existing risk factors and previous relapse significantly increased the likelihood of relapse.

For health care professionals formally referred to treatment programs, one of the keys to re-entry is signing a contract that delineates what is expected by the treatment agency or wellness program. These programs are responsible for overseeing treatment plans, urine drug monitoring and advocating for health care professionals with licensing boards. Generally, treatment is successful whether initiated by the health care professional or others. In 1988, for example, a survey examined pharmacist assistance programs in all 50 states and the District of Columbia [80]. While the survey reported that only 20% of impaired pharmacists in these treatment programs voluntarily disclosed their chemical use problem, just over 88% successfully completed treatment and returned to practice. More recently, McLellan et al. [79] reported on urine drug monitoring during a 5-year follow-up study of 802 physicians in 16 state Physician Health Programs. At the conclusion of the study, 81% were licensed and working. In sum, these studies suggest that the goal of returning a recovering health care professional to practice with the proper aftercare and monitoring program is realistic with a good chance of success.

Prevention and Education

What seems clear from the data presented is the need to highlight: (1) an appropriate respect for

alcohol use and, in particular, misuse; (2) the dangers of self-treatment, especially with any controlled prescription medications and (3) recognizing risk factors such as family history of alcohol or drug use that may predispose individual health care professionals to subsequent substance abuse under the right conditions as with other non-health care professionals.

That substance use rates reported by most of the studies referred to in this chapter would not be categorized as psychoactive substance abuse or dependence using criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision [27], should not imply that health care professionals are safe from addiction. Health care professionals work in stressful positions and people outside of each profession have little connection with the specific responsibilities and demands of each. In addition, health care professionals work with medications that are efficacious when used properly but when abused may facilitate a quick progression to dependence under the proper circumstances. Self-treatment removes the opportunity for oversight of a provider for appropriateness of use. Furthermore, as qualitative and review studies have determined [23, 24, 32, 70], substance related impairment often includes diverted medications. Non-prescribed substance use, no matter how infrequent and how little, is just as illegal for health care professionals [7] as it is for the general population.

Wright [123] admonished the medical profession for attempting to simply provide more substance abuse education for physicians and students, arguing that it was the type of education that was being presented that was questionable. Therefore, the quality of education with regard to medication use, be it alcohol or otherwise, cannot be stressed enough. Understanding the "disease model" is critical to the professional development of clinicians but doesn't provide the sort of preventative information necessary to sensitize one to substance use or abuse either in patients or in themselves. Education in the context of requiring health care students to attend Alcoholics Anonymous, Narcotics Anonymous, or Caduceus groups and sitting in on group counseling sessions or attending talks by health care professionals who have been alcohol and other drug dependent as they detail their story of addiction may provide the pathways that connect theory with practice. The data would suggest that the triggers and risk factors are different for each health care profession, but the interventions and successful treatments that promote abstinence, with minor variations, are similar.

While some suggest that stress alone does not cause addiction [10], the added factor of medication availability may enhance risk [23, 83, 117, 119], as availability has been found to be a significant risk factor for many health care professional groups [Dabney D (1997) A sociological examination of illicit prescription drug use among pharmacists. University of Florida, "An Unpublished Dissertation"] [72, 117]. The data suggest the majority of the initiation of minor opioid and anxiolytic use by health care professionals occurred after college when access increased in the workplace though obtaining prescriptive authority. In a similar manner, prescription medication initiation today by adolescents is primarily from available unused medications left and forgotten in the home medicine cabinet [109].

Universities and colleges routinely encounter the consequences of unhealthy alcohol or drug use by health care professionals but do not systematically present medical education designed to prevent these behavioral misadventures. The importance and quality of education with regard to alcohol or drug use, be it prescription medications or otherwise, cannot be stressed enough. While there has been some progress in curriculum and faculty development in many health care professional schools, much more needs to be accomplished for substance abuse education generally and the vulnerability of health care professionals specifically. It appears that medical education about substance use disorders generally is scanty at best. For example, when the physician Leadership on National Drug Policy conducted a survey of over 1,500 medical students at a random sample of 15 schools, 56% responded that they had received little education

about drug and alcohol abuse, and 20% said they received none [47].

A recent successful national training project for interdisciplinary faculty development across several traditional health professions as well as allied professionals and dentistry issued a strategic plan to improve health care professional education and reviews progress in several health disciplines [40]. That strategic plan made recommendations to strengthen substance abuse medical education: "because of health professional's vulnerability to impairment, information about the causes, risk factors, symptoms, and treatment options for substance abuse needs to be developed further and taught to all health professionals," ([41], p. 158). The plan further acknowledges that "Chemically dependent professionals unfortunately do not readily recognize their own impairments. . ..Guilt and shame over past behaviors prevent health professionals from admitting their problems, seeing the difficulties that addiction has caused in their lives, and voluntarily seeking help" ([41], p. 158).

As for the curriculum, understanding the "disease model" is critical to the professional development of clinicians but doesn't provide the sort of preventative information necessary to sensitize one to substance use or abuse either in patients or in themselves. Recommendations suggest that education in the context of requiring health care students to attend Alcoholics Anonymous, Narcotics Anonymous or Caduceus groups or sitting in on group counseling sessions give them a direct sense of the power of addictive disease and the strength needed to attain and maintain recovery.

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Identification and Treatment of Alcohol or Drug Dependence in the Elderly

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Contents

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Introduction

Substance abuse and dependence are considered significant problems in society warranting identification and treatment. However, substance misuse, abuse, and dependence in older adults are complex issues that are often not recognized and, if recognized at all, under-treated. Substance misuse/abuse, in particular, among elders is an increasing problem. Older adults with these problems are a special and vulnerable population that can benefit from elder-specific strategies focused on their unique issues associated with alcohol and medication/drug misuse/abuse in later life. There are concerns in the field that the standard diagnostic criteria for abuse/dependence are difficult to apply to older adults, leading to under-identification and treatment. This chapter will cover four major areas that can benefit both research and clinical professionals working with older adults: (1) prevalence, impact, and correlates of the substance abuse in this population; (2) screening and identification; (3) use of brief interventions to either encourage behavior change or facilitate treatment entry, if needed, and (4) treatment research and related issues.

Prevalence and Impact of Substance Use Among Older Adults

Community surveys have estimated the prevalence of problem drinking among older adults to

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_70,

range from 1 to 16% [2, 34, 53, 58, 59]. These rates vary widely depending on the definitions of older adults, at-risk and problem drinking, alcohol abuse/dependence, and the methodology used in obtaining samples. The National Survey on Drug Use and Health (2002–2003) found that, for individuals aged 50+, 12.2% were heavy drinkers, 3.2% were binge drinkers, and 1.8% used illicit drugs [59]. Estimates of alcohol problems are much higher among health care-seeking populations, because problem drinkers are more likely to seek medical care [64]. Early studies in primary care settings found that 10–15% of older patients met the criteria for at-risk or problem drinking [12, 27]. Two studies in nursing homes reported that 29–49% of residents had a lifetime diagnosis of alcohol abuse or dependence, with 10–18% reported active dependence symptoms in the past year [47, 62]. In 2002, over 616,000 adults aged 55 and older reported alcohol dependence in the past year (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition definition): 1.8% of those aged 55–59, 1.5% of those aged 60–64, and 0.5% of those aged 65 or older [57]. Although alcohol and drug/medication dependence are less common in older adults when compared to younger adults, the mental and physical health consequences are serious [45]. A new study using the 2005–2006 National Survey on Drug Use and Health [17] showed a significant level of binge drinking among those aged 50 to 64. The authors also found that 19% of the men and 13% of the women had two or more drinks a day, considered heavy or "at-risk" drinking. The survey also found binge drinking in those over 65, with 14% of men and 3% of women engaging in binge drinking.

Medication Misuse

Misuse of medications by older adults is perhaps a more challenging issue to identify. Older adults are at higher risk for inappropriate use of medications than younger groups. Older adults use more prescriptions and over-the-counter medications than other age groups, and studies show that about a quarter of older adults use psychotherapeutic medications, with 27% of all tranquilizer prescriptions and 38% of sedative hypnotics written for older adults. There over 2 million serious adverse drug reactions yearly, with 100,000 deaths per year. Adverse drug reactions are especially prominent among nursing home patients with 350,000 events each year [42, 50]. Older persons regularly use on average between two and six prescription medications and between one and three over-the-counter medications [49]. A survey of social services agencies indicated that medication misuse affects 18–41% of the older clients served, depending on the agency [73, 76].

Combined alcohol and medication misuse has been estimated to affect up to 19% of older Americans [55]. Substance abuse problems among elderly individuals often occur from misuse of over-the-counter and prescription medications. Drug misuse can result from the overuse, underuse or irregular uses of either prescription or over-the-counter medications. Misuse can relatively easily become abuse [66, 76]. Additionally, co-factors such as alcohol, and/or mental health problems, older age, and being female also increase vulnerability for misusing prescribed medications [36, 37].

Vulnerabilities for Substance Use Problems

Older adults have specific vulnerabilities for substance abuse problems due to the physical and psychological changes that accompany aging. These may include loneliness, diminished mobility, impaired sensory capabilities, chronic pain, poor physical health, and poor economic and social supports [26, 74]. Older adults also have an increased sensitivity to alcohol, over-the-counter medications, and prescription medications. The age-related decrease in lean body mass compared to total volume of fat, and the decrease in total body volume increase the total distribution of alcohol and other mood-altering chemicals in the body which increases vulnerability. Additionally, central nervous system

sensitivity increases with age. Liver enzymes that metabolize alcohol and certain other drugs are less efficient with aging.

A major concern in working with older adults is the interactions between alcohol and medications, particularly psychoactive medications, such as benzodiazepines, barbiturates, and antidepressants. Alcohol use can interfere with the metabolism of many medications and is a leading risk factor for the development of adverse drug reactions [15, 38, 46, 60]. There are individuals for whom *any* alcohol use, coupled with the use of specific over-the-counter/prescription medications, can be problematic. Further, co-occurring psychiatric conditions including comorbid depression, anxiety disorders, and cognitive impairment can be a complication of alcohol and medication abuse in older adults [16, 65].

The medical and emotional consequences of heavy or excessive alcohol consumption have been well documented. However, there is now more evidence of the medical risks of moderate alcohol use for some older adults. Moderate alcohol consumption has been demonstrated to increase the risk of strokes caused by bleeding, although it decreases the risk of strokes caused by blocked blood vessels [43]. Moderate alcohol use has also been demonstrated to impair driving-related skills even at low levels of consumption and it may lead to other injuries such as falls [64]. Of particular importance to the elderly is the potential interaction between alcohol and both prescribed and over-the-counter medications, especially psychoactive medications such as benzodiazepines, barbiturates and antidepressants, as discussed above. Alcohol is also known to interfere with the metabolism of medications such as digoxin and warfarin [1, 38, 46].

Comorbidities

There are a number of physical and mental health comorbidities associated with alcohol/medication/illicit drug misuse/abuse. In working with older adults, the most difficult-to-identify symptoms are often mental health-related. Epidemiologic studies have demonstrated that alcohol use in the presence of psychiatric symptoms is a common problem with wide reaching consequences in younger age groups. There is less research on the comorbidity of alcohol and psychiatric conditions in later life. Among 216 elderly presenting for alcohol treatment, Finlayson and associates found 25% had an organic brain syndrome (dementia, delirium, amnestic syndrome), 12% had an affective disorder, and 3% had a personality disorder [37]. In a similar study, Blow and colleagues reviewed the diagnosis of 3,986 Veterans Administration patients (aged 60–69) presenting for alcohol treatment [17]. The most common comorbid psychiatric disorder was an affective disorder found in 21% of the patients. Findings from the Liverpool Longitudinal Study found a five-fold increase in psychiatric illness among elderly men who had a lifetime history of five or more years of heavy drinking [70].

Comorbid depressive symptoms are not only common in late life but are also an important factor in the course and prognosis of psychiatric disorders. Depressed alcoholics have been shown to have a more complicated clinical course of depression with an increased risk of suicide and more social dysfunction than non-depressed alcoholics [24]. Moreover, they were shown to seek treatment more often. Relapse rates for those who were alcohol dependent, however, did not appear to be influenced by the presence of depression. Alcohol use prior to late life has also been shown to influence treatment of late-life depression.

Sleep disorders and sleep disturbances represent another group of comorbid disorders associated with excessive alcohol use. Alcohol causes well-established changes in sleep patterns such as decreased sleep latency, decreased stage IV sleep, and precipitation or aggravation of sleep apnea [79]. There are also age-associated changes in sleep patterns including increased rapid eye movement episodes, a decrease in rapid eye movement length, a decrease in stages III and IV sleep, and increased awakenings. The age-associated changes in sleep can all be

worsened by alcohol use and depression. Moeller and colleagues demonstrated in younger subjects that alcohol and depression had additive effects upon sleep disturbances when occurring together [52]. Furthermore, sleep disturbances (especially insomnia) have been implicated as a potential etiologic factor in the development of late-life alcohol problems or in precipitating a relapse [61]. Sleep disturbance is relatively common in older adulthood. Separating out the role of alcohol or drugs and psychiatric symptomatology with the overlay of sleep issues requires time and non-judgmental questioning to elicit the nature of the problems and to work toward positive outcomes.

Identifying Alcohol and Drug Use Problems in Older Adults

Many older individuals have unique drinking patterns and alcohol-related consequences, social issues, and treatment needs, compared to their younger counterparts [3, 8, 35]. Because of this, assessment, intervention, and relapse prevention planning for alcohol problems in late life are likely to require elder-specific approaches. The majority of older adults who are experiencing problems related to their drinking do not meet *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision [5] criteria for alcohol abuse or dependence [15, 21, 63]. Alcohol problems are typically thought to occur in persons who consume larger quantities and drink frequently. For some older individuals, any alcohol use can present problems, particularly when coupled with some psychoactive medications. *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision criteria are widely used and distinguish between abuse and dependence. However, these criteria may not be appropriate for many older adults with substance use problems because people in this age group do not often experience the legal, social, or psychological consequences specified in the criteria. In addition, a lack of tolerance to alcohol may not be as appropriate an indicator of alcohol-related problems in older ages. Most *Diagnostic and Statistical Manual of Mental Disorders* criteria for tolerance are based on increased consumption over time. This does not take into account physiologic changes of aging that can lead to physiologic tolerance at lower levels of alcohol consumption. Finally, the physical and emotional consequences of alcohol use may not be as relevant identifying alcohol problems in older adults.

Table 1 shows some of the signs of potential problems related to alcohol use or alcohol/medication misuse in older adults. Although some of these symptoms can be applied to other conditions in older individuals, they are important markers that provide the opportunity for professionals to ask more questions and determine differential diagnoses. Given the high rate of utilization of medical services by older adults, physicians and other health care professionals can be the key to identifying those in need of brief interventions and/or treatments and providing appropriate care based clinical need.

Table 1 Signs of potential problems related to alcohol and medication/drugs in older adults (need for differential diagnosis)

Anxiety	Increased tolerance to alcohol
Depressed feelings	Unusual response to medications
Disorientation	New difficulties in decision-making
Excessive mood swings	Poor hygiene
Falls, bruises, burns	Poor nutrition
Family problems	Idiopathic seizures
Financial problems	Sleep problems
Headaches	Social isolation
Incontinence	

Classification of Alcohol Use Patterns and Problems in Older Adults

There are two main methods that have been used over many years to understand alcohol problems in older adults: (1) the medical diagnostic approach, and (2) the spectrum-of-use approach. Both approaches use criteria that may not always

apply to older adults and can lead to under-identification of alcohol use problems in this population. These were originally described in 1990 by Atkinson [6] and have been applied in the literature since then.

The Medical Diagnostic Approach involves applying criteria for alcohol abuse/dependence to the older adult population as they are applied to younger adults. Clinicians often rely on the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision [5], a widely used set of criteria that distinguish between abuse and dependence. These criteria may not apply to older adults with substance use problems because they do not often experience the legal, social, or psychological consequences specified in the criteria. For example, "a failure to fulfill major role obligations at work, home, or school" may be less applicable to retired persons with fewer familial and work obligations [21]. A lack of tolerance to alcohol may not indicate that an older adult does not have problems related to alcohol use. Moreover, *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision criteria for tolerance are mostly based upon increased consumption over time which ignores the physiologic changes of aging that would account for physiologic tolerance in the setting of decreased alcohol consumption.

The spectrum-of-use approach uses definitions of abstinence, low-risk use, at-risk use, problem use, and alcohol/drug dependence to determine problems related to use. The spectrum-of-use categories are derived from both the clinical and research expertise of professionals in the field. Definitions for older adults regarding abstinence, low-risk, at-risk, and problem use, and abuse/dependence focus primarily, but not exclusively, on alcohol [11, 13].

Abstinence refers to drinking no alcohol in the previous year. Approximately 60–70% of older adults are abstinent. If an older individual is abstinent, it is useful to ascertain why alcohol is not used. Some individuals are abstinent because of a previous problem with alcohol. Some are abstinent because of recent illness, while others have life-long patterns of low-risk use or abstinence. Those who have a history of alcohol problems may require preventive monitoring to determine whether any new stressors could exacerbate an old pattern.

Low-risk use is alcohol use that does not lead to problems. Older adults in this category drink within recommended drinking guidelines (no more than 1 drink/day or 7 drinks/week, never more than 2 drinks on any one drinking day), are able to employ reasonable limits on alcohol consumption, and do not drink when driving a motor vehicle or boat, or when using contraindicated medications. Low-risk use of medications/drugs would generally include using medications following the physician's prescription. However, a careful check of the number and types of medications, and whether or not the patient is taking psychoactive medications, is important because medication interactions/reactions are not uncommon in older adults and the mix of medications and alcohol can be problematic. These individuals can benefit from preventive messages but may not need interventions.

Use that increases the chances that an individual will develop problems and complications is at-risk use. Persons over 65 who drink >7 drinks/week—one per day—are in the at-risk use category. Although they may not *currently* have a health, social, or emotional problem caused by alcohol, they may experience family and social problems, and, if this drinking pattern continues over time, health problems could be exacerbated. Brief interventions have been shown to be useful for older adults in this group as a prevention measure.

Older adults engaging in problem use are drinking at a level that has already resulted in adverse medical, psychological, or social consequences. Potential consequences can include injuries, medication interaction problems, and family problems, among others. It is important to reiterate that some older adults who drink even small amounts of alcohol can experience alcohol-related problems. Although quantity and frequency of alcohol use are important indicators of potential problems, they may not be the only marker for the need to intervene. The presence

of consequences, even if alcohol use is low, can be a key leading to the need for brief advice or brief treatments.

Alcohol or drug dependence refers to a medical disorder characterized by loss of control, preoccupation with alcohol or drugs, continued use despite adverse consequences, and physiological symptoms such as tolerance and withdrawal. Formal specialized treatment is generally used with persons who meet the criteria for alcohol abuse or dependence and who cannot discontinue drinking with a brief intervention protocol. Nonetheless, pre-treatment strategies are also appropriate for individuals with the highest problem severity. Brief interventions were recommended by the Center for Substance Abuse Treatment's Treatment Improvement Protocol on brief interventions and brief therapies for substance abuse, for use either as a pre-treatment strategy to assist individuals on waiting lists for formalized treatment programs—in the case of those who meet abuse or dependence criteria with no physical dependence or withdrawal—or as an adjunct to specialized treatment to assist with specific issues (e.g., completing homework for treatment groups, attendance at work, adherence to the treatment plan) [12].

Drinking Guidelines for Screening

The National Institute on Alcohol Abuse and Alcoholism and the Center for Substance Abuse Treatment's Treatment Improvement Protocol on older adults [21] recommended that persons aged 65 and older consume no more than 1 standard drink/day or 7 standard drinks/week [31, 54]. In addition, older adults should consume no more than 2 standard drinks on any drinking day.

The drinking limit recommendations for older adults are consistent with data regarding the relationship between consumption and alcohol-related problems in this age group [29, 30]. Recommendations are also consistent with the evidence on the beneficial health effects of drinking [30, 48, 67]. These are simply guidelines. There are individuals for whom abstinence is the best course due to medications used and physical and mental health disorders. Those decisions need to be made on a case-by-case basis.

Screening for Alcohol/Medication Problems in Older Adults

To practice prevention and early intervention with older adults, clinicians need to screen for alcohol use (frequency and quantity), drinking consequences, and alcohol/medication interaction problems. Screening can be done as part of routine mental and physical health care and updated annually, before the older adult begins taking any new medications, or in response to problems that may be alcohol- or medication-related. Clinicians can obtain more accurate histories by: asking questions about the recent past; embedding the alcohol use questions in the context of other health behaviors (i.e., exercise, weight, smoking, alcohol use), and paying attention to non-verbal cues that suggest the client is minimizing use (i.e., blushing, turning away, fidgeting, looking at the floor, change in breathing pattern). The "brown bag approach"—where the clinician asks the client to bring all of his/her medications, over-the-counter preparations, and herbs in a brown paper bag to the next clinical visit—is often recommended to determine medication use. This provides an opportunity for the provider to determine what the individual is taking and what, if any, interaction effect these medications, herbs, etc., may have with each other and with alcohol.

Screening questions can be asked by verbal interview, by paper-and-pencil questionnaire or by computerized questionnaire. All three methods have equivalent reliability and validity [10, 40]. Any positive responses can lead to further questions about consequences. To successfully incorporate alcohol (and other drug) screening into clinical practice with older adults, it should be simple and consistent with other screening procedures already in place [13].

Before asking any screening questions, the following conditions are needed: (1) the

interviewer needs to be empathetic and nonthreatening; (2) the purpose of the questions should be clearly related to health status; (3) the client should be alcohol free at the time of the screening; (4) the information must be confidential, and (5) the questions need to be easy to understand. In some settings (such as waiting rooms), screening instruments are given as self-report questionnaires with instructions for patients to discuss the meaning of the results with their health care providers.

The following interview guidelines can be used. For patients requiring emergency treatment or for those who are temporarily impaired, it is best to wait until their condition has stabilized and they have become accustomed to the health setting where the interview will take place. Signs of alcohol or drug intoxication should be noted. Individuals who have alcohol on their breath or appear intoxicated give unreliable responses, so consideration should be given to conducting the interview at a later time. If this is not possible, findings and conditions of the interview should be noted in the medical record. If the alcohol questions are embedded in a longer health interview, a transitional statement is needed to move into the alcohol-related questions. The best way to introduce alcohol questions is to give the client a general idea of the content of the questions, their purpose, and the need for accurate answers [14]. This statement should be followed by a description of the types of alcoholic beverages typically consumed. If necessary, clinicians may include a description of beverages that may not be considered alcoholic (e.g., cider, low alcohol beer). Determinations of consumption are based on "standard drinks". A standard drink is a 12-ounce bottle of beer, a 4-ounce glass of wine, or 1½ ounces (a shot) of liquor (e.g., vodka, gin, whiskey).

Screening for alcohol use and alcohol-related problems does not always follow a standardized format. Additionally, not all standardized instruments exhibit good reliability and validity when used with older adults. There are a few screening instruments that have been used effectively with older adults. In addition to quantity/frequency questions to ascertain use, the Michigan Alcoholism Screening Test-Geriatric Version, the Short Michigan Alcoholism Screening Test-Geriatric Version, and the Alcohol Use Disorders Identification Test are often used with older adults. Of these, the Michigan Alcoholism Screening Test-Geriatric Version and the Short Michigan Alcoholism Screening Test-Geriatric Version were developed specifically for older adults. The Alcohol Use Disorders Identification Test, developed by the World Health Organization, has been tested in a number of countries with various populations.

The Michigan Alcoholism Screening Test-Geriatric Version was developed at the University of Michigan [18] as an elderly alcoholism screening instrument for use in a variety of settings. The Michigan Alcoholism Screening Test-Geriatric Version was the first major elder-specific alcoholism screening measure to be developed with items unique to older problem drinkers. It is a 24-item scale with a sensitivity of 94.9%, specificity of 77.8%, positive predictive value of 89.4%, and negative predictive value of 88.6%. The Short Michigan Alcoholism Screening Test-Geriatric Version is a 10-item validated form [19].

The Alcohol Use Disorders Identification Test is well-validated in adults under 65 in primary care settings [9, 33, 71] and had initial validation in a study of older adults [19]. The Alcohol Use Disorders Identification Test is a 10-item scale with alcohol-related information for the *previous year only*. The questionnaire is often used as a screener. The recommended cut-off score for the Alcohol Use Disorders Identification Test has been 8, but Blow and colleagues [20] found a Cronbach's alpha reliability of 0.95, sensitivity of 0.83 and a specificity of 0.91 in a sample of older adults with a cut-off score of 7.

Broad-Based Assessment of Substance Use Problems

Clinicians can follow-up the brief questions about consumption and consequences such as

those in the Michigan Alcoholism Screening Test-Geriatric Version and the Alcohol Use Disorders Identification Test with more in-depth follow-up questions, where appropriate. In addition, information obtained in the "brown bag approach" regarding medication use will assist in making any diagnoses and brief intervention or treatment plans.

The use of validated substance abuse assessment instruments will provide a structured approach to the assessment process as well as a checklist of items that should be evaluated with each older adult receiving a substance abuse assessment. Specialized assessments are generally conducted by substance abuse treatment program personnel or trained mental and physical health care providers [51].

Despite problems with criteria used to assess older adults for substance use disorders, two structured assessment instruments are recommended [21], the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised [77] and the Diagnostic Interview Schedule. The Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised is a multi-module assessment that covers disorders of: substance use, psychosis, mood, anxiety, somatoform, eating, adjustment, and personality. It takes a trained clinician approximately 30 minutes to administer the 35 questions, which probe for alcohol abuse or dependence. The Diagnostic Interview Schedule was originally developed by Robins and colleagues [69] with *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition criteria and has been updated as *Diagnostic and Statistical Manual of Mental Disorders* criteria have evolved. The Diagnostic Interview Schedule is a highly structured interview that does not require clinical judgment and can be used by non-clinicians. The Diagnostic Interview Schedule assesses both current and past symptoms and is available in a computerized version. It has been translated into a number of languages including Spanish and Chinese.

Use of Brief Alcohol Interventions with Older Adults with Substance Dependence

Low intensity, brief interventions are cost-effective and practical techniques that were used as an initial approach to at-risk and problem drinkers in primary care settings and well validated through many studies in primary care [80] and emergency medicine settings [44]. In general, the results of brief intervention studies support the recommendations of the Center for Substance Abuse Treatment expert committee report [12] and the National Institute on Alcohol Abuse and Alcoholism [56] that early identification/screening and brief interventions are effective, should be a matter of routine practice in primary and other health care settings to detect patients with hazardous or harmful patterns of alcohol use. Early identification and secondary prevention of alcohol problems directed in straightforward, non-technical terms at an audience likely to be motivated to change could have broad positive public health implications. It appears that brief interventions with one or a few sessions have the potential of reaching the largest number and broadest spectrum of individuals from diverse settings.

There had been much less attention given to the use of brief interventions with older adults. The spectrum of alcohol interventions for older adults ranges from prevention/education for persons who are abstinent or low-risk drinkers, to minimal advice or brief structured interventions for at-risk or problem drinkers, and formalized alcoholism treatment for drinkers who meet the criteria for abuse and/or dependence. Formalized treatment is generally used with persons who meet the criteria for alcohol abuse or dependence and cannot discontinue drinking with a brief intervention protocol. Nonetheless, pre-treatment brief intervention strategies can be appropriate for this population. Brief alcohol interventions have been shown to be effective with older adults who are at-risk and problem drinkers [22, 34] and were recommended

by the Center for Substance Abuse Treatment Improvement Protocol on brief interventions and brief treatments for substance abuse. There are two main goals of brief interventions: (1) to motivate the individual to cut down or stop using, *or* (2) to motivate the individual who has more serious substance use problems to seek brief or more formalized treatment.

By following the categorization of patterns of use (see above)—at-risk use, problem use, abuse/dependence—clinicians are given flexible guidelines to work with older adults across the spectrum of problems related to alcohol and medications/drugs. Brief interventions can offer a step toward assisting this vulnerable group of older adults to make changes in their alcohol/medication/drug use that can have positive health benefits.

Detoxification and Withdrawal

Alcohol withdrawal symptoms commonly occur in individuals who stop drinking or markedly cut down their drinking after regular heavy use. Alcohol withdrawal can range from mild and almost unnoticeable symptoms to severe and life-threatening ones. The classical set of symptoms associated with alcohol withdrawal includes autonomic hyperactivity (increased pulse rate, increased blood pressure, and increased temperature), restlessness, disturbed sleep, anxiety, nausea, and tremor. More severe withdrawal can be manifested by auditory, visual, or tactile hallucinations, delirium, seizures, and coma. Other substances of abuse such as benzodiazepines, opioids and cocaine have distinct withdrawal symptoms that are also potentially life threatening. Elderly individuals have been shown to have a longer duration of withdrawal symptoms, and withdrawal has the potential for complicating other medical and psychiatric illnesses. There is no evidence, however, to suggest that older individuals are more prone to alcohol withdrawal or need longer treatment for withdrawal symptoms [25, 64]. Because of the potential for life-threatening complications, clinicians caring for older clients who may be abusing substances need a fundamental understanding of withdrawal symptoms and the potential complications as well as when to refer clients to treatment.

Formal Substance Abuse Treatment Outcomes for Older Adults

There has been very little research on the treatment outcomes and the unique needs of older adults in formal substance abuse treatment settings. Because traditional residential alcoholism treatment programs provide services to very few older individuals, sample sizes for treatment outcome studies have often been inadequate. The development of elder-specific alcoholism treatment programs in recent years may facilitate studies of this special population's needs.

Although alcoholism is a significant and growing health problem in the United States [4], there have been few systematic studies of formal alcoholism treatment outcome for older adults [8]. The study of treatment outcomes for older adults who meet the criteria for alcohol abuse/dependence has become a critical issue because of their unique needs for targeted treatment intervention. Because traditional residential alcoholism treatment programs generally provide services to few older adults, sample size issues have been a barrier to studying treatment outcomes for elderly alcoholics in most settings. The development of elder-specific alcoholism treatment programs in recent years has provided sufficiently large numbers of older alcoholics to facilitate studies of this special population [8]. A remaining limitation with this population is the lack of longitudinal studies of treatment outcomes. Previous research on elderly alcoholism treatment can be divided into two broad categories: treatment compliance studies and prospective studies of treatment outcomes.

Few older adults ever enter formal treatment for substance abuse. The Drug and Alcohol Services Information System report noted that

66,500 adults ages 55+ were admitted to treatment during 2002 [58], meaning that 0.1% of the over 62 million individuals in that age group in the United States receive substance abuse treatment. It is relatively rare that screening of older adults is conducted in primary care, emergency care, social service, and aging services settings, making the low rates of treatment unsurprising.

New Models for Screening and Treatment

The Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment published the Treatment Improvement Protocol #26 titled "Substance Abuse among Older Adults" [21]. It provided recommendations from the expert panel on innovative models for screening, brief intervention, and brief treatment approaches appropriate for the older population.

Several states followed the guidelines and recommendations and implemented screening and brief intervention services where older adults can be found (at home, senior centers). Brief interventions involve offering 1–5 "one on one" sessions. Brief interventions for older adults with alcohol problems or risk of such problems have been implemented in a number of settings including primary care [15]. Others have implemented more formal, elder-specific treatment using "brief therapy" or brief treatment employing relapse-prevention models, cognitive-behavioral treatment, and self-management skills [28]. This methodology has been implemented in day treatment or outpatient settings [32, 72, 75, 76].

Studies of Treatment Compliance in Older Adults

Treatment outcomes research on older adults with substance use disorders has focused primarily on compliance with treatment program requirements, with an emphasis on the individuals' fulfillment of prescribed treatment activities and goals, including whether or not those in recovery returned to drinking [8, 21]. The few studies that have addressed these issues in the aging population have shown that age-specific programming improved treatment completion compared with mixed-age treatment [7, 21, 64, 68].

There have been major limitations in the treatment compliance literature on older adults and few prospective studies conducted. Data issues have including a lack of drinking outcome data, failure to report on treatment dropouts, and variations in definitions of treatment completion. In addition, there have been few prospective treatment outcome studies including sufficiently large numbers of older subjects who meet the criteria for alcohol dependence have been conducted to address the methodological limitations of prior work.

Limitations of Treatment Outcome Research

Although it is important to examine factors related to completion of treatment to have a better understanding of client characteristics for those who complete treatment, the lack of information on treatment dropouts or on short- or long-term treatment outcomes, the paucity of females in these studies, the widely varying age cutoffs for inclusion in studies, and the use of "abstinence only" as the outcome, it may be more useful in future studies to measure more clearly non-abstinent drinking outcomes along dimensions such as whether drinkers ever drink to the point of intoxication, binge drinking episodes, consequences over time, physical and mental health status changes, and psychological distress changes over time. Finally, testing elder-specific treatment with mixed-age treatments will help to shape the field in the future as greater percentages of adults reach older ages.

Future Trends: Impact of the "Baby Boom" Cohort

The use of illicit drugs is currently relatively rare in this in older adults. However, research suggests that the number of illicit drug users in older adulthood is likely to increase due to the aging of the "baby boom" generation.

Older adults' higher risk for alcohol and medication, coupled with the rapid growth in this population, highlights the need for targeted intervention, treatment, and relapse prevention strategies. Demographic projections indicate that the aging of the "baby boom" generation will increase the proportion of persons over age 65 from 13% currently, to 20% by the year 2030 [78]. The extent of alcohol and medication misuse is likely to increase significantly as the "baby boom" cohort ages, due to both the growth in the older population as well as cohort-associated lifestyle differences [23]. The projected increase in the number of older adults with substance abuse problems is associated with a 50% increase in the number of older adults and a 70% increase in the rate of treatment needed among older adults [39].

Recent studies of consumption patterns suggest that the baby boom generation, as it continues to age, could maintain a higher level of alcohol consumption than in previous older adult cohorts [23]. Rates of heavy alcohol use have been shown to be higher among baby boomers than in earlier cohorts [46]. In addition, drug use is heightened in the baby boomer cohort [39, 66]. The increasing rate of problem substance use in this population may be attributed to an increase in problems related to the use of illicit drugs or non-medical use of prescription medications [23, 39, 41]. Further, these projections may be underestimates, as criteria used to define problem substance use may not be most appropriate for older populations. Increased substance abuse, coupled with the projected increase in the older adult population, will place increasing pressure on the treatment programs and health care resources [76].

Older adults are a diverse population with substance use patterns that differ across individuals and groups and cover the spectrum of use patterns include abstinence, low-risk use, at-risk use, problem use, and abuse/dependence. Developing brief, cost-effective methods to work with older adults who are experiencing problems related to their use of alcohol, medications, and illicit drugs is becoming a more crucial issue in this era of changing demographic and substance use patterns. It will be the challenge for current and future clinicians, trainers, and researchers to develop methods to ensure more positive outcomes for vulnerable older citizens.

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Alcohol and Drugs of Abuse in Pregnant Women: Effects on the Fetus and Newborn, Mode of Action, and Maternal Treatment

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Introduction

Several drugs and chemicals are known to be teratogenic to the human embryo when administered throughout pregnancy, especially during the period of organogenesis. The evidence for their teratogenicity has been shown by human epidemiologic and clinical studies as well as in studies carried out in animals such as rats, mice, rabbits, and primates. The most important disadvantage of the animal models used is the interspecies differences in toxicity and teratogenicity. These teratogenic insults occurring during embryonic life may be present immediately after birth, at infancy, or even later in life, especially if the damage involves the central nervous system [82]. Moreover, many of the insults to the central nervous system occur in the second and third trimesters of pregnancy, when most other organs have already passed the stage of active organogenesis. Briefly, the main stages of the human central nervous system development are the formation of the neural folds, their closure to form the neural tube that closes completely towards the end of the fourth week post-fertilization, and the formation of the main brain vesicles during weeks 5 and 6, with the medulla, pons, and midbrain undergoing much of their active development during that time. However, the cortical

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_71,

plate starts to develop mainly during weeks 8–9 post-fertilization, and the cerebellar cortex develops even later, mainly during the second and third trimesters of pregnancy. The cerebral cortex continues to develop actively throughout gestation and even in the early postnatal life, mainly by forming the different cortical layers, neuronal growth and sprouting, synapse formation, and myelinization. It is, therefore, expected that psychotropic agents such as ethanol, opioids, cannabis, and cocaine, as well as different psychotropic drugs, may affect the development of the central nervous system almost throughout the entire pregnancy [96, 81, 82]. Hence, such late effect will not necessarily be manifested by morphological changes in the central nervous system but rather by more subtle changes in intellectual capacity, learning ability, attention span, and behavior.

In this chapter, we will discuss only the possible effects of ethanol, opiates, cannabis, and cocaine use during pregnancy on the human embryo and fetus. We will survey studies concerning substance-abusing women either throughout pregnancy or following sporadic use. We also will discuss some animal studies, especially those related to mechanism of action. Unlike other drugs that impact the central nervous system or other organs, all drugs of abuse may affect both the mother and embryo, inducing mainly, but not exclusively, behavioral problems and intellectual deficits.

Effects of Maternal Alcohol (Ethanol) Consumption During Pregnancy

History of Alcohol Effects in Pregnancy

The history of maternal alcoholism and development of the offspring goes back to the Bible and to early Greek mythology. Samuel the prophet forbids Samson's mother from drinking wine during her pregnancy because she is going to give birth to an exceptional child blessed by God with special power, and the bridal couple, in Carthage, was forbidden to drink wine on the wedding night to prevent the birth of a defective child. In 1834, a report to the House of Commons (by a select committee investigating drunkenness) indicated that some of the alcoholic mothers gave birth to infants with "a starved, shrivelled and imperfect look". Later, in 1900, the earliest suspicion of the teratogenic effects of alcohol came from Sullivan, who reported an increase in the rate of abortions and stillbirths as well as increased frequency of epilepsy among live-born infants of chronic alcohol-abusing women [54]. The teratogenic effects of ethanol on human fetuses were first reported by Lemoine et al. in 1968. He described a common pattern of birth defects in 127 children born to alcoholic mothers in France that included growth deficiency, psychomotor retardation, low IQ, and atypical electroencephalogram [65]. Alcohol was used at the time to prevent premature labor, and its use was so widespread that if any causal correlation existed between prenatal alcohol use and birth defects, it should have been recognized and reported long before 1973. The adverse/harmful effects of alcohol use during pregnancy have been suggested for decades, and despite the numerous case reports, the implication of alcohol as a teratogen was greeted with skepticism by the medical community. Furthermore, it was rather difficult to document or diagnose formally the constellation of problems observed in these children, until guidelines for fetal alcohol syndrome were established [92].

Effects on the Developing Embryo and Fetus

Fetal Alcohol Syndrome and Alcohol Effects

Basically there seem to be 3 categories of prenatal exposure to ethanol related to the amount of alcohol ingested: exposure to heavy drinking (over 100 g of ethanol/day), which may cause

fetal alcohol syndrome, exposure to moderate drinking (between 50 and 100 g of ethanol/day), which may result in "alcohol effects" (the differences between these categories are not sharp), and binge drinking-occasions with intakes of 4–5 drinks of ethanol (altogether more than 100 g of ethanol/drink) [61, 73]. Most investigators are in agreement that binge drinking also may cause damage to the developing fetal brain [61, 83]. The amount of alcohol ingested, the length of the period of alcohol use, and the developmental stage of the embryo and fetus at exposure mediate the effects of ethanol intake on the developing fetus. It is important to note that a meta-analysis of reports on the incidence of fetal malformations in moderately alcohol-abusing women during pregnancy did not show an increase in congenital defects [86]. Alcohol drinking, even in moderate amounts, also is associated with an increased risk of spontaneous abortions, especially in the first trimester of pregnancy, and with infertility in males and females [61].

It has been demonstrated by many investigators that high alcohol consumption during pregnancy may seriously affect the embryo. The severity of the malformations ranges from fetal alcohol syndrome, which is evident in 4–6% of infants of heavy-drinking mothers, to minor effects, such as low birth weight, intrauterine growth retardation, a slight reduction in IQ of the infants, and an increased rate of congenital anomalies [54, 55, 65, 83, 92].

Alcohol consumption during pregnancy was associated with a variety of abnormalities in the newborn. However, the most common, serious, and specific syndrome of combined defects-fetal alcohol syndrome-has been described only for regular/daily alcohol users [2, 54, 65, 92]. Recognition of the syndrome was made by Drs. David Smith and Kenneth Jones in 1973 based on the evaluation of eight children born to mothers who were defined as chronic alcoholics [56]. The principal features of fetal alcohol syndrome were determined as prenatal and postnatal growth deficiency, short stature, developmental delay, microcephaly, fine-motor dysfunction, and facial dysmorphism manifested by short palpebral fissures, long smooth philtrum, thin vermilion border of upper lip, and maxillary hypoplasia. In addition, there may be cleft palate, joint anomalies, altered palmar creases, and cardiac anomalies [54]. The above-described facial dysmorphism tends to improve with the advancement in age of the affected individuals.

Anomalies of Other Organs

Alcohol is known to affect not only the central nervous system but also organs that are developmentally related to central nervous system derivatives, including those developmentally dependent on neural crest cells like the craniofacial complex and the heart.

Oro-Facial Clefts

A number of reports addressed potential correlation between alcohol consumption and oral clefts. However, effect estimates were often unstable due to numbers of the cases studied. In a case control surveillance study, Meyer et al. [75] collected 5,956 live-born infants with cleft palate, cleft lip, or both. Based on the maternal report of alcohol use during the first 4 months of pregnancy, the authors failed to link low levels of alcohol use and oral clefts. Even the highest level of alcohol consumption (three or more drinks per week, three or more drinks per drinking day, and maximum daily consumption of five or more drinks) did not result in a higher number of infants born with a cleft than did the use of less than one drink per week or less than one drink per drinking day. In addition, folic-acid-supplemented multivitamins used by some of the women did not modify the association between oral clefts and ethanol consumption [75]. Contradictory results were reported by Romitti et al. [95] based on the data from the National Birth Defects Prevention Study. The authors found a weak correlation between average periconceptional alcohol consumption and all orofacial clefts (combined and

isolated clefts). A moderate link was identified for multiple clefts and for Pierre-Robin syndrome. Estimates for this latter phenotype, however, were based on small numbers, reflecting the study criteria to exclude cases of known etiology. An increased risk of orofacial clefts was observed among infants born to binge-drinking (five or more drinks per occasion) mothers exposed in the first trimester of pregnancy. Maternal binge drinking may be particularly harmful since it results in a greater peak of blood ethanol concentration and, therefore, a prolonged alcohol exposure [24].

Cardiac Anomalies

There is sparse literature dealing with the effects of alcohol abuse in pregnancy on cardiac anomalies. It is accepted that about one-third of children with alcohol embryopathy will also have congenital cardiac problems. Krasemann and Klingebiel [64] retrospectively reviewed electrocardiographic and echocardiographic data of all patients with clinical signs of alcoholic embryopathy between the years 1976 and 2003. Electrocardiographic and echocardiographic measurements often showed slightly altered values in individuals with alcoholic embryopathy, resulting in the conclusion that alcohol abuse during pregnancy as a primary toxin can lead to minor cardiac abnormalities, even without structural congenital cardiac defects [64].

Reduced Fetal Growth

Intrauterine growth restriction is a well-known feature of alcohol embryopathy. There is a growing mass of literature suggesting the evidence of postnatal long-term height and weight deficits among children born to ethanol-using women. Further, Covington et al. [21] found a moderating effect of maternal age on children's weight at age 7, as children born to women over 30 years of age at the time of birth had significantly lower weight compared with those born to younger women [21].

Behavioral and Developmental Changes

Alcohol is considered one of the risk factors for attention deficit hyperactivity disorder, independently of prenatal nicotine exposure or other familial risk factors. One study showing a positive correlation between alcohol and attention deficit hyperactivity disorder included 26 prenatally alcohol-exposed children. Of the 24 children followed up, 10 were diagnosed with attention deficit hyperactivity disorder, 2 with Asperger syndrome, and 1 with mild mental retardation. The severity of the disorder correlated in a linear pattern with the amount of alcohol used by the mother during pregnancy. This effect was reversible, since discontinuation of alcohol consumption by the 12th week resulted in normally developed children. Moreover, consumption of less than one alcoholic drink per day in the last 3 months of pregnancy, despite heavier drinking earlier, did not result in attention deficit hyperactivity disorder, learning disabilities, or cognitive impairment at the age of 14 years [77].

It has been difficult to define and characterize developmental risks associated with binge drinking or moderate drinking in pregnancy [41], and some studies failed to demonstrate an association between alcohol exposure and sustained attention performance in school-aged children [10].

Alcohol in pregnancy may affect intellectual ability, which, together with attention span and behavior, is considered a higher function of the cerebral cortex. Studies in 7-year-old schoolchildren following prenatal exposure to moderate amounts of alcohol show a decrement of 7 points in IQ [108].

In addition, alcohol may affect the cerebellum. In the human cerebellum, Purkinje cell migration is completed and dendritic outgrowth begins around gestational week 26, extending to the third trimester of pregnancy. Consequently, a period of enhanced vulnerability of Purkinje

cells to binge alcohol exposure in humans would be predicted near the end of the second trimester and may extend over the first half of the third trimester [42]. Cerebellar developmental disorders and disproportionate reduction in the anterior cerebellar vermis have been identified by magnetic resonance imaging in children who were exposed prenatally to alcohol during each trimester of pregnancy [89]. Decreased cerebellar growth and decreased cranial-to-body growth in fetuses of alcohol-abusing mothers were also observed on fetal ultrasound performed in the 18th week of gestation [46]. If the mothers stopped drinking at the beginning of pregnancy, cerebellar growth was normal.

Mechanism of Alcohol Teratogenicity

Different mechanisms have been offered to explain the teratogenic effects of alcohol on the developing embryo. They stem from results of different experimental studies and include the following: (1) increased oxidative stress, (2) disturbed glucose, protein, lipid, and DNA metabolism, and (3) impaired neurogenesis and increased cellular apoptosis, especially of neural crest cells [16, 48, 59, 83].

Oxidative Stress

One process implicated is an alteration in the reduction-oxidation reaction status in the central nervous system. This hypothesis was supported by studies demonstrating that ethanol mediated changes in the production and/or activity of endogenous antioxidants in various organs, including the cerebellum and placenta [48, 59, 83].

Oxidative stress has been increasingly recognized as one of the mechanisms underlying ethanol toxicity. Ethanol can induce oxidative stress directly by formation of free radicals, which react with different cellular compounds, or indirectly by reducing intracellular antioxidant capacity, such as decreased glutathione peroxidase levels. The levels of oxidative stress markers were studied in placental villous tissue following 2 h of ethanol perfusion [59]. The results demonstrated a significant increase in oxidative stress, primarily involving the nitric oxide pathway in the trophoblast and DNA damage in the villous stromal cells. Alcohol-induced oxidative stress was also found to increase lipid peroxidation and damage protein and DNA.

Disturbed Prostaglandin Synthesis

Alcohol is known to affect prostaglandins, hence influencing fetal development and parturition. When mice were treated with aspirin (a prostaglandin synthesis inhibitor) prior to alcohol exposure, aspirin pretreatment reduced by 50% the alcohol-induced malformations in comparison with mice treated with aspirin after alcohol exposure [90].

Effects on Neurons

Several studies in rats and mice have shown that in utero exposure to alcohol caused structural defects in the hippocampus, cerebellum, and neural crest cells, with increased cell death [16, 48, 91].

In light of those different mechanisms of action, it is reasonable to presume that alcohol-induced teratogenicity is probably the result of injuries caused by several mechanisms [18].

Prevention and Treatment

Prevention

Since the diagnosis of fetal alcohol syndrome in young children is often difficult, the first challenge is identification and follow-up of children at risk. The second challenge is to prevent this disorder by preventing alcohol drinking. Unfortunately, there are only a few reports demonstrating success in reducing drinking of alcohol in pregnancy, and these reports even

declined from 1995 to 1999. The rate of binge drinking apparently remained stable, and chronic heavy drinking remained unchanged, suggesting that the education programs were not effective. Preventing alcohol abuse must, therefore, start with educational programs in schools and later during academic studies. Prevention programs need to be addressed primarily toward high-risk individuals and groups [53].

Treatment During Pregnancy

Assuming that oxidative stress is one of the major routes of ethanol-induced damage, it is reasonable to supplement with antioxidants in an effort to attenuate this damage. Antioxidants, such as vitamin C, vitamin E, folic acid, beta-carotene, and flavonoids can be supplemented by food, therefore reversing other nutritional deficits common among this population [18]. However, to our knowledge, only a few, if any, such programs exist.

Lactation

As alcohol is transferred to human milk, reaching levels similar to those in maternal serum, women drinking high amounts of alcohol should refrain from nursing their infants. Moreover, nursing infants suckle lower amounts of alcohol-containing milk. If nursing mothers drink only small-to-moderate amounts of alcohol, they should wait 2–3 h before nursing their infants [99].

Prevention and Treatment of Alcohol-Exposed Pregnant Animals

Alcohol-exposed C57BL/6 J mice were injected twice with 2.9 g/kg, 4 h apart, of EUK-134 (a potent synthetic superoxide dismutase plus catalase mimetic) on their 9th day of pregnancy. EUK-134 supplementation induced a notable reduction in cell death of the apical ectodermal ridge of the newly forming limb buds in ethanol-exposed embryos and reduced the forelimb malformations by about half (67.3–35.9%) [17].

Further support for the efficiency of antioxidants in attenuating the teratogenic effects of alcohol consumption throughout pregnancy comes from Wentzel et al. [116], who studied the effects of 5% vitamin E added to food on the outcome of ethanol-exposed rat pregnancies, showing a reduced rate of malformed or dead fetuses, but no change in the alcohol-induced reduction of body weight.

Animal Models for Alcohol-Induced Embryopathy

The growth spurt of the human brain is mainly during the third trimester of pregnancy, continuing into postnatal life. In rats, the brain growth spurt takes place entirely in the postnatal period. Therefore, rats must be exposed to alcohol during the equivalent periods of the brain development in humans, which is only in the early postnatal life [72]. The reduced Purkinje cell number demonstrated by Goodlett et al. [42] supports the contention that a significant amount of pathological loss of post-mitotic Purkinje cells occurs, yet it is dependent on the time of alcohol exposure. Hamre and West [45] found in newborn rats that postnatal days 4–6 were the most sensitive period for cerebellar Purkinje and granule cell loss following binge alcohol exposure [45].

Alcohol exposure of pregnant rats, equivalent to all three trimesters of human pregnancy, was shown to reduce cerebellar Purkinje cell numbers compared with the group that was exposed only in the third or first and second trimesters equivalent. In contrast, exposure to alcohol in the third trimester equivalent yielded a decrement in the olfactory bulb mitral cell numbers as compared with other timing groups (first or second trimesters) [45, 72].

Similar results were demonstrated by Ramadoss et al. [89] utilizing an ovine model to determine the critical period of vulnerability of fetal Purkinje cells following prenatal alcohol abuse, mimicking a human binge pattern during

the first and third trimesters of pregnancy. In these animals, unlike the rat model, the entire brain development occurs in utero. They found that the fetal cerebellar Purkinje cells are sensitive to alcohol throughout gestation [89]. The short- and long-term effects of ethanol were studied by Dembele et al. [23] in 7-day-old and 3-month-old rats following alcohol exposure. They found that prenatal ethanol exposure led to hypothalamic oxidative stress persisting into adult life and being significantly higher among the group of older rats, implying long-term damage of ethanol consumption during pregnancy [23].

In a meta-analysis of 22 studies using different strains of rats and one study on mice, Chotro et al. [19] found in 18/22 studies that prenatal exposure to ethanol increased ethanol intake among the offspring. The four remaining studies failed to show any effect whatsoever, a result interpreted and explained as the age of testing, 120 days and over [19]. Simpson et al. [103] have shown that alcohol exposure in rats decreased fetal body weight and bone length and delayed skeletal ossification. These effects persisted postnatally, leading to growth plate abnormalities and decreased skeletal maturity scores at 2–4 weeks of age. Fetal alcohol syndrome-like craniofacial malformations were demonstrated by Rogers et al. [94] following treatment of pregnant C57 BL/6 J mice with methanol on GD-7 during gastrulation. These malformations included anophtalmia, microphtalmia, holoprosencephaly (in varying degrees), and ear and jaw malformations [94]. The involvement of ethanol in cardiac anomalies was also studied in rats. Alcohol administration during pregnancy reduced cardiac mass and depressed function, evidently, due to microstructural changes of the myocytes, even when affected animals reached adulthood [64].

Conclusions

Maternal alcohol ingestion in pregnancy may have deleterious effects on the central nervous system and other organs of the developing embryo and fetus, depending on the dose and duration and on the developmental stage of the embryo at exposure. These embryotoxic effects of alcohol were observed in many animal species. It is, therefore, important to reduce alcohol drinking during pregnancy to a minimum. However, as of today, it is still difficult to define the minimal dose that will affect the developing embryo and the exact dose-response relationship.

Heroin-Dependent Mothers in Pregnancy

Pregnant mothers who are heroin dependent often belong to one of the following three categories: (1) women treated with opiates (i.e., methadone and in recent years also buprenorphine or naltrexone) and who carefully follow the treatment regimen, (2) women treated with opiates but who on occasion also use heroin or other “street drugs”, and (3) women addicted to heroin or other opiates and who hence use heroin, depending on availability. These women also have periods without drugs, a fact that may result in withdrawal symptoms in the mother and the fetus. In many cases, these mothers also use other psychotropic drugs such as benzodiazepines, phenothiazines, or barbiturates. Rarely, they may also use cocaine. Many of these women also smoke cigarettes and/or ingest different amounts of ethanol (alcohol). Moreover, they often do not seek medical care and suffer from medical neglect even during pregnancy. The addicted mothers are at increased risk for various acute and chronic serious infections, such as hepatitis B, hepatitis C, and HIV [82].

Relation Between Substance Abuse and Attention Deficit Hyperactivity Disorder

Several studies have found an association between attention deficit hyperactivity disorder and substance abuse. The prevalence of substance abuse is, therefore, much higher among

persons with attention deficit hyperactivity disorder, which was found to be common among opioid (heroin) abusers [117]. It is more difficult to treat opioid-dependent individuals with attention deficit hyperactivity disorder than it is to treat those without it [117]. Moreover, stimulant treatment of adolescents with attention deficit hyperactivity disorder can effectively reduce the rate of substance abuse [62, 117]. In addition, there seem to be specific differences between drug abusers with and without attention deficit hyperactivity disorder. Drug abusers with attention deficit hyperactivity disorder report an earlier start to use the substances; their substance abuse is more severe, and they may also need treatment for their attention deficit hyperactivity disorder to achieve abstinence. Similar types of genetic polymorphism to genes related to dopamine metabolism have been found among individuals with attention deficit hyperactivity disorder and those who are heroin dependent. For example, several investigators have shown in heroin-dependent individuals, or those with other substance abuse, a polymorphism to the catechol-O-methyl transferase gene, to the dopamine D4 receptor, or to the mu-opioid receptor gene [63, 102]. Similar gene polymorphism was also observed in individuals with attention deficit hyperactivity disorder.

Effects of Heroin and Opiates on the Fetus and Newborn

Although several reports of children with congenital anomalies born to heroin-dependent mothers have been published, there is no consistent pattern of anomalies and heroin is not considered to be a teratogenic agent and, in contrast to cocaine, is not considered to cause intrauterine fetal bleeding or abruptio placentae [27, 69, 70, 93, 107, 109, 112]. However, heroin (and opiate) use during pregnancy is associated with increased prematurity, low birth weight, small head circumference, and increased neonatal and perinatal mortality. Withdrawal symptoms may also develop in 40–80% of the newborns; a high incidence of sudden infant death syndrome during the first year of life was also described, although this is subject to some debate [57]. The use of methadone during pregnancy seems to be much safer for the developing embryo and fetus, with relatively few side effects, but withdrawal symptoms are frequent in the offspring of methadone-treated mothers to the same extent as with heroin.

Effects on Postnatal Development

Developmental delay, as well as behavioral and emotional problems, was often encountered in children born to drug-dependent mothers using heroin or methadone during pregnancy [27, 69, 70, 93, 107, 109, 112]. Some investigators have demonstrated an improvement of the developmental scores in these children with the advancement of age, but others have not. A high proportion of children suffered from inattention, hyperactivity, aggressiveness (attention deficit hyperactivity disorder), and lack of social inhibition [15, 28, 78–81, 100].

The environment in which a child is raised seems to be one of the most important factors that determine his or her developmental outcome. In children born small for their gestational age, the parental socioeconomic status influences the development, especially during the early years of life, with children in families from lower socioeconomic status failing to show developmental recovery. In fact, the relative impact of the clinical and biological factors of these children seems to be overshadowed by the "family" factors [114]. A similar phenomenon was repeatedly described in very low-birth-weight infants, where the major factors affecting cognitive development of the children were the home environment and their neurological status [12].

Studies describing the development of children born to heroin-dependent mothers often suffer from the fact that there may be many confounding factors influencing the results. They are often influenced by the fact that they suffer from

significant neglect. The outcome, therefore, is the result of interaction between in utero exposure to heroin and the postnatal environment. Hence, it is important, in evaluating the outcome of these children, to compare them with relevant controls [78–81].

We had the opportunity to study the developmental outcome of children born to heroin-dependent mothers who were either raised at home or sent for adoption (or foster homes) immediately after birth or at a very young age [78–81]. Since there is evidence of a correlation between socioeconomic status and cognitive functioning of children, and most adoptions are into middle or high socioeconomic status environments, adoption should have a positive effect on cognitive functioning [12, 13, 97]. Indeed, most adopted children score in the normal range on assessment of emotional development. This enabled us to "isolate" the prenatal effects of heroin on neurobehavioral development from the postnatal possible impact of environmental deprivation, which is so common in families of drug addicts.

Comparison groups were composed of children born to heroin-dependent fathers, children with severe environmental deprivation born to non-addicted parents of low socioeconomic status, and a group of normal, age-matched children. About 400 children from 6 months to 12 years of age were studied [78–81].

A lower birth weight and a shorter gestation were recorded in the children born to heroin-dependent mothers and, to a lesser degree, in the children born to heroin-dependent fathers when compared with the other groups. The head circumference and height at examination were lower in the children born to heroin-dependent mothers raised at home in comparison with controls. There was no difference in the weight at examination among the different groups of children.

Intellectual Developmental Outcome

We have found that preschool-aged children born to heroin-dependent fathers, thereby not being exposed in utero to heroin, function as poorly as children born to heroin-dependent mothers. However, paternal drug use in itself did not have a more deleterious effect on school-aged children than parental low socioeconomic status, and children born to non-addicted parents who suffered from environmental deprivation performed even less well than those born to heroin-dependent fathers or to mothers with non-addicted fathers. Finally, when preschool-aged children born to heroin-dependent mothers were adopted at a young age and hence raised in a "good" environment, their intellectual function was similar to that of control children. These results show that in utero exposure to heroin per se does not affect the cognitive ability of preschool-aged children, and most harm to those children is caused by their "poor postnatal environment" because the mother is heroin addict. However, there was a high rate of children with behavioral problems among those born to heroin-dependent mothers raised at home [79].

We then studied similar groups of children aged 6–12 years who attended regular school [80, 81]. At that age, the children born to heroin-dependent mothers had a very high rate (54%) of inattention and hyperactivity (attention deficit hyperactivity disorder). The rate of attention deficit hyperactivity disorder was reduced to 24% in the heroin-exposed adopted children while 24% of those born to drug-dependent fathers (and not exposed to heroin) had attention deficit hyperactivity disorder. It is important to add that 21% of the children with environmental deprivation had attention deficit hyperactivity disorder, while none of the control children had it, as evidenced from the abbreviated Conner's Questionnaire. We also studied their arithmetic and reading abilities and found that it was poor in the children born to heroin-dependent fathers, in those born to heroin-dependent mothers when raised at home, and in the children with environmental deprivation. However, the adopted children at that age had slightly lower cognitive abilities compared with controls, though the difference was not statistically significant. Their arithmetic and reading abilities were also lower.

As it is possible that the high incidence of inattention, hyperactivity, and behavioral disorders found among the children in our study is related to a high incidence of attention deficit hyperactivity disorder among their parents, who were, therefore, prone to substance abuse more than the general population, we used the Wender-Utah questionnaires to assess for maternal attention deficit hyperactivity disorder. We indeed found a very high rate of attention deficit hyperactivity disorder among drug-dependent mothers. However, there was no correlation with the rate of attention deficit hyperactivity disorder among their children, implying that in utero heroin exposure is responsible, at least partially, for the high rate of attention deficit hyperactivity disorder among the heroin-exposed children, whether raised at home or adopted. This is probably attributed to both genetic and environmental factors. This is in line with other studies showing a high rate of attention deficit hyperactivity disorder among the offspring of heroin-dependent parents [62, 117].

We also studied the development of these groups of children at 12–17 years of age. The findings were similar to those observed in children at school age, with a high rate of attention deficit hyperactivity disorder and learning and behavioral problems in the heroin-exposed children. Moreover, adolescents born to heroin-dependent mothers raised at home performed less well than adolescents with environmental deprivation, implying that heroin might have affected some of the higher cortical functions that are related to learning abilities and attention span. In that context, we should mention that other investigators [98, 106] have found that exposure to multiple risk factors is associated with poor developmental outcomes. Therefore, in utero heroin exposure and postnatal poor environment may have a multiple and long-lasting deleterious effect.

Our results, showing the benefit of a good postnatal environment on the intellectual and behavioral outcome of children born to heroin-dependent mothers, emphasize the importance of social and educational services for improving the outcome of children of drug-dependent parents, as well as of children from low socioeconomic status families.

Since in many cases where the mother is drug dependent it is expected that the father will be addicted as well, it is important to mention that children born to drug-dependent fathers were also shown to be at risk for developmental problems. Sowder and Burt [106] found that children born to heroin-dependent fathers were at high risk for early school behavioral and learning problems. Similarly, children born to drug-free parents of a similar underprivileged environment and low socioeconomic status were also at risk for early school problems, but to a lesser extent. These results are similar to our findings in school-aged children. Herjanic et al. [50] found slow mental development in 44% of children born to heroin-dependent fathers. By age 12, conduct disorders and behavioral problems were common among these children. Behavioral problems, attention deficit disorder, and attention deficit hyperactivity disorder were also described in the offspring of cocaine-using mothers [117]. Thus, whenever both parents are addicted, their children seem to be at higher risk than when only the mother is addicted.

Treatment of the Pregnant Mother

The most common approach for treating opiate addicts, whenever weaning is unsuccessful, is methadone treatment [14, 30]. Since it is not accepted to wean pregnant women from heroin, methadone is the preferred treatment in pregnancy. The daily doses vary and range from 10–20 mg up to 100 mg or even more, according to the individual needs. Pregnancy outcome in women who are on strict methadone treatment throughout the entire pregnancy and attend antenatal care seems to be good, with very little long-term effects on the infants except neonatal abstinence symptoms that are common and necessitate transfer to neonatal special care units [14, 81]. However, there seems to be no correlation between the presence of withdrawal

symptoms and developmental outcome even in children born to heroin-dependent mothers [79].

In the last few years, there have been two additional successful approaches to treatment, using either buprenorphine or naltrexone (an opiate antagonist) in low, intermediate, or high doses. In some cases, buprenorphine was administered through slow-release implanted devices [52]. Both of these methods are quite successful in maintaining normal pregnancy outcomes, but they do not seem to be superior to methadone in terms of maternal retention of treatment [74]. However, it is possible that these new modes of therapy are superior to the traditional methadone treatment for the fetus, as prematurity, fetal weight at birth, and other pregnancy complications were lower than with methadone maintenance, and not different from the control population [22].

Lactation

As heroin and other opiates are transferred to human milk, reaching relatively high levels, women using heroin or other opiates, including methadone, might be advised to refrain from nursing their infants, depending on the dose [99]. This is because of the depressive effects of large amounts of opiates on the central nervous system, including the possibility of causing respiratory depression in the suckling infants.

Animal Models for Heroin- and Opiate-Induced Fetal Damage

There are not too many studies on the effects of heroin on pregnancy in animals. This stems from the fact that in the absence of structural anomalies following exposure to heroin and opiates in experimental animals, it is difficult to use animal models that mimic the behavioral changes observed in men [53]. However, several studies were carried out on pregnant mice and rats, demonstrating functional and pathological changes in various parts of the brain in the offspring [47, 51, 57, 105]. Such studies have used in pregnant rats osmotic mini-pumps with opiates or opiate antagonists-buprenorphine, naloxone, and methadone-demonstrating changes in mu-opioid receptor G protein in the offspring, with male offspring showing more sensitivity than females [51]. Slotkin et al. [105] found in mice that administration of heroin during pregnancy causes changes in the hippocampal cholinergic neurons of the offspring, as it induced a deficit in muscarinic cholinergic receptor-induced translocation of protein kinase C gamma. These authors also demonstrated changes in adenylyl cyclase, the latter changes also occurring in the cerebellum where there are only few cholinergic neurons. Changes in signaling proteins distal to neurotransmitter receptors were proposed by the authors as a general mechanism related to several neuroteratogens [105]. Whether these changes are relevant to the human situation is currently unknown.

Of special interest is the fact that grafting of neural progenitor cells into the hippocampus of these mice offspring at adulthood reversed the behavioral deficits observed in non-treated, heroin-exposed mice [58].

Conclusions

Heroin exposure in utero seems to have little effect on the intellectual ability of young children if they are raised in a supportive environment. However, it induces a high rate of attention deficit hyperactivity disorder, which seems to be attributed to the direct effect of heroin on the fetal brain as well as to genetic and environmental factors. We should, therefore, try to improve the home environment of the children born to heroin-dependent mothers and thus minimize the damaging effects of maternal drug addiction. These results emphasize the importance of availability of social and educational services to improve the outcome of children of drug-dependent parents as well as of children from low socioeconomic status families.

Mothers Using Cannabis (Marijuana, Hashish) During Pregnancy

Cannabis

The cannabis plant has been cultivated for centuries and its leaves used as a source of recreational drugs. The dried leaves and flowering parts of the cannabis plant are known in different parts of the world by a variety of names, including Indian hemp and marijuana. The extract of the plant is termed hashish. Although many active compounds with various effects are found in the cannabis plants, the primary active agent is delta-9-tetrahydrocannabinol. This agent has been used recently for increasing appetite and controlling nausea. The main recreational use of cannabis is by smoking [33–38, 47]. The use of cannabis in pregnancy is quite common; in meconium analyses from about 1,000 newborns in Barcelona, Spain, traces of cannabis were found in 5.3% of the newborns. By this method it is possible to detect cannabis use only starting from the second trimester of pregnancy; hence, the true percentage of use is apparently even higher [71].

Delta-9-tetrahydrocannabinol is known to cross the placenta and may, therefore, affect the developing fetus [11]. Women who smoked various numbers of marijuana cigarettes during pregnancy may have impaired fetal growth and hence lower-than-normal birth weight with differences from controls of about 100 g. A continuous use of marijuana during pregnancy is also associated with lower gestational age at birth of about one week. Both phenomena seem to be dose related. There seems to be no increase in the rate of major congenital anomalies associated with the smoking of even large numbers of marijuana cigarettes. As most women who smoke marijuana also smoke cigarettes, it is important to control in such studies for cigarette smoking. Indeed, a meta-analysis of reports available through 1996 did not find a significant association between maternal cannabis use and birth weight when the possible effects of cigarette smoking were controlled [25]. There is no effect of marijuana use during pregnancy on subsequent childhood growth or pubertal development [37, 38].

Marijuana smoking is known to increase the content of carbon monoxide in the blood much more than regular cigarette smoking [99]. Hence, one of the suggested mechanisms for the possible negative effect of marijuana on fetal growth focuses on the relatively large increases in carboxyhemoglobin generated by smoking marijuana [118]. This effect reduces the oxygen-carrying capacity of the maternal blood, impairs the release of oxygen from hemoglobin in the tissues, and indirectly impairs fetal oxygenation. Placental blood flow also may be reduced by the increase in maternal heart rate and blood pressure that may accompany marijuana smoking. Delta-9-tetrahydrocannabinol may also, after its trans-placental passage, decrease fetal heart rate.

In several case control studies, marijuana smoking was associated with an increased rate of gastroschisis and ventricular septal defect but not with neural tube defects [110]. There is no pattern of anomalies associated with cannabis use. We should remember that women using cannabis also often use alcohol and smoke cigarettes.

Neonatal Effects

Increased tremulousness, altered visual response to light stimulus, withdrawal-like crying, and alteration in neonatal sleep pattern have been reported in newborn infants of marijuana-smoking mothers [20]. As with other signs of abstinence following maternal use of psychotropic agents, these findings usually diminish within several weeks.

Postnatal Developmental Effects

The studies on long-term developmental follow-up of children born to mothers using cannabis during pregnancy are mostly negative, with no long-term effects of marijuana on intellectual

abilities. In a series of studies performed by Fried et al., prenatally marijuana-exposed children were followed up until school age [34–37]. The children antenatally exposed to marijuana had, up to 4 years of age, a slight delay on cognitive testing due to some impairment in brain executive functions, especially verbal and memory abilities. It is interesting to note that similar findings were reported by these authors following cigarette smoking in pregnancy but not after exposure to low amounts of alcohol [35]. While these children were re-examined at 60 and 72 months of age, the language delay of the prenatally marijuana-exposed children disappeared, while in the children prenatally exposed to cigarette smoke it did not [36].

Lactation

Delta-9-tetrahydrocannabinol and its metabolites are concentrated in breast milk and absorbed by the nursing baby [85]. Although specific adverse effects have not been identified, one author recommends that breastfeeding be discontinued if marijuana is being used by the mother [18, 99]. The American Academy of Pediatrics lists marijuana among drugs of abuse that should not be ingested by nursing mothers.

Animal Studies

Several animal studies have shown teratogenic effects of marijuana, producing limb, digit, and neural tube closure defects in rats, while others were negative [40]. Pregnant hamsters injected with marijuana extract or resin had an increased incidence of malformed offspring, and high doses of a marijuana extract induced neural tube closure defects and phocomelia in rabbits [39].

Animal studies with delta-9-tetrahydrocannabinol itself have produced similar conflicting results. No teratogenic effects were noted in several studies in rats, hamsters, or chimpanzees [43].

Mothers Using Cocaine in Pregnancy

Historical Background

Cocaine is an alkaloid extracted from the leaves of the plant Erythroxylan coca. It was first isolated by Friedrich Gaedcke, a German chemist, in 1855 and has a long history of medical and recreational use. Cocaine causes transient euphoria through the well-documented biochemical stimulation of the dopaminergic system, apparently by inhibiting the dopamine transporters; however, the mechanism of the lasting and inheritable effects of cocaine is known only partially [3, 87].

For thousands of years, coca has been used in South America for special medical purposes and as a general stimulant, and remains one of the commonly used medicines in different areas of Peru and Bolivia. Cocaine was the first effective local anesthetic, and when its danger became obvious and substitutes were available, especially in the 1930s, its medical use declined [44]. The use of coca in pre-Hispanic America is confirmed by archeological and artistic sources (sculptures, ceramics, fabrics, and pictures). Diffusion of these pieces of evidence, historical and geographical, seems to point to the fact that coca was a strong, central element in the union of the different cultures of the continent [29].

The Aymara Indians of the Andes Mountains were the first to consume coca, which was reserved in the beginning to the priests and princes in religious ceremonies, extending later to the common people. Coca and cocaine were used once more in the nineteenth century. In 1870, Angelo Mariani brought to the market a kind of wine based on coca extract, with a great success. A competitive drink was produced by Pemberton in the USA, named “Vin Francais Cola”.

Cocaine was used medically for the treatment of asthma and hay fever, was officially agreed upon by the famous scientific societies in America, and was finally abandoned [1].

In 1559, the Italian neurologist Mantegazza was the first to try out the remedy on himself, advocating the use of coca as an internal medicine. In psychiatry, cocaine was used in patients with melancholia, exhaustion (physical and psychic), cachexia, and later as a substitution therapy for morphine addicts. Cocaine was first used in 1884 as a local anesthetic agent, first in eye surgery and later applied in dentistry and minor surgery. Among other indications, cocaine was aimed to treat asthma, pregnancy vomiting, and cramping pains [111]. Nowadays, cocaine is mainly used for recreational purposes. However, chronic users may develop addiction, dependency, and tolerance to cocaine.

Effects of Cocaine on the Embryo and Fetus

Cocaine is a small molecule, largely un-ionized at physiological pH; therefore, it readily crosses the placental barrier, and, because of a lower pH in the fetal blood, it flows readily from the maternal into the fetal blood. Due to low levels of esterases in the fetus, it is only slowly metabolized. By causing vasoconstriction, cocaine can induce fetal brain ischemia. As described in several studies, cocaine abuse during pregnancy was able to induce premature birth, lower birth weight, more respiratory distress, bowel and cerebral infarctions, reduced head circumference, and increased risk of seizures [60].

From the mid 1980s into the early 1990s, numerous reports raised concerns referring to the possible teratogenic effects of cocaine abuse in pregnancy on the embryo and fetus. Most observations included congenital anomalies, especially of the central nervous system, limbs, urogenital and gastrointestinal systems, growth retardation, microcephaly, central nervous system infarction, seizures, cortical atrophy and cysts, intraventricular hemorrhage, and sudden infant death.

More recent studies, however, did not find any clear association between prenatal cocaine exposure and an increased rate of major congenital anomalies. Behnke et al. [7] studied the rate of major anomalies in 272 offspring of 154 mothers using cocaine or crack during pregnancy in comparison with 154 control infants and found no difference between the groups in the rate of congenital anomalies. However, they found decreased birth weight, birth length, and head circumference among the cocaine-exposed infants and an increased rate of prematurity. Similarly, Bauer et al. [5] investigated the association between prenatal exposure to cocaine and the medical condition of the newborn infants. The observations demonstrated a decrease in birth weight (536 g), body length (2.6 cm), and head circumference (1.5 cm) among cocaine-exposed newborns, who were also born about 1.2 weeks earlier. Although relatively frequent among the exposed children, the central and autonomic nervous system symptoms attributed to cocaine effects were usually transient. These authors, too, did not find an increased rate of congenital malformations among the cocaine-exposed infants [5]. Thus, if an increase in major anomalies exists, it is small and without any specific pattern of anomalies. There may be, however, an increase in prenatal cerebral hemorrhages and infarctions as well as placental injuries.

Developmental Outcome

To assess the impact of cocaine exposure of the fetus on neonatal auditory information processing ability, Potter et al. [88] used habituation and recovery of the head-turning toward an auditory stimulus (across the 3 phases of the procedure). Their results exhibited a response pattern that is consistent with a slower speed of auditory information processing, implying that cocaine is a neuroteratogenic agent during the newborn period. Similarly, in a prospective longitudinal study of 154 mothers using cocaine during pregnancy, Eyler et al. [26] observed in their neonates, while using blinded developmental examinations, fewer alert periods and less

alert responsiveness, implying a reduced state of regulation, especially when cocaine was used in the third trimester of pregnancy.

However, studies on the later postnatal cognitive development of children prenatally exposed to cocaine report on contradictory results, and the majority of studies did not find a deleterious effect of cocaine alone on the intellectual abilities of the children. Assessing the possibility of an independent link between the levels of prenatal cocaine exposure and developmental test scores (after controlling for the confounding variables alcohol, cigarettes, and marijuana), Frank et al. [31] failed to find any significant interaction between prenatal exposure to cocaine or cigarettes on the Bayley Scales of Infant Development. In a later study, when analyzing cocaine exposure in pregnancy and IQ scores, they failed to find a distinct negative effect of cocaine on global or specific cognitive competence in preschool-aged children [32].

Singer et al. [104] studied the cognitive abilities at 4 years of age of 190 children prenatally exposed to cocaine in comparison with 186 non-exposed children who demonstrated environmental deprivation. There was no difference between the groups, and both had lower-than-average full-scale IQ scores. However, differences between the groups were found in several subscales of the Wechsler Preschool and Primary Scale of Intelligence-Revised (the psychometric test used by the investigators). These were in visual spatial skills, general knowledge, and arithmetic skills, where the cocaine-exposed children performed less well in comparison with the non-exposed. The results of this study, which were very similar to our findings in prenatally heroin-exposed children [79, 80], clearly demonstrate the importance of the environment for early cognitive development.

One important additional negative effect of cocaine exposure was implied by Noland et al. [76], showing in school-aged children a higher rate of commission errors on the Continuous Performance Task and suggesting that cocaine-exposed children had difficulty maintaining a good attention span. These results, again, are similar to those observed by us in children prenatally exposed to heroin [80].

Effects of Gender

Beeghly et al. [6] found that in utero cocaine-exposed girls scored lower on language-related tasks than boys at 6 years but not 9 years of age. Bendersky et al. [8] found that in utero cocaine-exposed 5-year-old girls were less likely to engage in aggressive behavior than similarly exposed boys. The results suggest that gender may be a risk factor among children who have been prenatally exposed to cocaine for some cognitive developmental processes and a protective factor for problematic social behavior.

Mechanisms of Action

Despite two decades of research, the mechanism underlying the cocaine-induced brain damage is still under debate [49]. Speculation on the mechanism of action of cocaine runs basically in two directions: cocaine-induced transient hypertension and vasoconstriction that damages the placenta, inducing placental infarctions with partial or complete abruption [9, 113], or increased oxidative stress [83, 119]. Since the first mechanism is now under debate, we will expand mainly on the second mechanism.

The mechanism of increased oxidative stress induced by cocaine was apparently first proposed by Zimmerman et al. [119]. However, in their study, the addition of antioxidants to the cocaine-treated mice did not prevent the occurrence of neural tube defects, possibly casting some doubt on this proposed mechanism.

Other more recent studies, however, suggest that oxidative stress is an important mechanism of cocaine teratogenesis. The offspring of cocaine-injected, pregnant rats showed low levels of nitric oxide in the brain on the first two postnatal days; these returned to normal on the fourth day. Thiobarbituric acid-reactive species

content in the hippocampus of cocaine-injected rats was, however, increased during days 1–4, showing an oxidative stress-related increase in lipid peroxidation. Prenatal cocaine-injected rats demonstrated, at day 25, significant learning impairment in the water-maze test as compared with non-treated rats, and had increased thiobarbituric acid-reactive species in their brain. This demonstrates that learning in the treated rats causes higher oxidative stress in the brain, possibly related to their impaired learning ability [4]. It can, therefore, be summarized that oxidative stress is playing an important and significant role in cocaine-induced disruption of the central nervous system.

To understand further whether cocaine-induced oxidative stress also causes apoptosis, Poon et al. [87] monitored the oxidative stress and apoptotic effects in human neuronal progenitor cells (Clonexpress) exposed to cocaine during culture. The results showed a significant increase in oxidative stress at 48 h, followed by cell death at 72 h. Thus, whenever the antioxidant capacity is compromised (e.g., in fetuses or in old age), the cocaine-induced damage may be higher.

Lipton et al. [67, 68] investigated whether cocaine-induced constriction of the umbilical/placental vessels that induce significant changes in uterine and placental blood flow also causes oxidative stress. They found that following a single prenatal injection of cocaine in pregnant rats, there was a reduction in the levels of reduced glutathione and of reduced alpha-tocopherol in the fetal brains. In addition, there was an elevation of the oxidized form of alpha-tocopherol. As to oxidized glutathione, a rise was found in the fetuses at the ovarian extreme, where the greatest degree of vasoconstriction was demonstrated, and a decrease in the fetuses at the cervical extreme, where cocaine-induced vasoconstriction is the least. The authors speculate that cocaine-induced vasoconstriction causes increased oxidative stress, thus tying both mechanisms of action. They also show the important role of oxidative stress in the teratogenic mechanism [68].

Prevention and Treatment

Home Intervention Programs for Children Prenatally Exposed to Cocaine

Regardless of drug exposure, children living in poverty are at risk of cognitive delays. Children from low-income families exhibit intellectual declines as toddlers and preschoolers. Indeed, home intervention programs or adoption at a young age yielded higher cognitive scores among drug-exposed infants [79, 80]. Schuler et al. [101] studied the effect of home intervention programs on the infants' developmental outcome among a group of inner-city residents with low socio-economic status. They found that home intervention led to higher scores on the Bayley Scales of Infant Development, mainly of the Mental Developmental Index. These developmental scores, however, declined during the first postnatal 18 months [101].

To determine the relation between prenatal cocaine exposure and children's standardized cognitive tests at age 4, Frank et al. [32] assessed 91 children, using the Wechsler Preschool and Primary Scale of Intelligence-Revised or the Wechsler Intelligence Scale for Children, 3rd ed. Unlike other widespread assumptions relating to the disabling effects of prenatal cocaine exposure on the cognitive abilities of preschool children, Frank et al. strengthened other studies' results, claiming that exposure during pregnancy does not negatively affect the global or specific cognitive functions [32]. They also suggested that children known as being prenatally exposed to cocaine benefit from the early intervention and preschool program.

Intervention Programs for the Mothers

Intervention for cocaine-using mothers during pregnancy should use programs similar to those used in non-pregnant women. The dropout rate from such programs was significantly lower than in non-pregnant women, implying-as was also

found for the treatment of pregnant women dependent on other drugs-that pregnancy may be a good time for prevention of further use of substances that may cause addiction [115].

Lactation

As cocaine and metabolites are transferred to human milk, reaching relatively high levels, women using cocaine should be advised to refrain from nursing their infants, depending on the dose. However, if there is only occasional use, then refraining from breastfeeding for about 24 h following intake is sufficient [99].

Studies in Animals

One of cocaine's important actions is to block the reuptake of dopamine, serotonin, and norepinephrine. In a rat model prenatally exposed to cocaine, Keller and Keller [60] examined the extracellular fluid levels of dopamine, serotonin, and metabolites and found changes in their levels compared with controls, together with long-term behavioral abnormalities. These changes subsided with the advancing age of the rats, similar to the behavioral changes that are observed in the offspring of cocaine-using mothers.

Investigating in utero cocaine-exposed rhesus monkey offspring, Paul et al. [84] found that two-thirds of controls and only a quarter of exposed subjects demonstrated clear evidence of reversal learning (i.e., the ability to adapt to the new environmental contingencies in a seemingly simple way). Zimmerman et al. [119] demonstrated that in mice, cocaine caused vasodilation in the fetal vasculature and an increased rate of neural tube defects, hypoplastic prosencephalon, and microcephaly. The administration of the antioxidants 2-oxothiazolidine-4-carboxylate and a-phenyl-N-t-butyl significantly reduced cocaine-induced vasodilation; however, it did not prevent neural tube defects [119]. Cocaine's vasoconstrictive property on the uterine and placental vasculature is enabled by its potential to increase catecholamine levels (especially norepinephrine) via inhibition of its reuptake. However, He and Lidow [49] found that the cocaine-induced vasoconstriction of the utero-umbilical and fetal brain vessels in the rhesus monkey does not seem to be the main cause of the cerebral damage, and that cocaine damages the fetal brain by a different mechanism. They examined the possible correlation between high levels of the cocaine metabolite benzoylecgonine, a potent vasoconstrictor, and cocaine-induced abnormal brain lamination and found that benzoylecgonine did not induce any brain damage while cocaine did.

Lipton et al. [68] found that cocaine can differentially reduce dopamine and glial-derived neurotrophic factor levels depending upon the fetus' location in the uterus. The extent of dopamine depletion was in correlation with the extent of cocaine-induced restriction of uterine blood flow, as indicated by additional studies [68].

A survey of studies in non-human primates indicates that prenatal cocaine exposure interferes with structural and biochemical development of the brain, consequently resulting in postnatal and adulthood behavioral deficits. Differences in the outcome between various models of prenatal cocaine exposure are likely to reflect the route, dose, gestational period, and daily pattern of cocaine use. This fact is most relevant to studies in human populations with cocaine abuse [66].

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Part XII
Legal, Disability, and Rehabilitative Issues

Forensic Issues

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Contents

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Introduction

Forensic psychiatry is the branch of psychiatry that addresses the intersection of psychiatry and the law. In the practice of medicine, psychiatry, and a variety of other clinical professions, legal or forensic issues are commonly encountered. Confidentiality, for instance, is a key legal and ethical concern in general medical and psychiatric practice but is subject to special treatment in certain addiction treatment settings, which may result in the federal confidentiality statute coming into play. It is important in the clinical practice of addiction medicine and psychiatry to be aware than this statute supersedes state confidentiality laws, broadly defines the confidential doctor/agency–patient/client relationship, and outlines sanctions for violating the statute, which could include loss of federal funding or special tax status for the agency in question. This chapter will address the range of forensic issues that are relevant for practicing physicians, psychiatrists, and addiction specialists and may be of interest to a wide variety of health professionals and scientists. Working in forensic environments is, essentially, practicing forensic medicine. For instance, in the above example, managing the special confidentiality requirements for certain patients or clients suffering from addictive illness requires forensic expertise and knowledge of the federal confidentiality statute and its implications. Further, physicians frequently venture into the forensic realm when they are asked to give opinions about disability, whether a patient can give informed

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_72,

consent for treatment, or whether an intoxicated individual could form the specific intent to commit a crime. Assessing fitness for duty in a physician with alcoholism or comorbid addiction and mood disorder and addressing the relevant regulatory (licensing board) issues, opining about the meaning of a positive drug screen in a medical review officer role, and treating addiction in correctional settings are other examples of the enormous scope of forensic situations in psychiatric and other medical practice. Needless to say, working with attorneys in many contexts and testifying in a court of law are forensic activities commonly encountered in medicine.

Because forensic issues flow from the law, not medicine, many doctors are uncomfortable with the concepts and demands of working at the clinical/forensic intersection. Physicians frequently see forensic issues as intrusive in their work rather than protective of their patients, and many do their best to avoid the courtroom. The authors encourage the reader to cultivate interest in the dynamic body of statutes, courts, and cases that constitute the law; familiarity will breed comfort. From the opposite vantage point, while the law has long addressed problems of mental illness, especially the law regarding criminal responsibility, it has been slow to recognize addictive illness, which until relatively recently was seen as moral weakness or depravity. At least some of this problem has to do with the voluntary element in drug use [8]. Courts and lawmakers are obviously not immune to biased societal attitudes toward those who suffer from addictive disease; nor are they educated about the nature of such illness.

In this chapter, we have chosen to organize the material according to the forensic context, including civil, criminal, and regulatory environments, and to first review some of the essential differences between the style of thinking and nature of practice in forensic contexts compared with the usual clinical thinking in medical practice. The authors also have chosen to include new and emerging areas of forensic interest, in part to underscore the dynamic nature of this field.

The Forensic Evaluation Process

There are two essential differences in performing any evaluation in a forensic context when compared with performing a clinical examination, be it determining whether someone is disabled, competent to make a will, or criminally responsible. Because the findings and opinions in forensic evaluations are meant to be communicated to another party, confidentiality is limited, though obtaining a release of information for that party is often advisable, depending on the context. Also, the purpose of the examination is to evaluate and reach conclusions regarding the referral questions, not to provide medical care to the examinee. It is not a doctor–patient relationship in the usual sense. Because an examinee often expects both help and at least a measure of confidentiality, both of these differences should be communicated to the examinee at the outset. Even after such advisement, examinees often lapse into looking upon the physician as a helper, so the physician should be alert to signs of this and be prepared to remind the examinee about the context. It is equally important for examiners to be watchful for signs that they want to help the examinee. Examiners also should carefully consider their feelings about and reactions to the examinee, which if left unattended could interfere with being neutral and objective. If the examiner develops doubts as to whether the examinee is competent to understand or agree to the conditions of examination, the report should reflect how this was assessed and the conclusions reached.

There are other technical differences between forensic evaluations and clinical evaluations. Because of the need to answer specific and complex questions, forensic evaluations often take more time than clinical evaluations and may require several interviews. Consider an examination in which a psychiatrist is asked to opine whether, due to hallucinogen intoxication, a criminal defendant was able to form the specific intent to commit a capital crime. Reviewing all relevant documents such as police investigative records and medical records will be an

essential task. Incomplete review of documents will undermine the authority of a forensic evaluation. Collateral information is frequently necessary, often from several sources. In assessing whether or not a physician is alcohol dependent, speaking to his or her spouse, employer, and office and hospital staff will be helpful. Forensic reports should be quite detailed, specifically addressing the referral questions in the context of a complete report, including all the data from the examination. This requires that the referral questions be accurately understood by the examiner. This in turn necessitates spending as much time as necessary communicating with the referring party—a court, lawyer, regulatory board, or employer—and making sure that all relevant documents are in the examiner's possession.

Medical and Legal Terminology and Reports of Evaluation

Encountering words that sound like clinical terms but are in fact legal terms is a common situation in forensic work. Other words may be "terms of art" within the legal system and cannot be defined. The forensic examiner must learn about and consider the legal framework. For instance, in Colorado, the Medical Practices Act, the law that regulates medical practice, lists "habitual intemperance" as unprofessional behavior for a physician [41]. "Habitual intemperance", a 19th-century expression used in many laws created in that era, is not in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [3]. Is it the equivalent of substance dependence? Does it include substance abuse? The forensic examiner cannot actually answer these questions without a legal definition. Asking for such a definition from the lawyers involved in the case is always a good step; the evaluator would be told, in this case, that it is a "term of art". The examining physician may be unable to say whether their clinical diagnosis meets the standard for this term. The answer may be left to a fact finder, which in the legal system is a judge or jury. The term "disability" appears in the same Colorado statute referenced above. The state may act against a license on the basis that the physician has a "disability". Again, this term is legal rather than medical in its meaning, referring to a condition that would meet the statutory requirement for unprofessional conduct. Now the examiner has the complex task of sorting out whether habitual intemperance is a disability, whether a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision—defined substance use disorder is a disability, and the relationship between clinical disability and disability under the statute.

In writing reports, physicians should discuss the relationship of a diagnosis or other clinical term to the legal terms used under that statute, regulation, bylaw, or definition in question. For instance, in the above example, if a substance-related disorder is found, the report should review how the diagnosis was reached, sort out the relationship of the clinical and legal terms, and acknowledge any outside sources of information used to understand the legal terms, in the process of answering the referral questions.

Working with Attorneys; Testimony

Due to space limitations, the authors give only a brief introduction to these topics. The reader is referred to forensic psychiatry texts or other works for this information [63, 68]. In these areas, the need for neutrality and objectivity, necessary in all forensic work, is paramount. The "hired gun", a medical evaluator who will testify favorably for any side, regardless of the facts, is anathema to the medical profession. The American Academy of Psychiatry and the Law has published ethics guidelines [1]; these should be reviewed carefully by physicians anticipating these activities. Remaining neutral may be harder than one imagines because of doctors' natural wish to be helpful to whoever is asking for their opinion. One must keep in mind that it is actually helpful for an attorney to hear an opinion unfavorable about his or her client

or case. In court, even the appearance of advocacy or subjectivity is deadly to the credibility of the medical expert witness. Ultimately, credibility is the only currency of the medical expert. A corollary of this principle is that the attorney representing the opposing side in an adversarial proceeding has a duty to attack the credibility as well as the opinions of the medical expert. While it is not easy to remain neutral and objective in the face of such attack, it is easier if one conceptualizes it as part of the job.

Psychiatrists and other physicians, as opposed to forensic psychiatrists, may testify only occasionally, so that lessons learned once may be forgotten before the next occasion arises. The authors recommend that physicians consult their forensic colleagues, forensic texts, and the attorneys involved in the case for help in orienting or re-orienting themselves to the demands of testimony, be it in court or in deposition.

Compulsion and Responsibility

In all of the legal environments discussed below, the psychiatrist may be asked to discuss the voluntary element involved in all substance use and what it means and implies about the character, reliability, credibility, and responsibility of the addicted individual. Kalivas and Volkow have written that understanding addiction must involve understanding why addicted persons continue to be vulnerable to relapse even after extended abstinence and understanding their difficulty in curbing drug-seeking behavior even in the face of serious adverse consequences [32]. The authors will not review here the recent advances in understanding of the neurobiology of addiction, as this subject is covered elsewhere in this book. Generally, as Kalivas and Volkow have argued, the brain circuitry involved in motivation is reorganized by repeated use of addictive compounds such that addicted individuals find that drugs of abuse become more salient than "natural" reinforcers such as food and sex. Thus, loss of pleasure from natural rewards accompanies loss control over the drug and drug seeking, and evolves from the high of initial drug use and the later blurring of recreational and addictive patterns of use. Kalivas and Volkow concluded, "Addiction can be viewed as a pathology in how importance is attached to stimuli that predict drug availability and how the brain regulates (chooses) behavioral output in response to those stimuli. Thus, end-state addiction is characterized by the excessive motivational importance of drug seeking." Hyman [30] proposed that addiction involves "pathological usurpation" or hijacking of the neurobiological substrates for learning and memory, which under ordinary conditions shape essential survival behaviors that arise in response to natural rewards and their cues. It is clear that addictive illness involves and produces a profound alteration in the nature of choice and decision-making about drug seeking, drug using, and the consequences of addictive drug use.

Bonnie [8] discussed issues concerning an addict's choice about using drugs. He rightly pointed out that one can resist a compulsion and that having a hard choice and having no choice are profoundly different conditions. While the "voluntariness" of drug-seeking behavior may be altered by addiction due to the neurobiologic vulnerabilities of addicts, drug use is not involuntary. Limited volition and lack of volition are fundamentally different. Bonnie explored issues of the addict's responsibility for becoming addicted, for behaviors caused by addiction, and for sustaining sobriety after diagnosis and treatment. In his analysis, staying sober is the clearest responsibility. Whether or not his view of responsibility for relapse comports with the science of how the brain is enduringly altered by addictive experience, the fact that the realistic threat of adverse consequences of relapse improves relapse rates underscores pragmatically the concept of responsible choice.

The addiction psychiatrist who is interested in the legal framework for considering these issues should be familiar with landmark judicial decisions in landmark cases. The United States Supreme Court has ruled in three such cases. *Robinson v. California* [62] held that it was unconstitutional to convict a person for being an

addict because to do so would be to punish him for having a disease, in violation of the Eighth Amendment, which prohibits cruel and unusual punishment. But what about behavior caused by or related to addictive illness? Is that punishable? In *Powell v. Texas* [59], the high court ruled that an extension or broad reading of *Robinson* would not hold. Powell was convicted of public drunkenness, and argued that this was a symptom of a disease, alcoholism, and that he was powerless to control it. The Court ruled that Powell could not be found criminally responsible for being an alcoholic but could be found responsible for being drunk in public. The majority of the justices decided that although Powell was an alcoholic, he did not experience an "irresistible compulsion" that he was "utterly unable to control". Bonnie wrote that the justices in *Powell* were cautious about accepting that conditions that impair volition (such as kleptomania and pyromania) could excuse criminal conduct, and were reluctant to constitutionalize addiction as a justification for such behavior; to do so would "unsettle the law of criminal responsibility". Ironically, this case represented Powell's 100th conviction for public drunkenness. (Criminal responsibility is discussed further, below.)

Montana v. Egelhoff [49] is a more recent landmark case. Egelhoff was convicted of murder even though he argued that his blood alcohol level of 0.36% rendered him incapable of the mental state required for conviction of the crime. The Montana criminal code excluded consideration of voluntary intoxication in determining the mental state of a defendant. The Montana Supreme court overturned the trial court, arguing that "all relevant evidence" should be considered when evaluating whether Egelhoff acted "knowingly and purposefully", the mental state required for conviction. The United States Supreme Court upheld the ruling of the lower court, not the Montana Supreme Court. Though four-fifths of the states permitted the use of information about intoxication in addressing whether a defendant had the mental capacity to form the specific intent to commit a given crime, the Court noted that under well-established common law, voluntary intoxication did not excuse committing a crime. The Court held that general acceptance of taking intoxication into consideration when determining mental state did not make such consideration fundamental. (See below for a discussion of diminished capacity.)

In the future, the neurobiology of choice, volition, and motivation will be better worked out, which will lead to even more spirited discussion of these matters in the courts and in forensic psychiatry. It is wise for all the physicians involved in addiction medicine to keep up with these developments. It will be a challenge to weigh and understand the significance of the effects of illness on behavior and responsibility for that behavior.

Civil Matters

Involuntary Commitment

State and federal laws govern involuntary commitment of a psychiatric patient and/or addicted individual, though there is considerable variation from state to state. Grounds for civil commitment are usually that the individual suffers from a mental disease that is causing dangerousness to self or others or grave disability. Because substance use disorders are mental illnesses according to the psychiatric nomenclature, they qualify as a "mental disease" that causes dangerousness or grave disability. However, there is state-to-state variability in this, as well as variable interpretation of the involuntary commitment statute in a given state over time. Further, some states have separate involuntary commitment laws specific to alcohol and/or drug problems. Those states also may require that an individual committed under such a statute be treated in a facility approved and designated by the responsible state agency. Such a facility need not be a psychiatric hospital. When addictive illness is comorbid with another psychiatric disorder that is also a cause of the dangerousness or disability, civil commitment to a psychiatric facility is appropriate. It is essential for psychiatrists and

other physicians to familiarize themselves with the range of statutory obligations and conditions for civil commitment in the jurisdiction in which they practice, including the regulations and case law in situations in which addictive disorder is the mental disease. In states with such laws, familiarity with specific commitment statutes for alcohol or drugs (and in some states it is only one or the other) is similarly necessary.

Civil Competencies

There are many areas in which a psychiatrist may be asked to evaluate whether someone is competent. These include competence to sign in to a hospital voluntarily, to consent to other surgical procedures, to sign a contract, and to make a will, among others. Addictive disorders can impair these competencies. Impairment is characteristically caused by problems with cognition or judgment related to intoxication, withdrawal, persistent cognitive problems caused by substance use, or the combined impairment of these functions linked to the addiction and a co-occurring psychiatric illness. In determining competence, one must know the criteria for competence for the particular act in question. It is wise to ask the attorney or court requesting the evaluation to provide the examining psychiatrist with a copy of the statute or case that defines the competence. If the examiner finds that the examinee is not competent, the report should be accompanied by an explanation of how the substance-related illness was diagnosed, how specific symptoms resulted in the compromise of competence, and which criteria for competence are compromised by those symptoms.

Disability

Eligibility for disability benefits and eligibility for protections under disability laws are the two areas to be covered in this section. The reader should note that "disability" is another word with a meaning that differs across contexts, in this case even across forensic contexts.

If an individual is covered by private disability insurance, the meaning of "disability" is defined by the policy. The evaluating physician should review that definition and be clear about the criteria before rendering an opinion [44]. Criteria can include being unable to perform all duties of the job or able to perform only one or more duties. The policy may cover disability for a specific job, say, transplant surgeon, or although the examinee is a transplant surgeon the policy may only cover the more general job of physician. In the latter circumstance, even if the physician could no longer work as a transplant surgeon as a result of addictive illness, the examiner could find the doctor "disabled" under the policy only if the doctor could no longer work in any field of medicine as a physician. In some policies, the coverage is job specific for a period of time, then general. Some disability carriers do not ask the evaluating physician to render an opinion about disability (a legal adjudication regarding whether they have met policy criteria for being found disabled) but rather ask for an opinion about impairment (a medical conclusion about loss of function) [44]. If rendering an opinion that an examinee who is suffering from a substance-related disorder (or additional other mental disorder) is impaired, the evaluator should describe how the diagnosis was reached, note the symptoms present, and illustrate how the symptoms cause loss of specific functions. If rendering an opinion about disability, one must add an account of the job duties affected by this impairment and address the policy criteria for disability. In looking at these questions, a physician could consider whether the claimant is disabled by active addiction, the need to obtain treatment, the need to pursue recovery activities so extensive as to preclude work, the need to recuperate and convalesce, or the need to handle a specific stressor [16]. Disability companies may be reluctant to consider the risk for relapse as relevant to disability and prefer to address only here-and-now impairments and restrictions related to active disease or treatment. If the examiner believes that relapse is a major clinical

risk and danger, it is vital to explain this in detail. For instance, one study of resident anesthesiologists addicted to the parenteral use of fentanyl found that when, after treatment, they returned to the operating room, death was a first symptom of relapse in an extraordinarily high number of cases [42] (though subsequent studies cast doubt on this finding [17, 55, 70]). It has thus been argued that this specific pattern of addiction renders an anesthesiologist permanently disabled from operating room practice. The authors note that many disability companies stress that losing one's license to practice one's profession, even if due to illness, does not necessarily imply that the professional is disabled.

Because both other psychiatric disorders and medical disorders often complicate addictive illness, the presence of such illness should be noted in disability-related examinations. How each disorder affects the other (for an excellent discussion of this, see Weiss [80]) and the ways in which functional impairment and limitations are produced (or not) are essential aspects of such a discussion.

Social Security provides disability benefits through Social Security Disability Insurance and Supplemental Security Income. The criteria for a finding of disability are specified in the Social Security regulations but will not be reviewed in this chapter (see [44]) because substance-related disorders alone do not qualify someone for compensation in this system. The Contract with America Advancement Act of 1996 abolished substance use disorders as a cause of disabling impairment. If an individual suffers from other psychiatric or medical disorders and also from addictive disease, he or she may qualify, but only if he or she would continue to be disabled upon stopping the use of substances [44]. In the same way, in the absence of another psychiatric or medical condition, an individual is not eligible for disability benefits under the Veterans Administration by virtue of suffering from an addictive disorder alone [6]. The reason for this exclusion relates to a United States Supreme Court ruling concerning a Veterans Administration case in which the alcoholic drinking was determined to be willful misconduct, and willful misconduct disqualifies someone for such benefits under Veterans Administration regulations [74].

Protections from workplace discrimination for disabled persons are offered by the Americans with Disabilities Act of 1990 [4]. The statute defines a covered disability as one that substantially limits one or more major life activities as a result of illness. The Americans with Disabilities Act protections require an employer to offer reasonable accommodation to a qualified (disabled) individual in performing his or her basic job functions unless such accommodation would impose undue hardship on the employer [24]. Those suffering from addictive disorders may be covered under the Americans with Disabilities Act, but only in a limited and specific manner. The Americans with Disabilities Act differentiates alcohol and illegal drugs, and protects those addicted to them differently [81]. Those with alcohol dependence are protected under the Americans with Disabilities Act, but in order for those addicted to illegal drugs to be protected they must be in or have completed treatment for addiction and must not be currently using such drugs. The Americans with Disabilities Act only protects those addicted to legal but controlled substances if they are under the care of a licensed health care professional. An addict's posing a danger to the safety of others (or possibly oneself) is not covered under the Americans with Disabilities Act. Courts have issued contradictory opinions as to whether the employee is protected in cases when performance problems or workplace misconduct is clearly causally related to the addictive disorder. Performance problems caused by using alcohol away from work may not be protected [6]. Recent case law has limited the Americans with Disabilities Act protections afforded to those with substance use disorders [81].

Professional Liability

Issues in the prescribing of addictive compounds to a variety of patients and in the management

of addicted individuals can give rise to malpractice claims and litigation. The most common allegations in such litigation include that prescribing addictive medication led to the death or suicide of a patient or to the patient developing an addictive illness, or that failure to assess and diagnose addictive illness led to inappropriate prescribing or inappropriate monitoring of addictive medications. Most of these claims involve the prescribing of opioids or benzodiazepines. Less commonly, such suits allege failure to recognize alcohol dependence or to consider the risks of cross-addiction. Cross-addiction is sometimes narrowly conceptualized as a person addicted to one drug becoming addicted to another substance. However, a more common cross-addiction problem is relapsing on one's drug of choice because of exposure to another drug of abuse. Litigation also arises out of the alleged failure to obtain informed consent concerning the addictive characteristics of medications prescribed for a variety of conditions and the ensuing risk of developing addictive illness [6].

Suicide is the most frequent precipitant for malpractice claims against psychiatrists and is not an uncommon source of claims for other medical practitioners who treat addictions and other mental disorders. Those who suffer from addictive illness, alone or with co-occurring other psychiatric conditions, are at significantly increased risk for suicide. Obviously, attempted suicide also is commonly associated with substance intoxication. Substance-related disorders and depression commonly co-occur either because addiction causes depression, depression heightens the risk for addiction, or they exist independently and affect each other. Since addiction also impacts the social and occupational arenas, morbidity and losses further enhance suicide risk. Clearly, managing suicide risk is an integral part of the job for anyone treating substance-related disorders.

Strategies for managing chronic non-malignant pain in a person suffering from an opioid or other addictive disorder remain controversial, as is the related question of the frequency with which pain patients develop addictive illness when treated with opioids [12]. All pain patients should be assessed for substance-related disorders and for risk factors for developing such disorders. Assessing the patient, discussing risks with the patient, and documenting one's reasoning about the risks and benefits of the prescribed treatment are all central to the management of liability risk in these cases.

The forensic assessment of alleged medical negligence requires being familiar with the standard of care concerning the medical practice at issue. Given that malpractice cases involving the management and treatment of addiction may also include questions on a wide range of subjects, such as the treatment of a co-occurring psychiatric illness, the appropriateness of prescribing and following the use of addictive substances, or the meaning of toxicology or autopsy findings in a person with an addictive disorder, it is necessary for the medical expert to know the relevant standards of care, including the presence of controversies and other unsettled areas of clinical protocol. It is vital for medical experts to be clear to referring parties as to the areas and limits of their expertise.

Confidentiality

The federal confidentiality statute (42 CFR, Part 2) was intended to guarantee that an individual who voluntarily seeks treatment for addictive illness is not subject to a penalty that someone who does not seek treatment for the same condition would not suffer—that penalty being loss of confidentiality concerning the addictive condition [22]. While this law specifically addresses alcohol or drug treatment programs or those who receive federal funds or federal exemptions (such as federal tax-exempt status), it is prudent to consider that it applies to all treatment and evaluation settings. The law greatly restricts communication about such a client or patient without a signed, written release of information. A few examples of communication permitted by the

statute include when there is a need to: address a life- or health-threatening medical emergency, report a crime committed in the program setting or in which treatment personnel are victims, report child abuse, or respond to a court order (among other conditions). Note that a subpoena is not a court order and is not an exception to the statute. The authors recommend consulting with an attorney knowledgeable about 42 CFR, Part 2, if treatment records are subpoenaed; responding to a subpoena without contesting it has been the source of successful litigation alleging violation of confidentiality. Under the statute, patients may rescind their release of information at any time, except when their treatment is a condition of parole or probation. The law presents many complexities that require interpretation in the context of each treatment situation. When does a person acquire the status of "patient" for whose protection the law provides? At the point of referral, the first phone call, or the first visit? This is only one of the myriad questions that may arise, given the breadth and complexity of the law. The structure of each program, agency, or other practice environment may be sufficiently unique that legal consultation is necessary to understand the implications of this statute. Other issues may arise because of conflict between the federal statute and various state laws. Generally, federal law trumps state law in confidentiality unless state law is more restrictive. Sorting out a program's or physician's risks and responsibilities requires careful thought and often legal input. For a more extensive discussion of 42 CFR, see [9].

Another law that protects the privacy of patient information is the Health Insurance Portability and Accountability Act of 1996, promulgated by the United States Department of Health and Human Services. This law applies to a variety of health care providers, including addiction treatment programs, if they electronically transmit individually identifiable patient information. However, because the confidentiality requirements are stricter in 42 CFR, Part 2, the authors will not address the Health Insurance Portability and Accountability Act in this chapter.

Duty to Protect or Warn

A physician's or psychiatrist's duty to warn or protect a specific person whose safety has been threatened by a patient may be in conflict with other legal and ethical requirements of medical practice, such as protecting the confidentiality of the threatening patient. That the patient suffers from an addiction neither alters the essence of this duty nor makes the conflict easier to resolve. This duty originated with *Tarasoff*, a California Supreme Court decision [73]. While this ruling has evolved in California, it is the basis of similar laws or case law in most states. The duty to warn is usually met by notifying the threatened person or the police of the patient's threat to harm; the duty to protect also may be met by involuntary commitment of the patient. Because law and case law vary so considerably between states, physicians and program personnel should be knowledgeable about the duty as it applies in the jurisdictions in which they practice. A major difference in the manner in which warnings should be given when the threatening patient is in addiction treatment, versus other psychiatric or medical treatment, is that under 42 CFR, Part 2, the notification to the threatened person or to law enforcement should not reveal that the patient is suffering from a substance-related disorder.

Child Custody

Child custody proceedings are at best adversarial and at worst a vitriolic environment. Even when divorce is first raised, in the hope to gain leverage or advantage, one parent may threaten the other that his or her real or alleged substance abuse will damage rights to child custody. It is not unusual for these questions to be raised in the custody proceedings, and addiction experts are frequently retained to evaluate such cases. In practice, courts vary considerably in how much weight they give to a mere history of an addiction in a parent. Many courts have ruled that a

parent who has obtained appropriate help for his or her addiction and/or can demonstrate recovery or abstinence is not disadvantaged. On the other hand, the court will want to know the evaluator's opinion as to whether or not the parent suffers from such a condition, his or her degree of insight, whether he or she has had appropriate treatment, the outcome of treatment, the prognosis, etc. The evaluator also should address the impact of the substance-related disorder on—and its interaction with—other medical and psychiatric illness. The court may ask for the evaluator's treatment recommendations. The evaluator also should be prepared to discuss the question of whether a child has been harmed or neglected by an addicted parent and the likelihood of this occurring in the future. The standard used by the courts in these proceedings is the parent's ability to attend to the best interests and safety of the child or children [33].

Criminal Matters

Competence to Stand Trial

Competence to stand trial in a criminal matter is related to the current mental state of the individual charged with a crime, not to his or her state of mind at the time of the crime's commission. Neither intoxication from a substance of abuse nor withdrawal from such a drug is likely to impair such competence because these conditions would have resolved long before the pre-trial process. Nevertheless, accused persons have been known to come to their competence evaluation severely intoxicated in hopes of being found incompetent. Some examples of substance-related conditions that can impact competence include enduring toxic states, such as an amphetamine- or hallucinogen-induced psychotic disorder, which may last for weeks, other persistent conditions, which may last months or longer, and brain injury caused by drug use.

Dusky v. United States [19] is the landmark United States Supreme Court case that defines incompetence to proceed in a criminal matter. It is utilized in all states with minor variations. *Dusky* states, "The test must be whether he [the defendant] has sufficient present ability to consult with his attorney with a reasonable degree of rational understanding and a rational as well as a factual understanding of the proceedings against him." The competence evaluator must examine carefully the current mental condition of the examinee, asking very specific questions about his or her comprehension of the legal process and assessing the ability to work rationally with the attorney in his or her defense. To determine a defendant's knowledge of the legal process, forensic examiners frequently ask defendants to recite and discuss the charges against them and the job of the various players in the courtroom. In determining their ability to cooperate with their attorney, it is useful to ask how they decide what is pertinent to discuss with their attorney and how they manage their relationship with their attorney when there is divergence about the best way to defend the case. It is also key to determine how accurately the defendant understands the possible outcomes of various legal strategies in the case. In all cases where the examiner finds incompetence, the written report and subsequent testimony should note the diagnosis and symptoms and describe the manner by which the symptoms interfere with competence criteria in *Dusky*. The examiner also should recommend any treatment that might restore competence and the likelihood of restoration. Because—as noted above—substance-related disorders only lead to incompetence proceeding under narrow conditions, it is especially important to explain how and why the condition continues to affect the accused, which will require knowledge of the toxicity of the drug responsible for the disorder and/or the nature of the brain injury associated with the use of that substance.

Sanity and Diminished Capacity

The question of sanity in a criminal case has to do with the state of mind of the defendant at the time of commission of the criminal act, not with his or her mental state at the time of

trial. The insanity defense has its roots in the common law of England, which recognized that under specific circumstances a mentally ill person should not be held responsible for a criminal act. In the majority of states (38) in the United States, the definition of insanity applies to defendants who, as a result of mental disease or defect, are unable to know or understand the nature and quality of their criminal act or are incapable of distinguishing right from wrong in relation to that act. This test is referred to as the M'Naghten standard, named after the defendant in an 1843 case in England [48]. M'Naghten is a cognitive standard, referring to what a defendant fails to know and understand. Several states use both the cognitive test and a volitional test. The volitional arm is often modeled after the standard published by the American Law Institute [2]. This volitional test considers that defendants can avoid criminal responsibility if they were, as a result of mental disease or defect, unable to conform their behavior to the requirements of the law. In most cases and jurisdictions, substance use of any kind, even when the defendant suffers from a substance use disorder, is not an allowable defense under an insanity plea in a criminal case. Most courts have found that voluntary ingestion of a substance of abuse does not excuse criminal behavior. That drugs of abuse and addictive illness can impair volition, however, may be relevant in states with a volitional arm in the law that governs the insanity defense. Clearly, it is imperative that forensic examiners know the laws in the state or states in which they practice so that they know exactly the applicable definition(s) of insanity, including the conditions that are excluded as arguments. When in doubt, the examiner should request that the referring court or attorney give him or her a copy of the relevant laws and cases.

A few specific clinical situations involving substance use may be relevant to sanity even under a strict cognitive test, such as involuntary intoxication, in which the defendant was poisoned or tricked into using a drug that resulted in criminal behavior. Another example is when a criminal act was committed during a withdrawal delirium. In a few states, a persistent drug-induced psychosis may be an admissible factor in an insanity defense. *People v. Kelly* [58] is a California case in which Kelly attempted to kill her mother after recent exposure to mescaline and a long history of hallucinogen use. She believed that her mother was "with the devils". She had a previous history of persistent psychotic states related to drug use and remained psychotic for several months after she attempted to kill her mother. The court ruled: "We hold that such a temporary psychosis which was not limited merely to periods of intoxication. . .and which rendered defendant insane under the M'Naghten test constitutes a settled insanity that is a complete defense to the offense here charged." In other states, in lower courts, cases similar to *Kelly* have not been opened to the insanity defense. *Kelly* also referred to "settled psychosis" and brain damage; brain damage due to addiction under certain circumstances may be used in an insanity defense [33]. *Kelly* also termed Kelly's mental condition as one of "pathological intoxication", further confusing an already puzzling concept [56]. "Pathological" or "idiosyncratic" intoxication is a state in which an individual undergoes a strange and previously unfamiliar reaction to drug exposure. There are a few jurisdictions in which the occurrence of pathological intoxication has qualified a criminal defendant to use the insanity defense.

Diminished capacity is another important legal concept in the domain of criminal responsibility; it is a partial defense, and, as in *Egelhoff* (see Section "Compulsion and Responsibility"), voluntary ingestion of a substance of abuse may be considered relevant. This defense only applies in cases in which a conviction requires proving that the defendant had the specific intent to commit the crime, meaning that the defendant had to deliberate or harbor the thought of the specific crime. Specific-intent crimes include first- and second-degree murder, as opposed to most felonies, which require proving only general intent for conviction. If upon examination a forensic evaluator finds, and the fact finder—the judge or jury—agrees, that due to ingestion of a drug of abuse a defendant could not form the

specific intent to commit second-degree murder, then the accused can only be found guilty of the lesser charge of manslaughter. Like the insanity defense and most other matters considered in this chapter, the diminished capacity (or "diminished responsibility") defense varies between jurisdictions. In fact, California has abolished the diminished capacity defense and replaced it with the concept of diminished actuality [61, 79]. Under this structure, the issue thus becomes whether a defendant actually formed specific intent, not whether he or she had the capacity to do so. A psychiatrist or other forensic evaluator cannot opine on the question of what actually happened; this is a question that can only be addressed by the finder of fact. The evaluator may still testify about the state of mind of the accused and the effects of drug use on his or her mental state. This may provide some information for the fact finder about specific intent. Knowing current state law is again necessary for psychiatrists and other forensic evaluators involved in evaluating someone in which such a defense is being considered.

In alcoholic blackouts, there is anterograde amnesia for some or all events that transpired during a drinking experience. In typical cases, the individuals are described by others as behaving purposefully, but they cannot recall their actions. Controversy about whether blackouts should be considered under the concept of diminished capacity rests on the issue of whether or not the individual experiencing the blackout is capable of forming criminal intent. The blackout syndrome certainly occurs, and memory loss is an essential feature, but whether or not behavior performed during a blackout is intentional is not clear [26, 43].

Imperfect self-defense is another construct in which substance use may be relevant in a criminal defense. The essential element is that the defendant believes, incorrectly, that he or she was in danger and the criminal act was thus believed to be in self-defense to prevent bodily harm or injury. Consider a person who kills another because of such a belief—a paranoid delusion caused by chronic stimulant dependence. If persuaded that this were the case, a court might find such a defendant guilty of manslaughter rather than murder.

Sentencing

The sentencing phase of a criminal trial is another arena in which a court may hear expert testimony about substance use and addiction, though it is hard to predict whether this testimony will be seen as aggravating or mitigating. Consider a vehicular homicide case in which at sentencing the addiction expert presents information about the defendant's severe sedative dependence and how sincere and successful the accused has been in subsequent recovery since the homicide. The defense may call the expert in hopes that the jury will think about a lesser sentence but find the jury members irate that the defendant did not responsibly seek treatment before anyone was killed, and thus be inclined toward a harsher sentence. Similarly, in death penalty cases, it may be difficult to predict whether testimony about drug or alcohol use or addiction will be viewed as aggravating or mitigating by a judge or jury. The ability of the expert witness to communicate effectively is of paramount importance in this phase of a criminal trial.

Pregnancy, Harm to the Fetus, and Child Abuse

In alarming developments, pregnant women have been successfully prosecuted for harming their fetuses by abusing drugs. Many states have seen such cases, but the first two, both in South Carolina, are instructive. In *Regina McKnight* v. State of South Carolina [39], McKnight's stillborn child's blood contained cocaine metabolites. She was charged with homicide by child abuse and sentenced to a 20-year jail term. In *Cornelia Whitner* v. State of South Carolina [83, 84], Whitner's child was taken from her care after testing positive for cocaine metabolites. Whitner was prosecuted under South Carolina's child neglect statute for having exposed her fetus

and subsequent child to cocaine. She was sentenced to a jail term of 8 years. The Supreme Court of South Carolina upheld these decisions upon appeal. The United States Supreme Court denied *certiori*—that is, declined to review either case on further appeal. This was despite numerous national professional organizations, such as the American Academy of Addiction Psychiatry and the American Psychiatric Association, having filed amicus briefs on behalf of *McKnight*.

In *Whitner*, the potential harm to the fetus was considered to be information that she should have considered to be ". . .well documented and in the realm of public knowledge. . . ." Thus, the court considered Whitner "on notice that her conduct in utilizing cocaine during pregnancy constituted child endangerment", as if knowledge could be expected to serve as the antidote to addictive drug use. The Court in *McKnight* reasoned similarly, finding that she had the requisite criminal intent to kill her child (defined as "the person causes the death of a child under the age of eleven while committing child abuse or neglect, and the death occurs under circumstances manifesting an extreme indifference. . .to human life" [66]). The successful prosecution of these cases followed from the interpretation that the South Carolina child abuse and neglect statutes applied to the unborn. McKnight pointed to sections of those statutes that addressed harm due to corporal punishment and/or abandonment, which could only apply to children. The Court considered whether "this demonstrates that the statute was clearly intended to apply only to children. However, section 16-3-85(B) [of the statute] also defines harm as inflicting or allowing to be inflicted on the child physical injury . . . and failing to supply the child with adequate health care . . . Either of these provisions may clearly be applied to an unborn child. Accordingly, given the language of the statute, and this Court's prior opinions defining a child to include a viable fetus, we find the plain language of the statute does not preclude its application to the present case."

An interesting twist on such prosecutions is *Lovill v. Texas*, in which Lovill, a pregnant probationer in treatment for cocaine addiction, experienced relapse, thereby violating her probation. The State decided to incarcerate her in order to protect her fetus, though such probation violations are typically treated with less restrictive actions. On appeal [37], this action was reversed. The Court of Appeals ruled that the prosecution represented a violation of Lovill's 14th Amendment protection against sex discrimination: "The evidence shows (1) that Lovill was treated differently than others who violated the terms of their probation but were not pregnant, and (2) that her pregnancy was a motivating factor in the decision to prosecute."

There are many criticisms of these decisions and similar prosecutions across the country. In most cases, there is a strong argument that science does not support the reputed harm attributed to drugs of abuse such as cocaine. As was argued in a similar case in Maryland [15] following *Robinson*, addiction is a disease, not subject to punishment and not cured by self-discipline or health warnings. Criminal penalties are likely to result in harm to newborns by virtue of separating them from their mother. Perhaps most importantly, it is likely that once it is known that mothers will be prosecuted under these conditions, they will avoid seeking medical care during pregnancy, including treatment for addictive illness or the many causes of fetal and maternal morbidity. Thus, mothers will be deterred from seeking care for themselves and their fetuses; their medical care and health will be undermined, and the very children intended to be protected by these legal actions will experience greater endangerment [67]. These recent decisions are important lessons in how, even in relatively well-informed contemporary times, the legal system can act on biased presuppositions and endanger individuals whom it is trying to protect. These cases also underscore the importance of the legal and medical/psychiatric communities communicating about such legal movements so that they can be addressed through the work of professional organizations serving as *amici*.

Addiction in Criminal Populations

A great majority, up to 95% in some studies, of those in prisoner populations suffer from addictive illness [34], and over half of state and federal prisoners reported being under the influence of drugs or alcohol at the time of their criminal offense [11]. These findings raise the important question of the relationship between substance use and criminality. Of course, this is a broad subject in which there are opposing views. One idea is that criminals become involved with drugs along with other criminal activities and that incarceration is the correct punishment [69]. Another analysis is that drug-abusing individuals commit crimes related to and caused by their addiction. A corollary of the latter analysis is that treatment is the only remedy for criminal behavior caused by addictive illness; punishment is less likely to remedy such behavior. Studies that show decreased criminal recidivism following addiction treatment support this point of view [25, 78]. These ideas also have given rise to the development of alternatives to incarceration such as drug courts (discussed below) and similar diversion programs. Court-ordered, coerced addiction treatment has been found to be effective [46].

Despite the fact that so many prisoners suffer from addictive disorders and that their crimes were committed while they under the influence, only about 40% of state and federal prisons provided on-site addiction treatment in 1997 [72]. Only about a third of state and a quarter of federal inmates reported receiving drug or alcohol treatment in that year [31].

Standards for correctional mental health care have been published by The National Commission on Correctional Health Care in 1999 and the American Psychiatric Association in 2000. The principle behind these recommendations is that the same level of mental health services should be provided to each individual in the criminal justice system as is available in the community [45]. The situation in correctional addiction treatment falls short of this target.

Among the many kinds of treatment programs offered in correctional settings, the most successful are residential programs [57], including therapeutic communities [82], which require 6–24 months to finish. The most successful groups in terms of success with criminal recidivism are those individuals who complete a therapeutic community treatment in prison and, upon release from incarceration, enter a community-based residential therapeutic community. Jails and prisons also utilize less intensive programs, especially for those who reside in the general population of prisoners (as opposed to higher security levels or protective custody), which may engage a prisoner up to 4 hours a day—short-term programs in which the goal is to motivate inmates to obtain addiction treatment in the community when released, i.e., group and individual therapies modeled after outpatient community treatment. Twelve-step programs are generally available, though in many jails and prisons not widely so—that is, there are few meetings, and they may not be available throughout the facility. Twelve-step programs are often problematic to utilize in correctional settings because of their emphasis on openness and honesty, while in most other prison venues the "convict code" ("don't rat on another inmate") and the need for protecting oneself physically and emotionally rule inmate behavior.

There also is a high rate of comorbid psychiatric illness among criminal offenders with addiction problems. However, there are few treatment programs in jails and prisons for this population. In correctional settings, there is a long history of bifurcation between the systems that address addiction problems and those that treat mental illness. The paucity of programming for comorbid conditions in part reflects this legacy. Another problem is that therapeutic communities and other residential programs in correctional settings are quite psychologically stressful because of their emphasis on one-to-one confrontational techniques. This makes it troublesome to tolerate if not contraindicated for inmates with moderate-to-severe mental illnesses. More intensive psychiatric services and

modified therapeutic community techniques are necessary for this population [21].

Drug Courts

Drug courts have taken hold in the popular imagination: one newspaper story reported that as an addicted woman graduated from a drug court program, "...Prosecutors and public defenders applauded when she was handed her certificate; a policewoman hugged her, and a child shouted triumphantly, 'Yeah, Mamma! [20]' " Although such optimism is encouraging, the drug court model deserves a rigorous evaluation. The diversion of non-violent drug offenders to drug courts is increasingly popular and, as defined by the United States Department of Justice, "...(integrates) substance abuse treatment, sanctions, and incentives with case processing to place nonviolent drug-involved defendants in judicially supervised rehabilitation programs" [18].

Engendered in the late 1980s as the crack cocaine epidemic overwhelmed United States jails and prisons, drug courts have evolved as collaborations between the justice system and addiction treaters—collaborations based on the ability of the two camps to speak and understand the other's professional language. Studies reveal that the high up-front cost of drug courts often—but not always—pay off in terms of improved outcomes for addicts and benefits to society, economic and otherwise. Challenges to the drug court model include the obvious bias to help addicts who commit crimes over other addicts who do not, objections to a government mandate for participation in quasi-religious programs such as Alcoholics Anonymous, inadequate data on the overall economic benefits of drug courts, and a philosophical concern about providing punishment for relapse.

Formal drug courts first arose in Judge Stanley Goldstein's 1989 Miami Circuit Court in response to the huge numbers of cocaine-linked offenders flooding the local jails. The prevailing ethos in the late 1980s was a simplistic response to addiction best exemplified by Nancy Reagan's 1982 recommendation that people should "just say no" [35] to drugs. It quickly became apparent to the court that addicted offenders responded well to the treatment services offered, and made quantifiable gains in terms of reduced criminal activity, educational strides, employment, and stabilized family interactions.

By establishing similar drug court dockets within their courts, judges around the country quickly followed Miami's lead, integrating to various degrees drug law enforcement with addiction treatment. By 2007, all 50 states had active drug courts, with 1,932 judges serving on a total of 1,662 drug courts nationwide, and with 386 more drug courts in the planning stages [10].

The concept of "therapeutic jurisprudence", which came to fruition in the late 1980s, was defined as "the study of the extent to which substantive rules, legal procedures, and the roles of lawyers and judges produce therapeutic or anti-therapeutic consequences for individuals involved in the legal process" [29]. This paradigm shift for the legal system was matched by a similar shift in the drug treatment system, an acceptance of the role of coercion in the treatment of addicted individuals: "...Addicts need not be internally motivated at the outset of treatment in order to benefit from it. Indeed, addicts who are legally pressured into treatment may outperform voluntary patients, because they are likely to stay in treatment longer and are more likely to graduate..." [65].

Unlike the judicial coercion inherent in civil commitment proceedings, entrance into a drug court system necessitates a choice by the addicted offender. He or she may choose to accept the legal consequences of the crime, a choice some make in order to avoid treatment. In many circumstances, the drug treatment entails a longer time under judicial supervision than the threatened jail sentence.

The United States Government Accountability Office conducted a 2005 meta- analysis of adult drug courts [76], in which they evaluated 23 programs and found demonstrable reductions in criminal recidivism, though less clear results for actual reductions in drug use.

The Government Accountability Office study was much clearer about the financial benefits of the drug courts assessed. Generally, the drug court model cost substantially more than the non-drug court model. However, the authors conclude that reductions in recidivism would more than compensate for this increased up-front cost. Another study reached similar conclusions [7].

Sentencing in drug courts will involve orders to maintain sobriety, attend treatment and support groups, and participate in tissue screening, as well as other requirements that are essentially clinical in their thrust. Addiction specialists are often asked to evaluate criminal offenders related to such sentencing issues. As in other areas of the law that make use of the concept of therapeutic jurisprudence—mental health courts and parental psychiatric evaluation in child-custody disputes—it behooves the addiction specialist to become familiar and comfortable with the actors and institutions of the legal system.

Regulatory Matters

Impairment and Fitness to Practice

The word "impairment" is used quite differently across the literature and verbiage about impaired professionals. It is sometimes used to refer to having an addictive illness, recovering from an addictive illness, or having an illness that can cause impairment. The authors define it as the inability to practice the profession with sufficient skill and safety to the clientele of that profession due to illness or injury [23]. The illness may be addictive, other psychiatric, or medical, including comorbidities of the three categories. Note that by this definition, having the illness, even if it impairs functioning outside of work, does not constitute impairment. Impairment should be distinguished from deficiencies of knowledge and skill to practice the profession, which have to do with competence. Impairment does not imply incompetence, and incompetence does not imply impairment. Psychiatrists and addiction specialists are often asked by professional licensing boards—regulatory boards that operate based on regulatory laws of the states in the United States—to evaluate practitioners to determine whether they are safe to practice. This raises the question of impairment and the practitioner's fitness for duty, concepts that are related [5]. Professions controlled by regulatory/licensing authorities include most medically related professions (medicine, nursing, dentistry, pharmacy, veterinary medicine, and podiatry) through their boards, attorneys through boards or the state supreme courts, and commercial and private pilots through the Federal Aviation Administration, among others. Each of these agencies has laws, regulations, and policies unique to them; physicians and others performing evaluations for such agencies must become familiar with them individually. For instance, the Federal Aviation Administration has specific ways of defining addictive illness as it applies to commercial pilots; working from the *Diagnostic and Statistical Manual of Mental Disorders* will not suffice.

Impairment, as defined here, usually occurs in the late stages of addictive illness, at least among professionals. Professionals tend to be strongly identified with their profession, and their self-esteem is quite tied to work performance. As a result, even when other areas of life—family, marriage, emotions, and health—are suffering as a result of an addiction, the professional will protect the sanctity of the workplace until the illness is completely out of control. A corollary of this analysis is that by the time impairment occurs, the professional's life—and not just his or her career—is in danger.

When addictive illness causes impairment, it is usually related to symptoms of cognitive dysfunction, emotional liability, impaired judgment, erratic behavior, or a combination thereof. Interference with these functions may be caused by the neurological consequences of substance intoxication, an acute or sustained withdrawal syndrome, or damage to other organs that secondarily affects brain function (e.g., severe liver disease in chronic alcoholism). Chronic

exposure to drugs of abuse also causes personality changes, especially irritability, reduced tolerance of frustration and ambiguity, and impulsivity—the psychotoxicity of extended substance exposure. Evaluating fitness for duty requires understanding the nature of the work that the professional is either fit or unfit to practice. In the report, the evaluator should connect the diagnosis to the symptoms, to the bearing of those symptoms on mental and physical functioning, to the relationship between any loss of function and its impact on the duties of the job in question. The report also should discuss treatment for the addiction (and/or the degree to which recovery and abstinence have been achieved), the prognosis, and the best strategies for monitoring the professional in the future. The interplay of the addictive illness with other psychiatric and medical conditions also should be addressed, along with how this might affect work function. Treatment and prognosis of all potentially impairing illness should be discussed because the regulatory authority will be concerned about both the present and future safety of the professional's clientele.

"Monitoring" is a technical term referring to how professionals are followed once their condition is known. Monitoring activities support but do not substitute for treatment. In fact, the success of physicians with addictive disorders, defined in terms of rates of recovery and rates of returning to or maintaining professional practice [17, 40], may be largely due to the systematic monitoring that they receive. Monitoring activities typically consist of periodic clinical assessment, random tissue testing for alcohol and drugs (and other laboratory testing for markers of addictive illness), and repeated contact with outside sources of information such as spouse, therapist, treatment program, and the professional's workplace. In the United States and Canada, those doctors with addictive disorders (and other illnesses) are monitored by physician health programs, a variation on the theme of peer assistance programs that are involved with many of the other professions. From profession to profession and from state to state, there is much variability in these programs in terms of the illnesses that they address, their structure, their relationship to the regulatory (licensing) authority, and the laws that govern that authority. Most peer assistance programs provide at least some degree of confidentiality from the licensing board, but only with the consent of the board. Addiction specialists involved in evaluating a professional's fitness for duty should be knowledgeable about the capabilities of the peer assistance program of that profession.

Every physician and other addiction specialist who treats or evaluates professionals should be familiar with the laws that govern the profession, especially as applied to any duties that they may have to report an addicted professional to the licensing authority and whether that report is immune for liability [64]. Taking the example of the Medical Practices Act, which governs physicians in Colorado [41], the condition of being addicted to alcohol or drugs is classified as unprofessional conduct. All physicians have a duty to report unprofessional conduct to the Board of Medical Examiners. Colorado law, however, provides a reporting exception for a physician involved in treating physicians with mental health problems, including addictions. However, there is an exception to the exception if the treating physician thinks that the physician-patient is not safe to practice. If a doctor makes a report about another physician to the medical board, the doctor is immune from liability, assuming that the action was taken in good faith.

Addiction psychiatrists and other addiction specialists may work in roles other than forensic evaluator in working with professionals, but all roles require knowledge and facility in the forensic world. For instance, working as a treating psychiatrist, especially if treating in the rubric of a professional's participation in a monitoring program or license stipulation, requires understanding the limitations upon the confidentiality of the treatment and the specific reporting responsibilities that come with that role. Other possible roles include that of medical directors of monitoring programs, which are embedded in specific legal and regulatory contexts and must be well understood for the program to be effective.

For all addiction specialists working with professionals, it is essential for them to understand the psychology, culture, mores, demands, and realities of that profession. That physicians do not function well as patients [23], that lawyers often reject the concept of illness as a factor affecting their behavior, that commercial pilots deny weaknesses, and that astronauts believe that they must be perfect in all dimensions, are extremely relevant to evaluating, assessing, and monitoring them.

Tissue Testing

Testing various body tissues for drugs of abuse is a standard practice in the regulation and monitoring of professionals and other workers when public safety is at risk. Commercial pilots, for instance, are randomly tested for drugs and alcohol; the Federal Aviation Administration prohibits pilots from using intoxicants, including legal ones such as alcohol, within 12 hours of flying. Other professionals are routinely required to undergo such testing if they are known to have an addictive illness. In 1988, the United States Department of Health and Human Services published guidelines [75] mandating a drug-free workplace for federal employees. These guidelines also have served as the model for employment policies and practices in private industry. Pre-employment screening, random testing, and testing for cause are the common types of testing. Working with government or private industry, an addiction specialist may serve in a clinical role, evaluating those found positive on testing, or in a medical review officer role, assuring that the process of drug testing and the interpretation of the results are appropriate. Medical review officer work requires knowledge of the techniques and procedures of tissue testing so that false positives and false negatives can be distinguished from accurate results. Urine is the tissue that is most commonly screened; all tissues have their advantages and disadvantages. The important variables include the ease of obtaining the sample, ease of tampering with, contaminating, or substituting the sample, length of the window of detection, and likelihood that brief drug exposure could be found in the tissue, among others. Besides urine, sweat (via a skin patch), blood, nails, and hair are the most commonly tested [77].

Sports

Although the absolute numbers of athletes troubled by addictive illness may seem too small to warrant discussion in this chapter, the types of drugs used and abused in athletic communities are sufficiently different, and how the relevant institutions are responding to these problems are sufficiently important, to merit discussion. Further, the precedents set in this domain may well presage how other arenas of society approach these problems.

Differentiating between addictive responses to substances and the voluntary use of substances for performance enhancement is an important role for the addiction specialist working for a sports organization. Although the categories of "addiction" and "cheating" may seem clear a priori, the two interact in multiple and subtle ways. For instance, the anabolic androgenic steroids are unlikely to engender classic withdrawal and tolerance unless they are taken in massive supraphysiologic doses; some athletes do take them in such doses. Although most sports organizations now classify stimulants as performance-enhancing substances, the stimulants can be used as part of an addictive diathesis, or, more commonly for the elite athlete, their use can evolve from performance enhancing to addictive.

Addiction specialists who understand the legal and procedural framework of modern sports programs can function in one of three separate roles. First, they can work as a medical review officer, whose essential role is overseeing drug testing and verifying the validity of the results. Second, they can work as a treating clinician with a well-defined and transparent reporting obligation. Third, they can develop and administer employee assistance programs for a

team or within a particular sport. In all these roles, the combination of addiction and forensic knowledge allows the physician or the professional to produce accurate and helpful case formulations and treatment recommendations.

As in other workplaces, the medical review officer must understand the complexities of drug and alcohol testing within the context of the particular industry and federal law, especially the Americans with Disability Act [71]. In a sports organization, however, the medical review officer must, in addition, understand the science of testing for the specific drugs used illicitly [28], the culture and demographics of the program participants, and some specifics about the sport itself. For instance, the medical review officer must schedule the timing of testing before or after competition in order to provide an accurate assessment of any drug use actually taking place, while considering the convenience and dignity of the athletes. Testing for stimulants before a competition is less useful than testing during or after the competition since illicit users take the substances just before the game. As a matter of fairness to athletes who suffer from legitimate medical or psychiatric conditions, there is a need for occasional therapeutic use exemptions [27]. The therapeutic use exemption allows an athlete to use a banned substance after an appropriate diagnostic assessment, legitimate prescription, and ongoing monitoring. Psychostimulants for the treatment of attention deficit disorder and attention deficit hyperactivity disorder are the most common class of medications for which athletes request a therapeutic use exemption. The addiction specialist working in the sports environment must fashion a plan that allows the attention deficit disorder and attention deficit hyperactivity disorder sufferer to use appropriately prescribed medication while denying an exemption to those who are merely using the medications to improve their athletic performance. In addition, the therapeutic use exemption program must contemplate other potentially therapeutic uses for banned substances, such as testosterone for testicular deficiency, diuretics for hypertension, and opioids for pain. Major sports organizations, including the Olympics [54], the National Collegiate Athletic Association [50], the National Football League [51], Major League Baseball [38], the Professional Golf Association [60], and the National Hockey League [52], have processes for evaluating therapeutic use exemption requests.

Addiction psychiatrists and other addiction specialists can serve as treating physicians for athletes; a good understanding of forensic issues is important even in this clinical context. Even without any reporting responsibility, the clinician should be aware of the high visibility of elite athletes in the public consciousness: individual courts [14], the United States Congress [36], and private investigative bodies [47] may request—or subpoena—information about the treatment of such individuals.

Treating an athlete for an addictive disorder, or any substance use, requires that the clinician understand the profound pressures and stresses that affect the athlete. In addition to the rewards of fame and sometimes money that elite athletic performance can bring, the family dynamics of these individuals can be quite disturbing and counterintuitive to the clinician. The desires of family members for material success and celebrity treatment can drive the athlete to behavior that he or she would not otherwise have considered, especially if the financial rewards of peak performance can put food on the table for an otherwise indigent family.

More significant than financial rewards, however, is the internal driving force that the athlete may feel. If one's core value from a very early age is to win at any cost, boundaries often become fluid. Athletes at the elite level are not paralyzed by worry about hurting themselves, or they would not be elite athletes. In 1995, a sports medicine specialist informally posed the following question to 198 Olympic-level athletes: "If I had a drug that was so fantastic that if you took it once, you would win every competition you would enter, from the Olympic decathlon to the Mr. Universe Contest, for the next five years. But it had one minor drawback: It would kill you five years after you took it. Would you still take it?" More than half of the athletes acknowledged that they would take the drug [13]. So, taking a chance on a performance-enhancing drug might

not be a great leap, given the single-minded determination that these athletes have in their emotional repertoire.

For athletes—elite or otherwise—the rationale for allowing a treating psychiatrist or other physician to report relapse to a regulatory authority may appear less convincing than for commercial airline pilots or physicians. For professional athletes, labor unions may necessitate that any monitoring protocol be negotiated under the rules of the National Labor Relations Board [53]. As with any other impaired professional who is part of a monitoring program, the burden falls on the treating physician to make sure that the patient is well aware of the reporting obligations, his or her options for having treatment elsewhere, and the right to withdraw permission for reporting.

The clinician who decides to manage an employee assistance program has different and more complicated obligations than the treating clinician or the medical review officer. The administrator must fashion a program that delivers good care to athletes, functions well from the perspective of management, and conforms to mandates from all applicable laws. An understanding of the sport's culture, and close liaison with coaches, medical staff, and athletic trainers, will ensure that the employee assistance program functions as well as possible in an inherently difficult environment. As is the case with employee assistance programs in other industries, the limits of confidentiality must be spelled out as clearly as possible.

As in all forensic work, the addiction specialist must be prepared to justify clinical and administrative decisions on the basis of evidence-based clinical care and respect for the applicable legal or procedural framework.

Conclusions

There is a broad array of forensic contexts and considerations that present themselves to physicians and other health care providers interested in addictive illness. The contexts range from civil to criminal to regulatory, and within each are complex conceptual problems that must be addressed by the practitioner. This requires mastery of the clinical and scientific elements unique to addictive disease and their intersection with the specific forensic environment. That intersection is approached through unifying principles: neutrality in examination and reporting, addressing multifaceted confidentiality issues, distinguishing clinical from forensic terms, understanding and respecting legal definitions and the institutions from which they flow, working with attorneys and courts to gain sufficient knowledge and comprehension of the forensic questions to be answered, and carefully attending to the policies, statutes, and regulations that define the parameters of the forensic work to be done. The legal realm is not a comfortable one for most medical and psychiatric practitioners; the authors suggest that becoming familiar with this territory and asking for expert consultation when needed will allow those interested in or specializing in addictive illness to enrich their professional experience.

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Disability and Addiction

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Contents

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Introduction

Substance use disorders affect the body and brain on multiple levels and may have long-term disabling effects on the ability to function independently and meet the demands of daily living [26, 30, 54]. Although extensive scientific and medical research describes the biological basis for addictive disorders [6, 31, 48, 91, 92], legal and policy practitioners and those in the social sciences still debate the origins and consequences of addiction. Some see addiction as a moral failing that must be dealt with as such, and others see addiction as a medical disease to be treated. There is disagreement about the degree of volition involved in substance use disorders, what activities related to substance use disorders are worthy of sanction and punishment, and what legal actions to take when illegal activities occur as an antecedent or consequence of substance use disorders [93]. The role of environmental context and the interaction between environmental context and neurobiological and genetic factors also figure into the debate [17, 93]. This debate is more than theoretical—arguments on both sides can have a direct effect on policies and practices that have a substantial impact on the daily lives of people with substance use disorders.

People with substance use disorders, both those in recovery and those who are currently using, often have difficulty finding access to resources, employment, health care, and education, and they are vulnerable to high rates of incarceration, morbidity, and mortality [51].

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_73,

However, although provisions are made for those in recovery, those with substance use disorders who are currently using illegal substances are specifically excluded from the protections of the Americans with Disabilities Act [4] and the disability entitlements provided by the Social Security Administration through Supplemental Security Income and Social Security Disability Insurance [24]. Those in recovery who are currently not using illegal substances are covered. However, the varying definitions of what qualifies as "in recovery" often render the process of obtaining benefits or protections difficult and cumbersome.

The public health burden of substance use disorders becomes magnified when individuals who are impaired cannot obtain needed treatment. Medicaid managed care provides health care to people with low income and few resources. Medicaid is a publicly purchased product funded by the federal government jointly with individual states and is administered by states. Most states do not require Medicaid to provide full coverage of substance abuse treatment. Without adequate coverage, people with substance use disorders are at increased risk of developing more severe substance use disorders, becoming homeless, contracting other serious medical illnesses, transmitting communicable diseases to others, and cycling in and out of the public health system with additional stigmatizing labels (e.g., "difficult", "repeater", "recidivist", "a train wreck", "trouble", "hopeless", "one of those").

The current policies governing entitlements, protections, and medical coverage raise fundamental concerns about civil rights, equality, and fairness for people affected by substance use disorders, both those in recovery and those currently using. These policies reflect varying understandings of what it means to have a disability. Given that disability is a legal and administrative term, rather than a medical one, this variation is not surprising.

The meaning of disability may vary according to jurisdiction and can change over time with respect to legislation, policy, regulations, and ideology. The term is specifically defined to determine those who are considered to have a disability under the Americans with Disabilities Act or who are eligible for state and federal disability and rehabilitation benefits. Individuals with addictions are protected under the Americans with Disabilities Act only if illegal drug use has ceased; those actively using illegal substances are not protected [24]. Those addicted to and currently using alcohol fall under the protection of the Americans with Disabilities Act. However, an employer may discipline, discharge, or deny employment to a person with alcohol problems whose alcohol use adversely affects job performance or conduct, and the Americans with Disabilities Act permits employers to keep the workplace free of alcohol use [89].

Under the Americans with Disabilities Act, a disability is defined as a condition that demonstrates at least one of three elements:

- A physical or mental impairment that substantially limits one or more major life activities
- A record of a substantially limiting impairment
- Being viewed as having a disabling impairment [4]

"Major life activities" include "caring for oneself, performing manual tasks, walking, seeing, hearing, speaking, breathing, learning, and working" [4]. "Substantially limiting" is defined as "unable to perform a major life activity that the average person in the general population can perform" [4]. Factors that influence this determination are the nature and severity of the impairment, its duration, and its impact over time. It is difficult to empirically establish when an individual's impairment "substantially limits" performance compared with the performance of an "average" person, so the interpretation of this provision is a matter of subjective judgment.

The Prevalence of Disability in People Who Abuse Substances

The prevalence of disability in people with substance use disorders has not been well

characterized [5]. Studies of the co-occurrence of disability and substance abuse give a partial picture of the landscape, and data from large national studies on drug and alcohol use add to that picture. This composite gives a general, if imperfect, overview.

The majority of the epidemiological data available on the prevalence of drug use in persons with disabilities measures the prevalence of co-occurring disabling mental disorders and substance use disorders. A 2002 report prepared by the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration's Division of Population Surveys, Office of Applied Studies, described the co-occurrence of serious mental illness and substance use disorders [29]. In 2002, 33.2 million adults ages 18 and older had either a serious mental illness or a substance use disorder. Of these adults, 4.0 million (12.2%) had both a serious mental illness and a substance use disorder.

The National Association on Alcohol, Drugs and Disability published a report in 1999 that measured prevalence of co-occurring disability for brain and spinal cord injuries as well as mental disorders. This report found that 50% of individuals with traumatic brain injuries, spinal cord injuries, or mental disorders had problems with substance use [20].

The National Epidemiological Survey on Alcohol and Related Conditions is a nationally representative face-to-face survey of the civilian, noninstitutionalized population in the United States, aged 18 years and older. Hasin and colleagues [40] examined disability in association with substance use disorder diagnoses in the National Epidemiological Survey on Alcohol and Related Conditions as measured by the Short Form 12 Version 2 [30]. The Short Form 12 Version 2 mental impairment scales included the mental component summary, mental health, social functioning (limitations caused by emotional problems), and role emotional functioning (the impact on social roles). Each Short Form 12 Version 2 score has an expected value of 50 in the general population and a standardized range of 0–100 points. Scores lower than 50 indicated a higher-than-expected rate of disability.

Mean Short Form 12 Version 2 scores for those with current alcohol abuse ranged from 48.8 to 49.8, or just below normal. Scores for those with alcohol dependence were lower, from 47.3 to 48.2. After adjusting for sociodemographic characteristics and other disorders, alcohol abuse was associated with low social functioning and role emotional functioning scores, whereas alcohol dependence was highly and significantly associated with low mental component summary, mental health, social functioning, and role emotional functioning. Overall, this is interpreted to show that, as compared with those who do not abuse alcohol, people who do experience greater limitations in emotional functioning as well as impaired social role abilities caused by these limitations. Disability increased steadily and significantly with the severity of alcohol dependence.

Compton and colleagues performed the same type of analysis for people with histories of drug abuse and dependence. The authors found that the mental component summary and the mental health, social functioning, and role emotional functioning scores on the Short Form 12 Version 2 for those with drug use disorders were approximately two points below average. Scores for those with drug dependence were as much as ten points below average. After adjusting for sociodemographic characteristics and other disorders, drug abuse (like alcohol abuse) was associated with lower mental component summary, mental health, social functioning, and role emotional functioning scores. Drug dependence led to much lower scores across the board, leading to the conclusion that drug dependence was clearly more disabling than abuse [21].

The National Comorbidity Survey: Replication was a nationally representative sample of respondents aged 18 years and older that measured the prevalence and correlates of mental disorders. It was funded by and implemented through the National Institute of Mental Health. According to the National Comorbidity Survey: Replication, 51.4% of people with a lifetime substance use disorder showed evidence of a mental disorder, and 50.9% of those with a mental disorder had a history of at least one substance use disorder [15].

For details on the prevalence of substance use disorders in people with disabilities, please see the section titled "Substance Abuse and People with Disabilities."

Discrimination Protections for Persons with Disabilities

Rehabilitation Act of 1973, Title V, Section 504

Historically, the legal protections for people with disabilities that are now in place began in 1973 in Title V of the Rehabilitation Act of 1973, Section 504 [68]. Section 504 titled "Nondiscrimination Under Federal Grants and Programs," protected both persons with addictive disease and those in recovery from such diseases under federal law. Specifically, the act stipulated that any organization receiving federal funds could not discriminate against people who were currently addicted to drugs or alcohol or in recovery from either condition [68].

Americans with Disabilities Act

The Rehabilitation Act of 1973 was a significant milestone that recognized the need to protect the rights of those with disabilities. It was, however, not comprehensive, so lobbying continued on the part of people with disabilities and their advocates. Their efforts bore fruit, and the Americans with Disabilities Act was enacted on July 26, 1990 [4]. The primary objective of the Americans with Disabilities Act is to extend maximum opportunity for full community participation to persons with disabilities in both public and private sectors of the United States. The Americans with Disabilities Act prohibits employment discrimination on the basis of disability in both private and public sectors, extending the protections of the Rehabilitation Act of 1973 beyond federally funded and conducted activities. In particular, the Americans with Disabilities Act applies to private employment, all publicly funded services, and public accommodations and services managed by private organizations.

When the Americans with Disabilities Act was being developed, however, there were efforts in Congress to exclude certain groups, including those with drug and alcohol addictions [28]. When the Americans with Disabilities Act was passed, protections for people who use illicit drugs that were present in Section 504 of the Rehabilitation Act of 1973 were dropped. Anyone who is currently engaged in the illegal use of drugs is not considered a qualified person with a disability under the Americans with Disabilities Act. However, those who have completed or are participating in a supervised rehabilitation program and are no longer using illegal drugs are protected, as are those who are erroneously regarded as engaged in illegal drug use [4]. The implication is that an individual who is addicted to heroin, for example, must be abstinent from the use of heroin to qualify for the protections afforded by the Americans with Disabilities Act. However, by definition addiction involves uncontrollable use of legal or illegal substances or both.

Many individuals who are impaired because of their addiction are unable to perform one or more major life activities and are viewed as disabled. It follows logically that at least one of the three criteria for disability as defined by the Americans with Disabilities Act has been met. However, the exclusion of people actively using illegal substances is likely meant to send a punitive message to those who are breaking the law. The sequelae of addiction (whether to caffeine, alcohol, nicotine, prescribed medications, or illegal substances) are similar, and distinctions made by drug class, with respect to the three criteria associated with disability, are hard to defend. The statute is particularly important for many people with substance use disorders who have co-occurring mental disorders. This population often faces difficulties in finding and holding jobs, in part because of the stigma attached to both addiction and mental disorders [37]. However, disabling psychiatric illnesses that meet any of the three criteria for

disabilities are considered qualified disabilities under the ADA.

In addition to the Americans with Disabilities Act's exclusion of those currently using illegal drugs, the act has several barriers that are of concern to the substance use disorders services and treatment community and to those with these disorders who wish to claim protection under the Act. As noted above, people with substance use disorders who are not currently using illicit drugs can claim protection from employment discrimination under the Americans with Disabilities Act. However, the meaning of "current" use is vague. Some court decisions have been equivocal about when recovery begins, requiring a period of active stability of, for example, six months, to be considered "in recovery," and therefore eligible for the Americans with Disabilities Act protections [95]. Employees who have alcoholism or who use illegal drugs must meet the same standards other employees are held to, even if their unsatisfactory behavior is attributable to their use of substances [4]. Lastly, employees must not pose a "direct threat" to others because of their substance use—a term that, like "current" use, has been debated frequently in litigation [95].

Protections against discrimination for people who actively use drugs and alcohol are influenced by current law and can change depending on case law rulings. Several recent decisions narrowed the focus of the Americans with Disabilities Act's protections and increased the barriers that individuals who are disabled or impaired must overcome to obtain equal opportunities in the United States. The emerging body of restrictive case law necessitated passage of the Americans with Disabilities Act Amendments Act of 2008 to reaffirm Congress's original intent.

Key Case Law for the Americans with Disabilities Act, 1990

Interpretation of the Americans with Disabilities Act is established through trial law as individual cases are considered; therefore, the rights accorded to people that are in recovery and those who are actively using are often determined in an administrative law hearing or through precedents established by court cases. The Americans with Disabilities Act offers technical definitions of disability and delineates the applications of and exceptions to these definitions. Nevertheless, the U.S. judicial system has the authority to interpret the act and determine the extent to which a particular impairment qualifies as a disability.

Raytheon v. *Hernandez*

Raytheon v. *Hernandez* [67] was a case that explored the extent to which employers can classify substance use disorder-related behaviors as willful misconduct rather than behaviors related to the substance use disorder. This case eventually appeared before the Supreme Court, and the decisions from *Raytheon* v. *Hernandez* may have an impact on how the Americans with Disabilities Act protections are applied to people in recovery from substance use disorders. Joel Hernandez applied for a position at Raytheon in 1994. He had previously worked for Raytheon (at that time Hughes Missile Systems) from 1966 to 1991. During his employment, he had experienced on-the-job challenges related to substance use disorder, but treatment efforts supported by his company were unsuccessful. One day Mr. Hernandez came to work with alcohol and cocaine in his system, which his employers confirmed through a drug test. Mr. Hernandez was offered the option to resign or face termination. He resigned.

After two years in recovery from his substance use disorder, Mr. Hernandez applied for a position doing the same work he had been doing before his resignation, submitting letters from his church and his Alcoholics Anonymous sponsor with his application. The company had a no rehire policy for ex-employees who had been terminated because of "misconduct," and Mr. Hernandez did not get the job. Mr. Hernandez surmised that he was being discriminated against because of his substance use disorder history. The Equal Employment

Opportunity Commission supported his claim of discrimination and granted him permission to sue Raytheon for violating his rights under the Americans with Disabilities Act [27].

The case was heard by the U.S. District Court in Arizona, which ruled in favor of Raytheon. Mr. Hernandez then appealed to the Ninth District Court of Appeals, which reversed the lower court's ruling [27]. Raytheon appealed the Ninth Circuit Court's decision, and the case was eventually argued before the Supreme Court of the United States on October 8, 2003, and decided on December 2, 2003 [67]. The Supreme Court upheld the ruling of the Arizona District Court in favor of Raytheon, stating that Mr. Hernandez was not passed over because of his substance use disorder history and, therefore, was not the object of disparate treatment because of his disability, as he claimed in his arguments.

The opinion of the Supreme Court, as delivered by Justice Thomas, was that "Petitioner's [Raytheon's] proffer of its neutral no-rehire policy plainly satisfied its obligation under McDonnell Douglas [a previous decision] to provide a legitimate, nondiscriminatory reason for refusing to rehire respondent" [67]. The opinion of the Court found that there was insufficient evidence to prove that Raytheon did not rehire Mr. Hernandez because of his substance use disorder history. In effect, the ruling allowed Raytheon to characterize Mr. Hernandez's behavior on the day he came to work under the influence of alcohol and cocaine as willful misconduct, rather than as behavior consistent with a treatable substance use disorder [17, 27, 28, 93].

The "Sutton Trilogy"

The "Sutton trilogy" refers to three rulings issued by the U.S. Supreme Court in Spring 1999. These cases addressed how the possibility of devices, medication, or even unconscious neuropsychological phenomena that mitigate a disabling condition can affect a person's disability status [52]. The first case, *Sutton* v. *United Air Lines, Inc.*, found that twin sisters with severe myopia that could be corrected to 20/20 vision with glasses were not protected under the Americans with Disabilities Act because the glasses mitigated the disability by improving their vision [80]. The second case, *Albertson's Inc.* v. *Kirkingburg*, found that Mr. Kirkingburg, a truck driver who was blind in one eye, was not protected under the Americans with Disabilities Act because he had developed the ability to compensate automatically for his lack of depth perception [3]. His compensation mitigated his disability. The third case, *Murphy* v. *the United States Postal Service, Inc.*, found that Mr. Murphy, a mechanic also required to drive a truck who was dismissed because his blood pressure did not meet Department of Transportation's health guidelines, was not protected by the Americans with Disabilities Act because, when medicated, his high blood pressure was near normal; also, he could still work as a mechanic, so he was not considered disabled [56].

In these three examples, mitigating factors included such things as medications, corrective lenses, and even neuropsychological phenomenon, all of which reduced the severity of the impairment. Recovery may be viewed as "mitigation" for people with substance use disorders, but a history of drug addiction still carries a significant burden of social stigma. People with substance use disorder histories may still require the Americans with Disabilities Act's protections, even though their technical "impairment" has been mitigated [28].

Americans with Disabilities Act Amendments Act of 2008

The Americans with Disabilities Act Amendments Act of 2008, which was signed into law on September 25, 2008, and became effective on January 1, 2009, amended the Americans with Disabilities Act of 1990 to redefine the term "disability." This change marks a broader interpretation of, and coverage for, individuals with a disability. The Americans with Disabilities Act Amendments Act of 2008

overturned the mitigating-measures holding of *Sutton* v. *United Air Lines* (1999), which had been applied to deprive many individuals with disabilities of the Americans with Disabilities Act's protections as described previously in this chapter [22]. A key purpose of the Act was to reinstate the "broad scope of protection" Congress intended to be available [4]. The new law clarifies that the effects of "mitigating measures," such as hearing aids and prosthetics, could not be used in weighing how a person's disability affects life activities [23]. The 2008 legislation also overturned the restrictive interpretation of "substantially limits," often narrowly interpreted by court rulings [22]. These changes now create an easier path for establishing that a person has a disability within Americans with Disabilities Act guidelines, and for a disabled person to seek protection under this Act. Passage of the legislation also extends protections to people with disabilities not immediately evident in the workplace, such as those of the immune, digestive, and neurological systems. The clarification that a major life activity includes the "operation of a major bodily function" may benefit some persons who are not currently using but do have some of the long-term disabling effects of drug or alcohol use described in the section of this chapter on "The Role of Addictive Disorders in Developing Disability." None of the changes, however, specifically referred to illegal use of drugs or alcoholism.

History of Entitlements for People with Disabilities and the Place of People Who Abuse Substances

In the past, Supplemental Security Income and Social Security Disability Insurance programs provided monetary assistance as well as medical benefits to individuals with substance use disorders because substance abuse was considered a qualifying impairment. The level of oversight and scrutiny of Supplemental Security Income/Social Security Disability Insurance recipients with substance use disorders was much higher compared with that of other beneficiaries. In particular, a referral monitoring agency was enlisted by the Social Security Administration to ensure that Supplemental Security Income recipients with substance use disorders were compliant with treatment. People with substance use disorders did not receive their own entitlement checks. Instead, the checks were sent monthly to a representative payee, who disbursed the funds. The benefits were not to exceed three years.

There were problems associated with this method of organizing benefits for those with substance use disorders. At one point, the number of people with substance use disorders receiving disability benefits increased by more than 500% in a four-year period, and the Social Security Administration found it difficult to establish whether recipients were in treatment. One study found the rates of rehabilitation and returns to work were very low. There was also evidence that representative payees were allowing income to be used to purchase drugs [38].

Under the Clinton Administration, enactment of the Contract with America Advancement Act of 1996 (PL 104–121) made important changes that affected people with substance use disorders [38]. In particular, the Social Security Administration terminated payments for Social Security Disability Insurance and Supplemental Security Income on the basis of addiction alone. When someone has a co-occurring disabling condition and an active substance use disorder, the Social Security Administration must currently determine whether the disability being claimed is the result of a medical condition or the result of the effects of active drug use. The disability must be present even if consumption of alcohol and drugs has ceased. This determination is made by theoretically removing the limitations resulting from the substance use disorder and then deciding whether the remaining limitations from other impairments would still be disabling. Only after such an analysis can a determination of disability be made [71]. This situation points to the complexities in classifying

addiction as a disability in the current legislative climate.

Before PL 104–121, people with substance use disorders who received Supplemental Security Income and Social Security Disability Insurance for at least two years were eligible to receive Medicaid (for Supplemental Security Income) and Medicare (for Social Security Disability Insurance) [71]. A significant amount of federal funds for substance use disorder treatment flowed to the states through the two programs. With the new legislation, determination of benefits is now made by the states, and states vary to a considerable degree in how they fund substance abuse treatment [6]. Some states fully cover a course of treatment, whereas others only partially reimburse substance abuse treatment.

The clinical and social effects of the decision to eliminate Supplemental Security Income and Social Security Disability Insurance benefits for substance use disorders in 1996 are substantial for people with substance use disorders who are now ineligible for this resource. Although the problems inherent in the previous legislation were removed by eliminating the entitlement, other concerns have arisen that have an impact on public health and the individual costs of addiction to society. First, participation in substance abuse treatment has been reduced because the incentive to seek treatment has been removed. One primary barrier to treatment for people with substance use disorders is lack of financial resources to pay for services [70], and loss of Social Security Disability Insurance and Supplemental Security Income results in loss of Medicaid and Medicare coverage that would have paid for substance abuse treatment [38, 94]. Finally, the substantial prevalence of people with substance use disorders and co-occurring mental illnesses [20, 36, 38] creates an empirical and scientific challenge for the Social Security Administration. It is difficult to make materiality determinations if the agency cannot separate the functional limitations that each condition imposes.

There is no evidence in the scientific literature that indicates whether and how the limitations from substance use disorders can be completely separated from the limitations of a mental condition when both are present. This paradox underscores a lack of reliability and validity in the disability determination process when people with co-occurring disorders apply for disability benefits; many cases will remain undetermined or delayed in the decision-making process. In the meantime, a person who is truly disabled may not be able to gain access to the resources that he or she needs to make a recovery that would both improve quality of life and reduce costs to society.

Availability of Treatment and Medical Coverage

The definitions of disability have several implications for the treatment and medical coverage of people with substance use disorders. These implications have been described in the philosophical, legal, policy, legislative, and advocacy literature [12, 45, 65, 71, 93, 95]. The nature of addiction leaves a person with a substance use disorder at increased risk for multiple other medical conditions, chronic diseases, and disabling impairments [12]. Should society be obliged to pay for medical services for people with substance use disorders who have knowingly initiated an activity that was not sanctioned by society, was dangerous, and was in some instances illegal? This is a point of philosophical debate [45]. Given that society does not have unlimited resources for everyone in need of health care, is society required to pay for medical problems that result from a behavior the individual, theoretically, voluntarily undertook while fully aware of the potential consequences beforehand?

Those who object to caring for people with substance use disorders usually advocate a moral argument. Those who do not object to caring for people with substance use disorders may argue that it is unjust as well as naïve to assume that society has the capacity to determine the extent to which any behavior is voluntary in a given context. There is also empirical evidence from

the bio-behavioral underpinnings of addiction that it is a brain disease [6, 31, 51, 91, 92]. There is, therefore, a disparity between the language and underlying assumptions of the scientific research, which generally describe addiction as a chronic and relapsing treatable condition, and federal law, which deprives some people with substance use disorders of the resources and rights granted to those with non-substance use disorder conditions.

For example, the Americans with Disabilities Act protects qualified individuals with disabilities from discrimination in the workplace and addresses benefits with respect to employer-sponsored health plans under Title I of the act [4]. Title II of the Act provides protections from discrimination by public entities such as federal, state, and local governments through a contractual agreement [4]. Medicaid managed care, which is a publicly purchased product, falls under Title I of the Americans with Disabilities Act [71].

In applying the Americans with Disabilities Act to health insurance, including managed care, only certain practices can be challenged. Courts tend to distinguish between matters related to benefit design (e.g., what to cover, how much to cover, and other issues that go to the basic design of the benefits extended to employees) and cases that relate to the individual allocation of benefits. Benefit design decisions determine the structure of the benefit plan for all members and affect every member of the group regardless of individual health needs. However, other issues arise when the terms of the benefit plan are applied to individual cases [71].

Currently, Medicaid managed care is intended to benefit individuals and families with low incomes and few resources. It is jointly funded by the states and the federal government, and managed by the states. At this time, most states do not require health insurance policies to provide the same level of coverage for substance abuse treatment as is offered for medical or surgical treatment, and in some states substance abuse services are not even covered at the level of mental health treatment [57]. Although 44 States mandate parity between mental health and surgical or medical conditions, only 18 of these require parity for substance abuse or alcoholism [42]. Benefit design, or the amount of coverage associated with managed care models, has contributed to or reinforced discriminatory and disparate health care coverage for people with substance use disorders.

The Impact of Past Policy on Treatment

Understanding the sources of funding for treating substance use disorders is relevant to discussions about current policy and practice as they affect coverage for service costs. A recent analysis of national cost estimates for substance abuse treatment [57] found that 77% of substance abuse treatment spending nationwide in 2003 was funded primarily through public programs, including states, local governments, Medicaid, Medicare, and other federal funding. Private insurance represented only 10% of these treatment expenditures, although it covered 37% of all other health care expenditures [36]. The authors of this analysis speculate that the difference in spending by private insurance for substance use disorder treatment versus all health care may be related to fear of the consequences of disclosing "current" drug use in the work setting. The fact that there are no protections for discrimination against people who currently use drugs under the Americans with Disabilities Act or through other means may have discouraged employees from seeking treatment through private insurance [36]. Another interpretation is simply that employer-funded treatment does not usually support the level of care offered by other sources, so expenditures are less.

The disparate insurance coverage for substance use disorders, along with more stringent controls and monitoring for substance abuse treatment than for general health care, may also account for the lower percentage of substance abuse treatment spending covered by private insurance [36]. Either of these hypotheses is consistent with the systematic marginalization of

people with substance use disorders, although their health care needs are on a par with those suffering from any other medical condition.

The Impact of Legislation Requiring Mental Health and Addiction Parity

Until recently, Congressional actions to address the lack of insurance parity for health care to address substance use disorders were unsuccessful. In October 3, 2008, however, the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (usually referred to as the Parity Act) was signed into law. Ultimately, this Act will end discriminatory coverage in the vast majority of health plans in America [34].

The Parity Act requires covered health plans to provide the same financial terms, conditions, and requirements for mental health and addictions as they provide for medical and surgical conditions. Parity will be implemented by states, Medicaid agencies and Medicaid health plans, commercial health plans, health maintenance organizations, and managed behavioral health organizations, taking effect for most plans on January 1, 2010. Those *not* required to comply with its provisions include Medicare, employers with fewer than 50 employees, and plans that can show that because of the new requirements, their total premium costs increase more than 2% in the first year or 1% in a subsequent year [53]. The plan also will not result in greater access and coverage in states with Medicaid programs that do not cover substance abuse disorders.

Following is a brief summary of the Act:

- Mental health and addiction treatment cost-sharing, deductibles, co-pays and other forms of coinsurance as well as annual limits and lifetime limits must be equal to those covering medical and surgical conditions.
- Limitations on the scope of treatment and treatment frequency and duration cannot be more restrictive than those limiting medical conditions and care.
- Where allowed for other conditions, out-of-network benefits for mental health and addictions treatment must be provided and must be equal to those provided for medical and surgical benefits.
- Stronger state parity laws are not preempted by the Act.
- Plans can determine coverage on a case-by-case basis, but they must provide members, consumers, and providers with their criteria for determining medical necessity and with reasons for benefits/coverage or claims denial.

As a result of this legislation, people with substance use disorders who qualify for protection under the Americans with Disabilities Act and who are insured by a qualifying health plan will have coverage limitations on par with their medical and surgical coverage. The parity law will improve on the state-level parity and mandates of 32 states that currently offer no substance abuse parity and will enhance coverage in the 18 states that do provide some form of substance abuse parity.

The inclusion of substance abuse in this version of parity comes as no surprise. There is little argument with the overwhelming evidence that substance abuse and addictive conditions are serious medical conditions that take a great toll on the lives of individuals, their families, and their communities. Numerous studies have demonstrated the neurological, physiological, and genetic dimensions of addiction. The notion that addictions cannot be treated successfully has been disproven by outcome data, and scientifically valid evidence exists to support a wide range of best practices in treatment. Lawmakers who supported parity in 2008 understood and affirmed these facts.

The Role of Addictive Disorders in Developing Disability

Most drugs of abuse can cause adverse health conditions, but the conditions rarely rise to the level of a disability as defined by the

Americans with Disabilities Act or the Social Security Administration. If a person has discontinued drug use, the source of a disabling condition is immaterial to the protections provided by the Americans with Disabilities Act and eligibility for benefits from the Social Security Administration. Disabling conditions that are protected under the Americans with Disabilities Act can include infectious diseases and psychological illnesses as well as substantial physical impairment. The long-term physical effects of different substances vary widely; disabilities that arise from drug use include human immunodeficiency virus, difficulties with memory or cognition, clinical depression and drug-induced psychosis, brain damage from injuries sustained while under the influence of a drug, and musculoskeletal impairments arising from spinal chord injuries. People who abuse drugs are most likely to become disabled through impaired function while under the influence of the drug (e.g., falls and injuries from accidents or injuries from driving while intoxicated).

This section explains the long-term effects of the different classes of drugs of abuse, with details about neurological, physical, sensory, and functional impairment from each class. It examines the most common and debilitating effects of alcohol, illegal stimulants (e.g., cocaine, methamphetamine and methylenedioxymethamphetamine; prescription medications that are diverted to use as drugs of abuse, and substances that are used as drugs of abuse [e.g., androgenic anabolic steroids and solvent inhalants]). The risks to children born to mothers who abuse drugs and the complicated relationship between current disability and drug abuse and dependence are also discussed.

Table 1 provides a summary of many of the common medical consequences of alcohol and abuse of certain illegal substances (opioids and cocaine), as well as medical consequences that can result from injecting drugs. These consequences are classified according to the organ systems affected.

Alcohol

There is extensive literature on the many disabling conditions that can arise from alcohol abuse and dependence. Details of a few of the most common physical and neurological complications are provided below. Long-term alcohol abuse can harm most of the body's organ systems, including the liver, the immune system, the cardiovascular system, and the skeletal system [1, 39].

Injury

The most common disabling condition related to alcohol abuse is spinal cord injury from car crashes, falls, and other accidents [83]. Up to 50% of patients with spinal cord injuries were intoxicated at the time of injury, and those who were intoxicated at the time of injury are likely to have a history of alcohol abuse [41, 83]. Alcohol use is a major risk factor for both fatal and nonfatal injuries; the prevalence of nonfatal injuries is higher among people who abuse substances than in the general population [11, 41, 55].

In a literature review that examined the role of substance abuse in the cause of injury for patients using rehabilitation services, Hubbard and colleagues found that up to 79% of rehabilitation patients had alcohol-related traumatic injuries and that 35% of automobile injuries, 55% of motor vehicle deaths, 40% of drownings, and 30% of noncommercial airplane crashes were related to alcohol. Up to 72% of patients with head injuries from car crashes had positive blood alcohol levels. There was a 25–68% prevalence of preinjury alcohol addiction in head injury patients. Possible gender differences in these rates are worth noting; one study showed that, although 62% of males had positive blood alcohol levels at the time of head injury, only 27% of females had positive blood alcohol levels. Drinking or intoxication appeared to be involved in up to 79% of spinal cord injuries [41].

Table 1 Common medical consequences of alcohol and illegal substance abuse

	Drug of Abuse			
Organ system	Alcohol	Opioids	Cocaine	Injection effects
Cardiovascular	Cardiomyopathy Atrial fibrillation Hypertension Dysrhythmia Coronary artery spasm Myocardial ischemia Coronary artery disease Sudden death	N/A	Angina Aortic dissection Atrial Ventricular fibrillation Cardiomyopathy Supraventricular tachycardia Hypertension Moyamoya vasculopathy Left ventricular hypertrophy Ventricular dysrhythmias Myocarditis Sudden death	Endocarditis Thrombophlebitis
Endocrine	Hypoglycemia/ hyperglycemia Diabetes Ketoacidosis Hypertriglyceridemia Hyperuricemia and gout Gynecomastia Reversible hyperparathyroidism Osteopenia Infertility Amenorrhea	Osteopenia Gonadotropin alteration Decreased sperm motility Menstrual irregularities Amenorrhea	Diabetic ketoacidosis Amenorrhea	N/A
Gastrointestinal	Gastritis Esophagitis Pancreatitis Diarrhea Malabsorption Parotid enlargement Malignancy Colitis Barrett esophagus Gastroesophageal reflux Mallory-Weiss syndrome Gastrointestinal bleeding	Constipation Ileus Nausea	Ischemic bowel Colitis Nausea	N/A

Table 1 (continued)

	Drug of Abuse			
Organ system	Alcohol	Opioids	Cocaine	Injection effects
Hematologic	Macrocytic Aanemia Pancytopenia Macrocytosis (from #1) Leukopenia Thrombocytopenia Coagulaopathy (from liver disease)	N/A	N/A	Hepatitis C-related cryoglobulinemia Hepatitis C-related purpura
Hepatic	Steatosis (“fatty liver”) Acute hepatitis Chronic infectious or toxic hepatitis Alcoholic hepatitis Cirrhosis Portal hypertentionhypertension Spontaneous bacterial peritonitis	Granulamatosis	Ischemic necrosis Hepatitis	Acute and chronic infectious Hepatitis B, C, or Delta
Infectious Disease	Hepatitis C Pneumonia Tuberculosis Human immunodeficiency virus Sexually transmitted disease Spontaneous bacterial peritonitis Brain abcessabscess Meningitis	Aspiration pneumonia Also: See injection	See injection	Hepatitis B, C, or delta Human immunodeficiency virus Sexually transmitted disease Endocarditis Cellulitis Pneumonia Septic thrombophlebitis Septic arthritis Osteopyelitis Epidural and brain abscess Mycotic aneurysm Soft tissue abscesses and infections Mediastinitis Malaria Tetanus

Table 1 (continued)

Organ system	Drug of Abuse			Injection effects
	Alcohol	Opioids	Cocaine	
Musculoskeletal	Rhabdomyolysis Compartment syndromes Gout Fracture Osteopeniea Osteonecrosis	Osteopenia	Rhabdomyolysis	N/A
Neurologic	Nephropathy (Peripheral and autonomic) Seizure Hepatic encephalopathy DKorsakoff's dementia Wernicke's syndrome Cerebellar dysfunction Marchiafava-Bignami syndrome Central pontine myelinolysis Myopathy Amblyopia Stroke Withdrawal delirium Hallucinations Toxic leukoencephalopathy Subdural hematoma Intracranial hemorrhage	Seizures (overdose and hypoxia) Compression neuropathy	Stroke Seizure Status epilepticus Headache Delirium Depression Hypersomnia Auditory hallucinations Cognitive deficits	N/A

Table 1 (continued)

Organ system	Drug of Abuse			
	Alcohol	Opioids	Cocaine	Injection effects
Pulmonary	Aspiration Sleep apnea Respiratory depression Pneumonitis (chemical or infectious)	Respiratory depression/failure Emphysema Bronchospasm Pulmonary edema	Respiratory failure Nasal septum perforation Gingival ulceration Perennial rhinitis Sinusitis Heloptysis Upper airway obstruction Pulmonary hemorrhage Pulmonary hypertension Emphysema Interstitial fibrosis Hypersensitivity pneumonia Septic pulmonary embolism Interstitial pneumonitis Alveolar hemorrhage Barotraumas Thermal airway injury Hilar lymphadenopathies	
Renal	Hepatorenal syndrome Rhabdomyolysis Acute renal failure Volume depletion Prerenal failure Acidosis Hypokalemia Hypophosphatemia	Rhabdomyolysis Acute renal failure Factitious hematuria	Rhabdomyolysis Acute renal failure Vasculitis Necrotiaing angiitis Accelerated hypertension Nephrosclerosis Ischemia	Focal glomerular sclerosis (human immunodeficiency virus, heroin) Glomerulonephritis (hepatitis, endocarditis) Chronic renal failure Amyloidosis Nephrotic syndrome (hepatitis C)

This table is based on the sources [7, 35, 50, 58, 59, 66, 69]

Several studies have identified the high risk of injury in people with alcohol use disorders. In a case-control study at an emergency department in Mexico City, the prevalence of substance abuse or dependence in the last 12 months was 12.3% for alcohol compared with a prevalence of 1.8 % in a representative sample of residents of Mexico City of the same age group [11]. A retrospective cohort study of medical claims data on patients with alcohol- or drug-related primary or secondary diagnosis by Miller and colleagues estimated the excess risk of medically treated and hospitalized nonoccupational injury for people younger than age 65 with medically identified substance abuse. They found that people who were medically identified as abusing substances had a higher risk of injury in a three-year period. People who abused alcohol and drugs were almost four times as likely to be hospitalized for an injury during the three-year period as controls, and the risk of injury was substantially higher for female than male users of substances [55].

Organ Systems

Liver

Liver disease is a common debilitating result of alcohol abuse. Long-term, heavy alcohol use is the leading cause of illness and death from liver disease in the United States, with more than 2 million suffering from alcoholic liver disease ranging in severity from fatty liver to end-stage cirrhosis. Women develop alcoholic hepatitis and alcoholic cirrhosis after fewer years of drinking and smaller daily amounts of alcohol than men do [1, 55].

There are three forms of alcoholic liver disease: fatty liver, which is usually reversible with abstinence; alcoholic hepatitis, characterized by persistent liver inflammation; and cirrhosis, characterized by progressive scarring of liver tissue [77]. More than one type of liver disease can be present at the same time. Individuals with both cirrhosis and alcoholic hepatitis have a death rate of more than 60% over a four-year period, with most deaths occurring within the first 12 months of diagnosis [14, 55].

Alcohol initially causes liver injury by generating harmful metabolites, and continuing alcohol use exacerbates the initial injury. Chronic alcohol use leads to inflammation and weakens the ability of the liver to repair itself. It also leads to increased firbrogenesis, a major source of eventual cirrhosis [77].

Neurological and Social Functioning

Neurological complications from alcohol also lead to substantial long-term disabling conditions. Lasting cognitive impairment in people with alcoholism can be direct, through brain damage from long-term alcohol exposure, or indirect, as a result of head trauma, central nervous system infection, hepatic failure, or nutritional deficiency. Direct neurologic consequences of long-term alcohol use include Wernicke-Korsakoff syndrome, Marchiafava-Bignami syndrome, and central pontine myelinosis. Wernicke's syndrome, in which decreased attentiveness, alertness, and memory are usually accompanied by disordered eye movements and ataxia, is often followed by Korsakoff's dementia, a lasting amnestic disorder. Marchiafava-Bignami syndrome and central pontine myelinosis are related to damage to the myelin sheath of neurons in the corpus callosum and pons, respectively [14, 73]. Studies have shown that alcohol also directly damages the cerebrum sufficiently to cause dementia [14].

Alcohol dependence and abuse have profound effects on social and neuropsychiatric functioning. In a report on the results from the National Epidemiological Survey on Alcohol and Related Conditions, Hasin and colleagues measured the prevalence, correlates, disability, and comorbidities associated with alcohol abuse and dependence in the United States. Adjusting for sociodemographic characteristics and other disorders, alcohol abuse was associated with lower social and role function. Alcohol dependence was significantly associated with lower mental health and social and role function. The

level of disability was closely correlated with severity of alcohol dependence [39].

Immune System

Excessive alcohol consumption can lead to increased rates of illness and death from infectious diseases. People who abuse alcohol suffer from increased susceptibility to bacterial pneumonia, pulmonary tuberculosis, and hepatitis C virus. Individuals with alcoholic liver disease are at high risk of contracting hepatitis C virus. Individuals with alcoholic liver disease who are hepatitis C virus-positive have more severe liver disease and are younger than hepatitis C virus-negative individuals. This may reflect impaired immune function caused by alcohol abuse. Compared with people who do not abuse alcohol, those who do may also be at increased risk for infection with human immunodeficiency virus from risky sex practices while intoxicated. There is also research currently under way to investigate the possibility that alcohol consumption itself may increase susceptibility to human immunodeficiency virus infection or hasten the progression from human immunodeficiency virus infection to full-blown acquired immunodeficiency syndrome. Some alcohol-related organ damage may result in an autoimmune reaction [1, 73].

Cardiovascular System

Chronic heavy drinking is a leading cause of cardiovascular illnesses such as cardiomyopathy, coronary heart disease, high blood pressure, arrhythmias, and stroke. In alcoholic cardiomyopathy, long-term heavy drinking can enlarge the heart and impair its ability to contract. Symptoms of cardiomyopathy include shortness of breath and insufficient blood flow to the rest of the body. Women may have a greater risk than men of developing alcoholic cardiomyopathy. The condition may be at least partially reversible with abstinence [14].

An association between heavy alcohol consumption and increased blood pressure has been observed in more than 60 studies in diverse cultures and populations [1]. Heavy drinking can disrupt the heart rhythm both acutely (during an episode of drinking) and chronically (during long-term use). Intoxication can cause certain types of arrhythmia in both those with alcoholism and otherwise healthy individuals. The development of arrhythmias from binge drinking—a condition seen most frequently around the holidays—is known as "holiday heart syndrome." Sudden death attributable to arrhythmia is one of the causes of mortality in people with alcoholism with or without preexisting heart disease. Such deaths often occur during periods of abstinence, suggesting that arrhythmias are more likely to develop during alcohol withdrawal [1, 14, 73].

Skeletal System

Epidemiologic studies have found a significant association between alcohol consumption and bone fracture risk. In addition to the increased risk of accidental injury from impaired gait and balance, people with alcoholism may also suffer from a generalized decrease in bone mass. Heavy drinking may lead to osteoporosis, characterized by severe back pain, spinal deformity, and increased risk of wrist and hip fractures [1, 14, 73].

Special Populations

Older Adults

Older adults present a particular challenge. Alcohol abuse affects the elderly differently than it affects the young [32]. In people ages 55 and older, long-term and continuing alcohol abuse can have a wide range of physical, psychological, and social effects [25]. Although it causes fewer traumatic fatalities in this population, it is more likely to exacerbate

co-existing illnesses through alcohol–drug interactions, dietary or medication noncompliance, cognitive impairment, aggravated psychiatric illness, or co-morbidities [32]. As is true with younger adults, older adults consuming high amounts of alcohol have increased risks of coronary heart disease, hypertension, gastrointestinal bleed, and hemorrhagic and ischemic stroke, as well as increased rates of alcohol-related liver disease and increased risk of a range of cancers [25]. However, in older adults, these risks are heightened by the aging process and increase morbidity and mortality among older people in medical settings [46].

Alcohol consumption is one of the three main risk factors for falls. It can also contribute to the onset of dementia and other age-related cognitive deficits, Parkinson's disease, and a range of psychological problems, including depression and anxiety [25, 85]. Alcohol is a major contraindication for many medications prescribed for older people. Adverse interactions between alcohol and medication are common, and higher alcohol consumption in older age is associated with a range of social problems including self-neglect, poor nutrition, social isolation, and hypothermia [25].

Illegal Drugs of Abuse

Stimulants (e.g., cocaine, amphetamine, and methylenedioxymethamphetamine) and opioids (e.g., heroin) are illegal in the United States. People who use illegal drugs are at risk for injury and disease through a variety of social factors; in addition, long-term use of most of these substances can lead to documented changes in physical and neurological function.

In a study by Adrian and colleagues that compared the risk for morbid conditions of people who abuse legal drugs, illegal drugs, and alcohol in a large sample of patients in a Canadian hospital, the investigators observed that morbidity from illegal drugs affected fewer body systems, involved far fewer medical conditions, and was lower for most diagnoses when compared with alcohol. However, people who used illegal drugs were more likely to exhibit mental disorders as well as a higher likelihood of injury and poisonings than those who used alcohol, especially people who use legal medications, where poisoning was a result of misusing what are generally legal, therapeutic, prescription medications. People who use illegal drugs were much more likely to present with infectious and parasitic diseases than did people who abused other substances, suggesting more impaired immune function [2].

Toomey and colleagues identified the neurological deficits resulting from cocaine and/or amphetamine abuse by evaluating a group of twins. One twin of each pair was a heavy abuser of one or both drugs whose use had ended at least one year before evaluation. All subjects were tested on attention, executive functioning, motor skills, intelligence, and memory. Persons who had abused drugs demonstrated lower attention and motor skills than their nonabusing twins, showing that cognitive deficiencies persist even after one year of abstinence from drug use [86].

Cocaine

The most common long-term effects of cocaine include complications from stroke, depression, induced psychosis, cognitive deficits, and trauma-related injuries. Cocaine abuse can result in severe depression over the long term. Cocaine psychosis includes such symptoms as aggression and disturbing hallucinations, and people who use over the long term may experience permanent psychosis [60, 73].

People who abuse cocaine often exhibit lasting cognitive deficits even after cessation of use [13, 64]. In a study comparing 20 people in recovery who chronically abused with controls matched for age and education, O'Malley and colleagues used a series of standardized neuropsychological assessment procedures to assess cognitive impairment. They found that people who abused cocaine were 35% more likely than the control population to score in the impaired range of the Neuropsychological

Screening Exam. Those who abused cocaine also performed more poorly on tests for abstract thinking and reasoning and verbal memory. Neuropsychological performance was directly related to the severity of cocaine abuse, suggesting that cocaine played a direct role in affecting cognitive functioning [64].

Cognitive deficits from cocaine are often related to perfusion abnormalities or changes of blood flow in the brain [13, 30]. A study by Browndyke and colleagues showed the relationship between cognitive performance and the magnitude of perfusion abnormality. Their findings indicated significant regional perfusion abnormalities among people who abuse cocaine relative to normal controls and substantial deficits in neuropsychological functioning for people who abuse cocaine [13].

Although the incidence of cerebrovascular dysfunction from cocaine use was relatively low until the late 1990s, it began increasing toward the end of the decade. The vasoactive properties of cocaine and its metabolites can predispose people who use it to more severe cerebrovascular events at an earlier age than those who do not use it, with a poorer prognosis. In a study by Nanda and colleagues, the investigators found that people who abused cocaine were more likely to experience subarachnoid hemorrhage at an earlier age and had poorer outcome than did matched controls [51].

Heroin

The medical complications that arise from the use of heroin are related to the effect of the drug itself as well as the routes of administration, and several of the complications are relevant to all people who inject drugs [84]. Some of the most common and debilitating consequences of heroin use are human immunodeficiency virus/acquired immunodeficiency syndrome; hepatitis B, C, and delta; acute renal failure; abscesses and cellulites; and trauma-related injuries [60, 73].

In relation to the many infective complications of heroin use, recent research suggests that opioids significantly influence peripheral immunomodulatory functions. Endogenous opioids act as immune stimulators, but exogenous opioids such as heroin and related compounds tend to suppress various immune functions. Immune suppression, along with poor nutrition, intravenous routes of administration, polydrug use, and poor living conditions, may explain the prevalence of cutaneous and systemic infection often seen in individuals dependent on heroin.

Hyperalgesia is also a problem in many people in recovery from heroin. A recent study by Rosenblum and colleagues showed that chronic severe pain was prevalent among individuals in substance abuse treatment and that a large minority of those using a methadone maintenance program experienced significant chronic pain. The levels of pain measured in the study were high enough to cause functional impairment in the individuals observed [72].

Methamphetamine

Methamphetamine abuse is a fairly recent phenomenon, so studies on its long-term effects are just emerging. Research from the past decade suggests that methamphetamine dependence may cause long-term neural damage in humans, adversely affecting cognitive processes such as memory and attention. The neurotoxic effects of methamphetamine affect neurotransmitter systems, interfering with normal functioning of dopaminergic, serotonergic, noradrenergic, and glutamatergic systems [62, 63]. A review of the literature by Nordahl and colleagues found that neuroanatomical, neurochemical, and imaging data support the conclusion that methamphetamine abuse causes damage to multiple neurotransmitter systems that are distributed throughout the brain, noting that the permanence of the damage has not yet been determined [63]. The literature review also pointed to studies that showed that long-term methamphetamine use is associated with impaired performance on a number of cognitive tasks, including verbal memory and motor function, manipulation of information, abstract reasoning, and task-shifting strategies [63].

The cognitive impairment observed in people who abuse methamphetamine may also be related to abnormalities of frontal lobes of the brain [19]. Chung and colleagues reported that decreased gray-matter densities and glucose metabolism in the frontal region of the brain were correlated with impaired frontal executive functions (cognitive abilities that control and regulate other abilities and behaviors) in people who abuse methamphetamine. Executive functions are necessary for goal-directed behavior and come into play when adapting to change, in planning for the future, and in abstract thinking.

In a study comparing people who abuse methamphetamine with healthy subjects, Chung and colleagues used diffusion tensor imaging to describe the differences in frontal white-matter integrity and assessed differences in frontal executive functions with the Wisconsin Card Sorting Test. They found that frontal white matter was compromised in people who abuse methamphetamine and that these people showed more errors in the Wisconsin Card Sorting Test relative to healthy subjects. They also noted that the neurotoxic effect of methamphetamine on frontal white matter may be less prominent in women than in men, possibly because of estrogen's neuroprotective effect [19].

Methylenedioxymethamphetamine ("Ecstasy")

Methylenedioxymethamphetamine and related compounds have serious acute and chronic toxic effects that resemble those seen with other amphetamines. Neurotoxicity to the serotonergic system in the brain can also cause permanent physical and psychiatric problems, including confusion, depression, and impaired memory [43, 62]. The brains of people who used methylenedioxymethamphetamine over a long term, when examined while free of the drug, have abnormally low levels of serotonin and its metabolites in the cerebrospinal fluid and other significant alterations of neurotransmitter functioning. In these people there is upregulation of serotinin receptors during abstinence, in response to the decrease in serotonin release caused by the action of the drug. Electroencephalographic studies show changes similar to those seen in aging and dementia and a change in response to auditory stimuli. The prolactin and cortisol responses to stimulation of the serotonin system were reduced in the people who used methylenedioxymethamphetamine. These changes persisted for up to a year or more after the last use of the drug [43].

The demonstrated neurotoxic effects of methylenedioxymethamphetamine on the serotonin system may be the cause of a variety of mental and behavioral problems that outlast the actual drug experience by months or years. These problems are quite varied, but they all involve functions in which serotonin is known to play an important role. Some persistent problems include impaired verbal and visual memory (with the degree of impairment being roughly proportional to the intensity of the preceding use of the drug), decision-making, information processing, logical reasoning, and simple problem solving as well as greater impulsivity and lack of self-control, recurrent paranoia, hallucinations, depersonalization, flashbacks, and even psychotic episodes. Finally, people who use methylenedioxymethamphetamine can experience severe depression that is resistant to any treatment other than selective serotonin reuptake inhibitors [43].

Inhalants

Inhaled solvents are the most commonly abused substances classified as inhalants. Long-term abuse of solvents can cause damage to most organ systems, including the central and peripheral nervous systems and hepatic, renal, pulmonary, and cardiovascular systems. Solvent abuse can also affect bone marrow formation and lead to anemia. Cognitive effects include confusion, forgetfulness, and irritability [16]. The psychiatric and neurological sequelae of chronic solvent abuse are serious and potentially irreversible [16].

A study of the psychiatric and neurological effects of solvent inhalation in a group of 22 individuals with histories of chronic solvent abuse (primarily of toluene-based solvents) found that the chronic inhalation of toluene-based adhesives can produce a paranoid psychosis that may persist. The authors also found a high incidence of temporal lobe epilepsy and a decrease in IQ. They pointed to toluene as a major factor in the morbidity associated with people who chronically abuse solvents [16].

To measure the consequences of long-term exposure to inhaled solvents, Yücel and colleagues reviewed neuroimaging and neuropsychological studies, examining chronic toluene misuse in humans. They found that toluene preferentially affects white matter structures and periventricular/subcortical regions in the brain. They hypothesized that the lipid-dependent distribution and pharmacokinetic properties of toluene would likely explain the pattern of abnormalities, as well as the common symptoms and signs of toluene encephalopathy. The commonly observed neuropsychological deficits such as impairments in processing speed, sustained attention, memory retrieval, executive function, and language are also consistent with white matter pathology [96].

Anabolic Steroids

The abuse of androgenic anabolic steroids can cause high blood pressure, heart attacks, and liver cancer. [42]. Long-term use of anabolic steroids may cause a range of adverse cardiovascular effects, some of which may be irreversible, including cardiomyopathy, dyslipidemia and other artherosclerotic effects, hypertension, myocardial ischemia, and arrhythmias [42]. Anabolic steroids are capable of increasing vascular tone, arterial tension, and platelet aggregation and may give rise to atherothrombotic phenomena [74]. Although there are few reports of ischemic stroke related to anabolic steroid abuse, Santamarina and colleagues reported a case of a 26-year-old male amateur athlete who suffered a posterior territory ischemic stroke, whose only significant risk factor was nonmedical use of stanozolol, an anabolic steroid [74].

Neuroendocrine effects from anabolic steroid abuse can cause infertility and major depressive disorders [42]. In a study of the long-term side effects of high doses of self-administered anabolic steroids, Bonetti and colleagues observed 20 male bodybuilders who voluntarily self-administered anabolic steroids. The subjects were tested every six months over two years. Physical examination, hematological, metabolic and endocrine variables, semen analysis, hepatic and prostate ultrasound, and echocardiographic evaluations were performed. The most important long-term adverse effects observed were lower fertility and sperm counts and impaired lipid profiles associated with increased cardiovascular risk [10].

More rarely, the long-term use of orally active anabolic steroids can have adverse hepatic effects, ultimately resulting in hepatocellular adenomas or carcinomas, although these hepatic effects are often reversible. In vitro studies have shown that concentrations of anabolic steroids comparable with those likely present in many people who abuse steroids can cause apoptosis in human endothelial and neuronal cell lines as well as apoptotic death of myocardial cells in rat models, suggesting the possibility of irreversible neuropsychiatric toxicity as well as a mechanism for the cardiovascular effects already noted. Steroid abuse also appears to be associated with a range of potentially prolonged psychiatric effects, including dependence syndromes, mood syndromes, and progression to other forms of substance abuse, although the prevalence and severity of these various effects are not yet known [42].

Prescription Medications

Individuals who have a history of substance abuse are more likely to abuse other agents, including prescription medications. Drugs classified as prescription medications have become

a major category of abused substances, and there is evidence that the abuse of prescription medications may soon overtake that of illegal drugs. Abused prescription medications include sedative hypnotics, stimulants, and anabolic steroids (discussed above). Other abused prescription medications include anticholinergics and ketamine.

The increasing therapeutic use of opioids coincides with increasing abuse in individuals receiving opioids and nonmedical use of other psychotherapeutic agents, including pain relievers, tranquilizers, stimulants, and sedatives. Opioid use, abuse, and nonmedical use are prevalent in both adults and teenagers in the United States. The 2006 National Survey on Drug Use and Health found that more than 20% of people in the United States ages 12 and older had used prescription psychotherapeutic agents nonmedically during their lifetime. There are multiple adverse consequences to long-term use, including effects on the hormonal and immune system, abuse and addiction, tolerance, and hyperalgesia [49].

Sedative-hypnotic medications, which include benzodiazepines, barbiturates, and non-benzodiazepine anxiolytics are generally prescribed to treat insomnia or anxiety. In current practice, the term "sedative-hypnotic" often refers to benzodiazepines (e.g., diazepam and lorazepam). Neuropsychiatric effects of prolonged sedative-hypnotic addiction include deficits in memory, motor coordination, visuospatial learning, processing speed, and verbal learning. These phenomena have been difficult to study because some of the cognitive difficulties may result from sedation while others result from inattention or abnormally high plasma levels. However, recent meta-analyses have demonstrated that these effects can occur even after drug discontinuation. After drug discontinuation, cognition improves but may not return to the baseline level of function [18].

Prescription therapeutic psychostimulants available in oral formulations through non-refillable prescriptions include amphetamine and amphetamine-like stimulants, such as dextroamphetamine, methylphenidate, and diet pills, which are prescribed for the treatment of attention deficit/hyperactivity disorder, narcolepsy, and obesity. Prescription stimulants are classified as controlled substances with a high potential for dependence or abuse when used outside appropriate medical supervision [18]. With long-term use, stimulants may cause insomnia, irritability, aggressive behavior, and psychosis (e.g., paranoia). Medical complications of acute intoxication with stimulants include altered mental status, autonomic instability (e.g., hyperthermia), seizures, or development of serotonin syndrome [18]. Methylphenidate and dextroamphetamine have been associated with cerebral arteritis, renal necrotizing vasculitis, and systemic and pulmonary hypertension [18, 76, 81].

Risk of Addiction and Disability for Children Born to Mothers Who are Addicted

Drug use during pregnancy can lead to severe problems for the fetus, ranging from increased rates of miscarriage to withdrawal symptoms upon birth to congenital birth defects that persist throughout life. Different drugs of abuse affect the fetus differently, and the severity of the effect is generally related to the level of use during pregnancy. It is important to keep in mind that the effects of illegal drugs on intrauterine development are confounded by ethanol and tobacco use, malnutrition, inadequate prenatal care, and incompetent parenting.

Withdrawal symptoms are seen in the majority of newborns of mothers addicted to heroin or methadone [90]. Opioid use during pregnancy causes a neonatal withdrawal syndrome considerably more severe than that encountered in adults, with symptoms such as tremor, screaming, sneezing, lacrimation, fever, tachycardia, tachypnea, vomiting, and diarrhea. Neonatal withdrawal syndrome is often fatal if left untreated. Some studies have found that infants exposed in utero to heroin are born small for

their gestational age, at risk for respiratory distress, and cognitively impaired later in life, although other studies did not find long-term developmental or cognitive problems after correcting for other risk factors [14].

In a retrospective case controlled study of pregnant women who abused narcotics, Lam and colleagues found that the major antenatal complications were prematurity, small size for gestational age baby, antepartum hemorrhage, and high prevalence of venereal disease. The babies born to mothers with drug addictions had lower birth weight, smaller head circumference, and shorter body length. Neonatal withdrawal symptoms occurred in 83% of all drug-exposed neonates, and the perinatal mortality rate was 2.5 times higher than that of the control group [47].

Cocaine has been shown to affect birth weight and head size [78]. It also has mostly transient central and autonomic nervous system effects [8]. Amphetamine use during pregnancy increases the likelihood of perinatal mortality during premature births [90]. The recent Infant Development, Environment and Lifestyle study screened newborns for exposure in utero to a variety of legal and illegal drugs of abuse. The Neonatal Intensive Care Unit Network Neurobehavioral Scale was administered within the first five days of life for all neonatal subjects. Smith and colleagues analyzed Infant Development, Environment and Lifestyle data to measure methamphetamine effects on newborns, including exposure group effects, heavy methamphetamine use effects, and dose-response relationships with amphetamine metabolites. Exposure to methamphetamine was associated with increased physiological stress in newborns. Heavy methamphetamine use was related to lower arousal, more lethargy, and increased physiological stress. More specifically, first trimester methamphetamine use was related to elevated stress abstinence; and third trimester use was related to a poorer quality of movement. Higher level of amphetamine metabolites in meconium was associated with increased central nervous system stress [79].

Alcohol is an established teratogen. Also, fetal alcohol syndrome can result from drinking during pregnancy. Fetal alcohol syndrome consists of characteristic facial anomalies, impaired prenatal and postnatal growth, and microcephaly with mental retardation. The severity of the syndrome is dose related, with lower amounts of ethanol producing cognitive disturbance without the associated musculoskeletal anomalies [18].

Most studies on the effects of drugs on fetal development and drug abuse have focused on alcohol or illegal drugs of abuse. However, many solvents are strongly teratogenic and cause major birth deformities when used during pregnancy. A study in Manitoba of women who abused solvents during pregnancy found that 21.4% of them delivered infants preterm. Of the newborn infants, 16.1% had major anomalies, 12.5% had facial features similar to those in children with fetal alcohol syndrome, and 10.7% exhibited hearing loss [75].

Substance Abuse and People with Disabilities

People with mental and physical disabilities are at increased risk for substance abuse because of their use of substances (prescribed or used as self-medication) to control pain and the stress of physical handicaps, mood disturbances or other mental problems, vocational difficulties, and problems of self-image. As noted in the section titled "Alcohol," alcohol often contributes to or causes physically debilitating injuries, and other drugs of abuse are also involved in disabling accidental injury [41, 87]. Patients who are congenitally disabled and those with disabilities caused by traumatic injury are prescribed psychotherapeutic medications. The difficulties of life with a disability place many of these people at risk for prescription misuse and abuse [40].

Drug and alcohol abuse in individuals with disabilities from spinal cord injuries can be as high as 79%, both before and after the injury that caused the physical disability [40, 41]. In patients with brain injuries, drug and alcohol

use may decline after the injury, but prevalence of abuse can still be at least 27% [41]. Those with congenital conditions that lead to disability are also at risk for high rates of substance abuse. In a survey of people with multiple sclerosis, Bombardier and colleagues found that up to 19% of those questioned reported some form of substance abuse [9].

The characteristics and prevalence of substance abuse among those with intellectual disabilities are not well characterized, and the issue of substance abuse in those with mental disabilities is somewhat hidden [82]. A study by Taggart and colleagues of adults with co-occurring substance use disorders and intellectual disabilities found that alcohol abuse was most common, followed by abuse of a combination of illicit drugs and/or prescribed medication [82].

The co-occurrence of alcohol and drug abuse disorders and physical and intellectual disabilities creates a complex situation for those receiving Supplemental Security Income disability benefits [5]. At least 50% of people who self-reported as "disabled and unable to work" have co-occurring drug and alcohol use problems [5]. Although most of those with co-occurring substance use disorders and physical and intellectual disabilities are still able to receive Supplemental Security Income benefits despite the changes mandated by the Contract with America Advancement Act of 1996, the current Medicaid managed care environment creates challenges of access to and payment for substance abuse treatment [5].

People with disabilities who abuse substances tend to enter treatment for substance abuse at a much lower rate than those without disabilities [46]. Some barriers to care include lack of transportation, difficulty with physical access to the treatment center, and limited knowledge among treatment providers about the special needs of people with disabilities [5, 46]. A report on alcohol and drug treatment services in Ontario found that, although a substantial percentage of clients had physical disabilities and developmental handicaps, few of the centers had services tailored specifically for persons with disabilities or resources for clients who are physically disabled. Staff felt that clients with developmental handicaps would be better served by specialized programs with additional staff training, while those who were physically disabled could be adequately served by "mainstream" services. Several centers indicated that they would not want better resources for the physically disabled, even if funding was available [88].

Conclusion

The relationship between substance use disorders and disability is intricate. The legal and administrative concepts of disability and the reality of what is actually a disabling condition are often disparate. Although a person with an substance use disorder may effectively be limited in his or her actions and abilities, the moral and legal status of addiction leaves these disorders in a gray area. To complicate matters further, substance use disorders can have long-term effects that render a person, even someone in recovery, permanently compromised—cognitively and/or physically. These effects may often reach the level of disabilities, regardless of the severity of the substance use disorder. In turn, many people with disabilities are at greater risk for developing substance use disorders.

The political climate can substantially affect the help that people with substance use disorders can expect from federal, state, and local agencies. Many people with substance use disorders have faced substantial barriers, including physical limitations, job discrimination, and difficulty obtaining coverage for substance abuse treatment. However, there have been few protections for people with substance use disorders, and being in legal and administrative limbo because of their disorders has left many of those afflicted in a precarious position.

Access to care has also been difficult for many persons with these disorders, particularly those who live in poverty. However, the passage of the Paul Wellstone and Pete Domenici Mental Health and Addiction Equity Act will

end discriminatory coverage by group plans covered in the act and require that access to care be comparable to that provided for surgical and medical conditions. As Medicaid managed care and many employer-sponsored plans respond to these requirements, a slow shift in available treatment options is expected that will benefit many people who rely on publicly-funded addiction treatment and others who rely on employer-funded plans [34].

This chapter tells the story of a moral, legal, political, physical, and mental struggle over disability and addiction that ends with some promise and hope. "If there is no struggle there is no progress; this struggle may be a moral one, or it may be a physical one, and it may be both moral and physical, but it must be a struggle" (Frederick Douglass, August 3, 1857).

Acknowledgments The author would like to acknowledge the efforts of Clarinda Mac Low and Susan Hills, Ph.D., in the development of this chapter.

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The Homeless

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Contents

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Introduction

Understanding the composition and needs of the homeless represents a major challenge for all researchers and providers, not least for a group endeavoring to present a chapter summarizing available knowledge about this complex population. Starting with seemingly simple questions, such as defining homelessness, and moving to much more complex questions, such as treatment and other interventions for this population with multiple needs and problems, numerous interrelated issues must be considered. Complicating this discussion, existing research studies share limited methodological commonalities, often making direct comparisons of the findings from the diverse endeavors speculative at best.

Despite these challenges, the purpose of this chapter is: to conceptualize the homeless as a population and discuss population prevalence; to detail rates of substance use and abuse, other mental illness and medical risk factors, and comorbidities; and to identify service models that have been demonstrated effective. Conceptually, this task begins with the complex issue of identifying just what is meant by a "homeless population" and understanding how different inclusion criteria lead to very different prevalence estimates and identified

B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_74,

characteristics of the population. Following the discussion of the definition of homeless population, given the disproportionate rates of substance use and abuse relative to housed populations, the next task is to understand the issues surrounding substance use and disorders, including general estimates of all substances combined and those specific to individual substances. Once substance use and abuse have been presented, it becomes important to understand rates of other psychiatric and other medical illnesses, especially the remarkably high rates of psychiatric comorbidities. This chapter will conclude by discussing treatment needs and reviewing the increasingly available evidence for the effectiveness of specific types of interventions.

Before beginning this examination of homelessness, it is important to note a few caveats. This chapter focuses almost exclusively on homeless adults, specifically single homeless adults. The length constraints of a single chapter preclude discussion of various subpopulations, such as homeless children, runaway and homeless adolescents, single women with children, or homeless families. Further, except where those issues have specific relevance for individual-level risk factors, this chapter does not investigate structural and economic causes for homelessness. A broader consideration of homelessness as an economic or social phenomenon would need to include discussions around housing availability and affordability, extreme poverty, social inequalities, and the impact of policy decisions on rates of homelessness.

Homelessness

Historical Context

Multiple historical events have been linked with current conceptualizations of homelessness, including such disparate populations as those created by sixteenth-century Elizabethan Poor Law, colonization of the North American continent, and itinerant workers in the late nineteenth century [104]. For example, Elizabethan Poor Laws were the first attempt to provide service for landless and homeless poverty populations. In the nineteenth century, discussions of homelessness often focused on itinerant workers, or "hobos". Historically, homelessness has not necessarily been identified as a "problem". Wright [104] points out that various descriptions of the homeless, some as recently as the 1950s and 1960s, have romanticized the lives of hobos and migrant workers. However, starting with changes in the population from the time of deinstitutionalization in the 1960s, there is a general consensus that homelessness has emerged as a serious and increasingly important social issue [3, 6, 35, 38, 104], and that this issue is closely interrelated with substance use and abuse and other psychiatric illness [2, 81].

It is also important to consider the conduct of research on this population from a historical perspective. Although there are no doubt exceptions, early research on homelessness (for the sake of the current discussion, operationalized as published prior to 1970) was generally ethnographic or even anecdotal in method. Seminal works, such as those by Whyte [102], Gans [33], and Liebow [47], focused on the complex interactions among small groups of urban dwellers. Although more recent re-examination of these works demonstrates the significance of illicit substances in the lives of these "streetcorner" groups [47], questions of "how many" or prevalence of these disorders were not addressed in these studies.

The 1970s and 1980s witnessed an explosion of research on homelessness, with over 500 published articles and books listed on the subject in those two decades [87]. Unfortunately, a vast majority of this research was also methodologically flawed, either presenting population descriptions incorporating a convenience sample or services-limited research consisting of program descriptions or non-randomized studies comparing different interventions [55, 87]. It was not until the late 1980s that leaders in the field called for research to "move beyond" demographic descriptions to conduct more complete and methodologically sophisticated research

[57, 97] addressing complex epidemiologic issues [93].

In the last two decades, numerous methodologically sound cross-sectional studies have concluded that addiction and other psychiatric disorders are disproportionately prevalent among the homeless population. Unfortunately, because of sampling-related issues emanating from varied definitions applied to the problem of homelessness, changes in the population over time, and the lack of an acceptable national sample, our subsequent discussions of homelessness and associated comorbidities represent at best an incomplete snapshot of the problem. Thus, answers to the specific questions of "how many" (e.g., "What is the prevalence of psychiatric illness in the homeless population?") vary with these methodological differences, even among studies deemed methodologically adequate for most purposes. Given this situation, we will present ranges of likely prevalence estimates rather than providing specific figures of undeterminable validity.

Operationalizing Homelessness

Historically, homeless samples in research studies have often been limited to service-using populations, especially individuals using services directed to homeless populations, such as overnight shelters. General consensus, however, is that this subset captures only a segment of the homeless population that may not be representative of the larger homeless population [28]. Perhaps the most commonly accepted definition of homelessness is that of the 1987 Stewart B. McKinney Homeless Assistance Act [54] which defines a homeless person as "(1) an individual who lacks a fixed, regular, and adequate nighttime residence and (2) an individual who has a primary nighttime residence that is (a) a supervised, publicly or privately operated shelter designed to provide temporary living accommodations, (b) an institution that provides a temporary residence for individuals intended to be institutionalized, or (c) a public or private place not designed for or ordinarily used as a regular sleeping accommodation for human beings."

Understanding differences among specific definitions of homelessness requires consideration of a number of factors. These factors include what personal circumstances are considered homeless (e.g., inclusion of individuals doubled up/marginally housed versus only counting individuals literally without housing), how long one must be homeless to be included (one night versus a longer spell), and whether one self-identifies or is identified by some external criteria as homeless. Currently, operational definitions of homelessness have focused either on individuals who are literally homelessness or those marginally housed. Definitions of literal homelessness include not just those found in shelter settings, following the definition in the McKinney Act [54], but also individuals sleeping "on the streets" and in other locations not considered appropriate housing (e.g., subways, abandoned properties). Definitions of literal homelessness vary both in duration and in the types of non-housing locations included [28, 66]. Inclusion of marginally housed individuals broadens the definition of homelessness to include individuals with precarious housing situations such as those living in single room occupancy buildings and staying with others without paying rent, and has been used to provide broader estimates of the lifetime prevalence of homelessness [49]. Most recently, researchers have identified an additional dimension to measuring homelessness with given definitions that may affect estimates of population prevalence. Eyrich-Garg and colleagues [28] have discussed differences between "subjective" (self-identified) and "objective" (identified by others) determinations of homelessness, and have demonstrated significant differences in risk patterns among samples of heavy-drinking women identified with different methods of determining homelessness.

As discussed above, the many definitions of homelessness emerging from variations on an array of elements comprising this concept are destined to yield inconsistent sample characteristics and prevalence estimates. Because there

is no unified definition of homelessness, there can be no single gold standard for determining the status of homelessness of individuals, and, therefore, it should be understood that in the remainder of this chapter, the relevant research to be reviewed necessarily consists of work derived from samples based on a variety of non-uniform definitions of homelessness from different perspectives. Although we will be careful to identify both definitions of homelessness and the resulting types of samples included in specific studies (and to present critiques of current estimates in part based on this limitation), readers are encouraged to pay attention to these issues and remain cognizant of how these choices can subtly or even dramatically influence estimates of homelessness prevalence and observed characteristics of the population being studied.

Population Size Estimates

A number of methodological and conceptual issues must be considered in answering the question: "How many homeless people are there?" Similar to the complexities described around defining homelessness discussed in the previous section, issues requiring explication in interpreting estimations of population size include considerations of the sampling source and measurement methods (e.g. agency-based versus epidemiologic samples, neighborhood versus urban area versus national samples, point versus recent or lifetime prevalence estimates versus incidence).

Early prevalence estimates of homeless populations consisted of cross-sectional point prevalence estimates projected from samples counted at one or more overnight shelters. In one of the more thorough studies of this type, Burt and Cohen [11] estimated that there were 194,000 adult users of homeless shelters and soup kitchens in cities of 100,000 or more in a given week in 1987. Although basing their estimate on national shelter numbers represented a methodological improvement on previous estimates, because their estimate excluded multiple other sources of homeless people (e.g., soup kitchens, unsheltered locations), it was generally considered a substantial underestimate. Other commonly discussed population estimates (e.g., census enumeration) attempted to determine the size of homeless populations on a given night using single enumeration methods. However, we agree with an assertion made by Burt and Cohen [11] and endorsed by many others that these single-night estimations are also likely to miss substantial proportions of the literally homeless population, and thus represent significant undercounts. Populations underrepresented include the literal homeless (particularly those sleeping in hidden locations, such as in abandoned buildings) and those housed for single nights or for short spells. For these reasons, we will not further consider single-night estimates here.

Perhaps the best of the prevalence estimates emerge from Burt et al.'s [12] seminal work on homelessness. Using data from the 1996 National Survey of Homeless Assistance Providers and Clients (a survey of a variety of providers for two one-month periods) and extrapolating from previous estimations, they were able to arrive at reasonable estimates of how many service-using individuals were homeless on a given day or week, and estimating the total number of homeless individuals (both accessing and not accessing services) for the same periods. Readers wishing to understand more about how these estimates were reached are invited to explore the details of the various methods and estimates provided in this work [12].

In examining the various estimates, the best defensible figures of homeless service users who were homeless at the time of receipt of services were approximately between 440,000 and 840,000 in a given week and between 260,000 and 460,000 on a given night (including adults and children) in the National Survey of Homeless Assistance Providers and Clients [12]. Using their methods for estimating the proportion of individuals not using services, Burt and colleagues argued that between 1.4 and 2.1 million adults were homeless in a given year. This number is not out of line with other estimates for

approximately the same time period [23]. More recently, using multiple enumeration strategies, the "Homelessness Counts" report gave a higher estimation of around 750,000 on a given night [60]. Importantly, in estimating lifetime prevalence, a telephone household survey found that 6.5% of adults had experienced a spell of literal homelessness at some time in their lives, and that 3% had been homeless within the past year [48, 49], numbers far greater than any of the previous estimates.

An ongoing debate in the homelessness arena is the accuracy of these population estimates over time and their applicability to current population size and generalizability across locations. In terms of current population estimates, a relative consensus holds that the size of the homeless population increased in the 1980s [74] and that the population size has remained stable or grown since. However, as the National Alliance to End Homelessness pointed out [60], consistent enumerations are lacking beyond the flawed census attempts in 1990 and 2000 [51], and, therefore, any discussions around changing size of the population are more speculative than factual. Thus, the estimates presented here, while representing best available evidence, cannot be considered precise or even necessarily accurate. In terms of generalizability of findings across locations, Culhane and colleagues [52] have used administrative records from homeless service providers to attempt to examine population size across multiple jurisdictions. Their results, although representing the state of the art, point out once again the difficulties in estimating population size, as they find rates ranging from 0.1 to 2.1% in different cities of the overall population on a yearly basis using similar approaches to those applied in administrative records data collection.

Although discussions of overall population size over time have been inconsistent at best and lacking at worst, some persuasive evidence points to recent changes in the composition of those who are homeless. North and colleagues [66], using three comparable representative samples each examined a decade apart within a single urban environment, noted significant increases in substance use and mood disorders among homeless cohorts over time. Their findings suggest that the homeless population may be changing, and that some of the differences found across studies are likely attributable to changing characteristics of the population rather than simply variation created by use of different sampling strategies and study of different environments. Further, they argued that observed changes in the population over time may represent unintended consequences of changes in national policy.

Chronic Versus Short-Term

Efforts to understand the composition of the homeless population require examination of linked issues of duration of homelessness and number of spells of homelessness that have long received considerable attention in the homelessness literature and have focused efforts to help this population toward specific subgroups with distinct characteristics. Currently, much of the Federal policy is aimed at addressing the "chronic" homeless population. Classifications of homelessness generally break the population into some variation of three not-always-distinct groups: crisis/first-episode, episodic, and chronic [1, 8, 12, 45, 69, 103]. Estimates of proportions for the chronic subgroups vary from almost half falling into the chronic category [11] to less than one-quarter [8, 12] and as low as ten percent [23]. Caton and colleagues [17] examined predictors of remaining homelessness over 18 months in a cohort of newly homeless individuals, finding that shorter duration of homeless spells was associated with employment, no history of substance treatment or incarceration, and younger age. These observed differences indicate that these subgroups are distinct, with the additional implication that they may have differing treatment needs.

A Critique

Careful readers will note that much of this discussion of the homelessness population has included repeated cautions about the role of

methodological issues in shaping the findings, including the definition of homelessness, sampling methods (e.g., service-using versus non-service-using samples), and evolution of the population over time, to name only a few. Although numerous articles, books, and governmental reports have debated each of these issues separately and together, a broad conclusion from this literature is that it collectively yields only a vague understanding of the size and composition of the homeless population. We echo numerous other writers in noting the frustrations and complexities of integrating a large, methodologically flawed body of information that has been unable to describe this multifaceted population coherently or precisely. Much more could be written, including similar discussions of proportions of the population falling into various demographic sub-groupings, but all would be marred by this same general critique. Given the focus of this chapter on substance use disorders and associated psychiatric and medical risk factors, we will now move away from this general discussion of the homeless population to the central task of examining substance use disorders and comorbidities.

Substance Use Disorders

Association Between Substance Use Disorders and Other Risk Factors and Homelessness

Before launching a discussion of rates of risk factors among the homeless population, it is important to address the relationships of substance use disorders and other risk factors with homelessness. Generally, an implicit assumption in the popular literature holds that the disproportionate findings of these risk factors in the homeless population indicate that substance use and abuse/dependence and other mental illness "cause" these individuals to become homeless. However, evidence on onset of homelessness and psychiatric disorders has called into question this assumption.

Research on the causal nature of psychiatric disorders on homelessness has, in fact, concluded that the association between these factors is not simply unidirectional. O'Toole and colleagues [67] found evidence for changes in alcohol and drug abuse patterns after first onset of homelessness, including escalating use for some individuals and diminished use among others. North and colleagues [65] compared the relative timing of onsets of substance use disorders and other psychiatric disorders with first episode of homelessness and found that the proportion of homeless individuals with onset of their illnesses prior to the onset of their first episode of homelessness was similar to the proportion of a national community sample with onset of illness before an age comparable to that of the homeless sample's age of first homelessness. Earlier assumptions of direct unidirectional causality from psychopathology to homelessness have largely been abandoned by the experts who now argue that there are also multiple indirect effects related to having a psychiatric disorder that may not only increase individual risk for entering homelessness but also create barriers to exiting homelessness [32, 39, 67, 100].

Prevalence Rates

When we use the term "substance use disorder", we are referring to substance abuse or substance dependence as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (editions III, III-R, or IV depending on when the research was conducted). Meeting diagnostic criteria for either alcohol use disorder or for any specific drug use disorder (e.g., cocaine use disorder, cannabis use disorder, opioid use disorder) qualifies one for a diagnosis of substance use disorder.

There is a general scientific consensus that the prevalence of substance use disorder is disproportionately high in the homeless population. According to epidemiologic studies, the lifetime prevalence of substance use disorder is estimated

to be in excess of two-thirds of homeless people [43, 76]. Women range between 31 and 63%, and men between 71 and 75% [9, 76, 90, 91]. Systematic shelter-selected samples (e.g., 30) yield similar lifetime prevalence rates. The current (12-month) prevalence of substance use disorder is estimated to be somewhere between 38 and 52% [66, 76].

One study [66] found that substance use disorders accounted for the vast majority of all lifetime psychiatric disorders among a representative sample of homeless people. A lifetime psychiatric diagnosis was detected in 88% of men and 69% of women, and a lifetime substance use disorder was identified in 84% of men and 58% of women.

Alcohol and Drug Use Disorder Comorbidity

The overlap between alcohol use disorders and drug use disorders is considerable in the homeless population. Approximately 61% of homeless women with lifetime alcohol use disorder also report a history of lifetime drug use disorder [91], and approximately 40% of men and women who report a history of lifetime drug use disorder also report a history of lifetime alcohol use disorder [90, 91]. A substantial proportion of the homeless population meets criteria for both alcohol and other drug use disorders. Approximately 36–42% of homeless people meet lifetime criteria for both alcohol and other drug use disorders [66, 76]. Somewhere between 29 and 33% of women meet lifetime criteria for both alcohol and other drug use disorders [76, 91], and approximately 38% of men meet lifetime criteria for both types of disorders [76]. Approximately 18% of homeless people meet current (12-month) criteria for both alcohol and other drug use disorders [76].

Many homeless people with substance use disorders also have at least one other psychiatric disorder. Epidemiologic studies have shown that of homeless people with lifetime alcohol use disorder, 32–38% meet diagnostic criteria for a lifetime non-substance psychiatric disorder [9]. Of men with a lifetime non-substance psychiatric disorder, 60% meet diagnostic criteria for lifetime alcohol use disorder and 24% meet diagnostic criteria for lifetime drug use disorder [9]. Of women with a lifetime non-substance psychiatric disorder, 46% meet diagnostic criteria for lifetime alcohol use disorder and 20% meet criteria for lifetime drug use disorder [9].

Alcohol Use Disorder

Prevalence Rates

Alcohol use disorders are highly prevalent in the homeless population, ranging from approximately 53–63% according to epidemiologic studies of lifetime rates [43, 66, 76]. Lifetime prevalence ranges from 17 to 40% in women and 56–68% in men [9, 90, 91]. Most individuals who meet criteria for lifetime alcohol use disorder also meet criteria for current alcohol use disorder [76, 90, 91]. Current year prevalence rates for the disorder among homeless populations are estimated to be between 39 and 42% [66, 76], approximately 32% in women and 41–50% in men [76, 90, 91].

Studies comparing prevalence rates of lifetime and current (6-month) alcohol use disorder between homeless persons and housed groups have found significantly higher alcohol use disorder rates among the homeless [43]. However, this finding may not generalize to particular homeless subgroups. For example, lifetime rates of alcohol use disorder do not appear to differ between first-time, non-mentally ill, shelter-seekers and persons applying for government assistance [16]. Shelter-using, mentally ill women have be found to have higher current (6-month) rates of alcohol use disorder than their housed, mentally ill female counterparts [15]; however, no significant difference was detected in the current (6-month) rates of alcohol use disorder between shelter-using, mentally ill men and housed, mentally ill men [14].

The literature indicates that excessive alcohol use is a strong discriminator between homeless and housed families. For instance, single female parents who were homeless reported a history of using alcohol excessively 23 times more frequently than single female parents who were housed [5].

Other Drug Use Disorders

Overall Prevalence Rates

As with alcohol use disorder, drug use disorder is overrepresented in homeless populations. Lifetime prevalence of drug use disorder is estimated between 31 and 58% [43, 66, 76]. According to North and colleagues [66], drug use disorders in the homeless population have increased significantly in prevalence over the past two decades. Women's lifetime rates range between 23 and 51%, and men's lifetime rates range between 40 and 61% [66, 76, 90, 91]. Current (12-month) prevalence of drug use disorder is estimated to be between 31 and 38% [66, 76], approximately 32–35% for women and 18% to 38 for men [66, 76, 90, 91]. Current (12-month) prevalence among shelter-using mentally ill women appears to be in line with these estimates [15], but shelter-using mentally ill men appear to have a substantially higher prevalence of drug use disorder (77%) [14].

Drugs of Choice

The literature is clear that the drug associated with the highest rates of abuse and dependence among the homeless is cocaine. Cocaine use disorder has grown substantially in the homeless population through the 1990s and 2000s [66]. Lifetime cocaine use disorder prevalence rates ranges from 16 to 40% for women and from 37 to 46% for men [66, 76, 90, 91]. Current (12-month) cocaine use disorder rates are approximately 26–29% for women and 24–33% for men [66, 76].

The drug with the second highest abuse/dependence rate is cannabis. During the mid-1980s, cannabis appeared to be the most prevalent drug of abuse (8% for women and 7% for men) in the homeless population [9], but that has changed. Lifetime cannabis use disorder prevalence estimates range between 7 and 28% for women and 30 and 37% for men [66, 76, 90, 91]. Current (12-month) prevalence of cannabis use disorder is approximately 8–12% for women and 10–16% for men [66, 76].

Stimulant, opioid, and sedative use disorders have estimated lifetime prevalence rates between 3 and 10% [66, 76]. Current (12-month) prevalence is similar for stimulant, opioid, and sedative use disorders [66, 76].

Some differences emerge for subgroups of the homeless population. First-time shelter-seeking men appear to have lifetime prevalence rates of cocaine (33%), cannabis (32%), and heroin (11%) use disorders that are similar to those of their housed counterparts [16]. First-time shelter-seeking women, however, have elevated prevalence of cocaine (40%) and heroin (23%) but not cannabis (22%) use disorders, when compared with their housed counterparts [16].

Injection Drug Use

In this brief section, we present information on a particular type of drug ingestion—injection drug use. Note that we discuss use (as opposed to drug abuse/dependence) and that this use may or may not be part of a drug use disorder. Injection drug use is important to mention apart from diagnosis because sharing works is a risk factor for contracting and spreading HIV. Many cities view needle-sharing as such a problem that they fund needle-exchange programs in which people can exchange their used needles for sanitary ones free of charge.

Epidemiologic studies have found that 22% of the homeless population has a lifetime history of injection drug use, with 10% of men and 5% women injecting within the past year. The relative proportions of injection drugs of choice were

heroin (94%), cocaine (58%), stimulants (45%), other opiates (20%), sedatives (19%), and hallucinogens (7%). Sex and age appear to play a role in the likelihood of injection drug use. In one study of severely mentally ill homeless people, rates of injection drug use across study recruitment sites ranged from 16 to 26% for men and 6 to 8% for women [95]. Younger persons in this subpopulation (e.g., under the age of 45) were more likely than older persons to have injected drugs at some point in their lives [95].

Looking Forward

Substance use disorders among the homeless have been studied for many years now. Research needs to continue to identify shifts in the abuse/dependence of popular substances. It is not yet known whether the recently documented trends of increasing oxycodone abuse in the general substance abuse treatment-seeking population [13] and methamphetamine abuse observed in the general population [88] are also reflected in the homeless population.

Non-Substance Psychiatric Disorders

Besides substance abuse, other psychiatric illness is an important issue to examine in homeless populations because of its prevalence, its relationship to homelessness, and its implications for service use and outcomes (for both homelessness and psychiatric illness). It can compromise a person's economic situation (e.g., psychiatric care costs, medication costs, inability to work), medical status (reducing ability to care for oneself), and social status (in terms of family and friendships).

Mood Disorders

Major depression is the most prevalent non-substance Axis I disorder in the homeless population. The lifetime prevalence of major depression is estimated to be between 18 and 21% [43, 66], with greater prevalence found among women (around 25%) [91] compared with men (around 18%) [90].

Major depression can be challenging to assess and difficult to interpret in homeless populations. North and colleagues [65] studied the relationship between ambient weather and same-day assessments of major depression in homeless people using a structured diagnostic interview. They found that men were more likely to meet diagnostic criteria for major depression when the weather was cold and wet. Yet, this difference was not detected among women, who are often allowed to spend days in the shelters (probably because most of them have children) while men are thrust out into the day's weather each day. North and colleagues concluded that the symptoms of major depression can be difficult to separate from the "miseries of homelessness", including hardships of exposure to inclement weather, especially for men. It is possible that the methods used to measure major depression in many epidemiologic studies do not distinguish between the major depression that people typically present with in psychiatric treatment settings and emotional distress and disillusionment among homeless people coping with the extraordinary hardships of being homeless (physical and mental discomforts, hunger, fatigue, social isolation, demoralization, lack of privacy, and the presence of danger). If this is the case, then the standard treatments for major depression (e.g., medication, talk therapy) may not be appropriate for distressed homeless people as with clinically depressed treatment populations. Treatments for major depression are likely to be ineffective for ameliorating the situational distress and misery of homelessness that may be quite difficult to differentiate from major depression.

Instead of using a systematic diagnostic instrument to provide diagnosis of major depression according to *Diagnostic and Statistical Manual of Mental Disorders* criteria (e.g., the Diagnostic Interview Schedule, the Composite International Diagnostic Interview, or the Structured Clinical Interview for *Diagnostic and*

Statistical Manual of Mental Disorders), many studies use proxies such as symptom screens, measures of distress or depressed mood or distinctions of "clinical caseness". Studies based on such nondiagnostic measures have asserted that almost three-quarters (73%) of homeless samples can be defined as having clinically significant emotional distress or clinical caseness for some sort of depressive-like syndrome [75], and approximately one-third of epidemiologic and first-time shelter-user samples (ranging from 33 to 37%) have been reported to suffer from "extreme distress" [75, 93]. As we stated before, being homeless can make one extremely stressed and unhappy. Even diagnostic instruments may over-represent distress as major depression in this population, but they are far less likely to fall into this error than nondiagnostic screening tools. We suspect that high rates, such as 73%, for emotional distress/clinical caseness are a result of inadvertent capturing of the agonies of homelessness and their obfuscation with diagnostic syndromes.

The next mood disorder we will discuss is bipolar disorder. Breakey and colleagues [9] estimated the lifetime prevalence of bipolar disorder in homeless populations of the mid-80s to be around 7–8% for both women and men. Another epidemiologic study of homelessness estimated the lifetime prevalence of bipolar disorder to be around 11% [43]. A study conducted in the early 2000s [66] estimated lifetime rates of bipolar disorder to be around 9%.

Anxiety Disorders

Anxiety disorders, including panic disorder, generalized anxiety disorder, and post-traumatic stress disorder, are prevalent in the homeless population as well. One epidemiologic study estimated the lifetime prevalence of any anxiety disorder for shelter users to be around 39% and the 6-month prevalence to be around 22% [30]. However, prevalence estimates of these disorders have been lower in more recent epidemiologic studies. Similar to our discussion of the challenges of diagnosing major depression in the homeless population, it can be difficult to diagnose anxiety disorders correctly in this population. Real threats of violence, theft, lack of food, and a need to avoid the police in some cities (for fear of being arrested for vagrancy) understandably generate anxiety for many homeless people. This situational anxiety can be difficult to distinguish from symptoms of psychiatric disorders such as panic disorder and generalized anxiety disorder.

Post-traumatic stress disorder appears to be the most prevalent anxiety disorder among homeless people. Lifetime prevalence of post-traumatic stress disorder is estimated to be around 20% for all homeless people [66]—34% for homeless women [91] and 18% for homeless men [90]. Current (12-month) prevalence is estimated to be slightly less (15%) [66].

Panic disorder is typically the next most prevalent anxiety disorder in studies of homeless populations. The lifetime prevalence of panic disorder in the homeless population is estimated to be around 8–9% [43, 66]—3% in women [91] and 5% in men [90]. Current (both 6-month and 12-month) prevalence of panic disorder appears to be slightly less overall (5%) but very similar when reported separately by sex (women: 3%; men: 4%) [43, 90, 91].

Generalized anxiety disorder is the last anxiety disorder we will discuss. Lifetime rates of generalized anxiety disorders range from 7 to 14% [43, 66, 90, 91]. Current (both 6-month and 12-month) prevalence rates of the disorder appear to be slightly lower, ranging from 5 to 11% [43, 66, 90, 91].

Psychotic Disorders

When asked to conjure up an image of a homeless person, most people imagine someone who is severely mentally ill. They think of someone who is psychotic (hearing voices and seeing images that do not exist) and who talks to or yells at imaginary others, such as someone suffering from schizophrenia. Systematic research

shows, however, that a very small percentage of the homeless population fits this description. Contrary to anecdotal evidence, psychotic disorders, most often represented by schizophrenia, are not nearly as prevalent as the news media's sensationalistic presentation of them in the homeless population. Epidemiologic studies have estimated the lifetime prevalence of schizophrenia to be between 4 and 17% [9, 43, 63, 66]. First-time homeless shelter-using men have reported a prevalence estimate within this range—8% [93].

Personality Disorders

The most consistently measured Axis II diagnosis in the homeless literature is antisocial personality disorder. The prevalence of antisocial personality disorder appears to be remarkably, disproportionately high among homeless populations. Epidemiologic data show that between 16 and 20% of the homeless population meet criteria for the lifetime disorder [30, 66], with approximately 10% of women and 25% of men qualifying for the diagnosis [90, 91]. Some researchers [29] have argued that meeting criteria for antisocial personality disorder can be a functional and adaptive, survival pattern of behavior in the context of homelessness rather than a strictly pathological phenomenon. Therefore, they would argue that using the diagnosis in the homeless population is culturally insensitive. North et al. [64] refuted this argument, contending that onset of adult antisocial personality disorder almost always occurs prior to the onset of homelessness and correlates with childhood conduct symptoms, and, in their analysis, the rates of antisocial personality disorder did not decline significantly when they removed criterion symptoms related to homelessness from the algorithms. They concluded that although homelessness may exacerbate the manifestations of antisocial personality disorder, it is a valid diagnosis in this population.

Other personality disorders have received generally less attention in the scientific literature. A pioneering study in the 1980s by Bassuk and colleagues [4] examined rates of *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition—diagnosed personality disorders in sheltered homeless families. In this study, an astounding 71% of homeless mothers in their sample met diagnostic criteria for at least one personality disorder. Diagnoses provided by psychiatrists yielded the following prevalence rates of various personality disorders: dependent (24%), atypical (10%), borderline (6%), narcissistic (4%), antisocial (4%), passive-aggressive (4%), mixed (4%), schizoid (3%), and histrionic (1%). The authors of the study were quick to point out that Axis II diagnoses are less reliable than Axis I diagnoses and that many external environmental factors—e.g., poverty, racism, and sexism—may play a role in determining observable features masquerading as personality traits in this population barraged by extraordinary stressors.

Overall Prevalence Rates

According to a major epidemiologic study conducted in the early 2000s [66], 49% of homeless people have a lifetime history of at least one non-substance Axis I disorder, most of which is accounted for by major depression. This means that (1) half of the homeless population does not have any history of non-substance Axis I disorder and (2) of those with a lifetime history of non-substance Axis I disorder, very few have chronic and persistent severe mental illness (e.g., schizophrenia, bipolar disorder). We exclude major depression from chronic and persistent severe mental illness (see [82] for definitions).

The Roles of Sex and Race in Psychiatric Disorders Among the Homeless

A common theme among the psychiatric disorders in the homeless population is differences in findings by sex and race. Homeless Caucasian women have been found to have a greater prevalence of schizophrenia, major depression, and

bipolar, panic, generalized anxiety, and post-traumatic stress disorders than homeless women of color [63]. This indicates that the homeless women of color may have less major psychiatric illness than homeless Caucasian women. Although we cannot determine causality, these data lend support to ideas that racism, oppression, social inequities, and social injustices may play a proportionately greater role in the homelessness of women of color.

The prevalence of cocaine, opioid, and amphetamine use disorders is greater among homeless men than among homeless women, and more homeless women have alcohol and cannabis use disorders, major depression, and schizophrenia compared with homeless men [9, 76].

Medical Illness

Medical illness is also disproportionately over-represented in the homeless population. Life on the streets and in the shelter system can be dangerous, stressful, and hazardous to one's health. It can be difficult to locate a free place to shower and wash one's clothes to maintain proper hygiene; this makes it difficult to prevent as well as treat illness. Few homeless people have health insurance and can take preventive health care measures (perhaps, in part, because of competing immediate demands such as food and shelter). Many may wait for health conditions to become urgent or emergent before seeking medical attention and then use emergency rooms rather than regular outpatient services for treatment [37].

We cannot state that all medical problems in the homeless population are the direct result of homelessness. Housed low-income populations often have poor health as well. This poor health can be attributed to a variety of factors including poor diet, lack of preventive health care, and lack of exercise. Medical problems among those who are low-income and become homeless are generally problems well known to be associated with circumstances of extreme poverty and other associated social problems. It is, however, likely that being homeless exacerbates the health problems that are already endemic in these populations.

HIV/AIDS

HIV/AIDS has recently begun to receive increased attention in homeless populations. The prevalence of HIV/AIDS among the homeless and marginally housed populations has been estimated to be between 10 and 15% in San Francisco [10, 77], 6 and 19% among the mentally ill homeless in New York City [26, 94], and 16% among soup kitchen attendees in New York City [50]. One study [24] found that people with HIV/AIDS in Philadelphia were 3 times as likely to be homeless as people without the infection. Another study [89] found that homeless injection drug users had a greater prevalence of HIV than housed injection drug users (19% vs. 11%).

Risk for engaging in risky sexual behaviors, which increase one's chances of contracting HIV, is increased in association with intoxication with alcohol and other drugs in homeless populations as in other populations [31]. Because many homeless people, particularly women, trade sex for food, clothing, drugs, or a place to stay, they are at heightened risk for contracting the virus [101]. Homeless people, especially those who are most transient, may not have a reliable place to store their works; therefore, they are more likely than others to borrow injection equipment [22, 34] or visit a shooting gallery [34]. This places them at even greater risk for contracting the virus.

Infectious Diseases

People who experience homelessness may be exposed to or carry infectious diseases. One study of people using soup kitchen services in New York City [50] found high rates of

hepatitis B exposure (21%), hepatitis B carrier (6%), hepatitis C seropositive (19%), and syphilis exposure (15%) [18, 85]. The Centers for Disease Control and Prevention reported the rate of tuberculosis among the homeless to be 6.5% in 1997 [18].

Homeless Services

Following the considerations presented above, treatment of homeless individuals requires attention to a variety of interrelated treatment needs. A general consensus in the treatment literature is that information sought to identify specific treatment needs must address issues around housing, psychiatric and medical illness, employment and economic factors, family [70] and social supports [27], and contextual elements such as availability and accessibility of services [12]. It is equally clear from both the services literature and the review of risk factors presented in this chapter that individual treatment requires attention to these multiple needs.

Research has further identified a series of barriers that complicate delivery of services to homeless individuals. These include suspicions harbored by homeless individuals about the consequences of receiving treatment [46], "hang out" or "street" groups that discourage treatment engagement [71], and disjuncture between professionally assessed needs versus those perceived by the homeless individual [20, 62].

Despite the complex needs identified in this chapter and the multiple factors complicating service delivery, it is possible to make some general statements about what constitutes effective treatment for this population. Perhaps most simply, there is a positive association between amount of service use and the achievement of favorable outcomes [7, 42, 58, 72, 73, 83]. A second consistent finding is that achievement of a broad variety of outcomes requires effective matching of needs to services, as well as integration of care [19, 25, 36, 41, 44, 53, 80]. A third finding is that coordination of intensive services with transitions to housing increases the likelihood of positive outcomes [73, 79, 92, 96, 105].

Research on effective treatment for homeless individuals has generally focused on the development and testing of intervention models. Although an in-depth discussion of services research is beyond the scope of this chapter, examining existing intervention models provides insight into effective approaches and can help point to opportunities for individual treatment and broader service responses. The past decade has seen the development and testing of a variety of effective models of intervention for homeless populations. Perhaps the most promising of these models is the Housing First approach to permanent housing [68, 98, 99]. This model, which combines immediate noncontingent housing and supportive services, has been demonstrated to have relatively substantial effect sizes in increasing housing stability and other associated outcomes [61]. Importantly, Housing First services have also been shown to be equally effective as treatment-first approaches in outcomes around drug and alcohol use over time [68]. In a comparison of permanent housing with assertive community treatment and intensive case management, although all three service types did better than their various comparison conditions (generally treatment as usual, which in most instances was case management), permanent housing was shown to have greater effect sizes for housing outcomes than assertive community treatment or intensive case management [61].

A number of other models have demonstrated promise through either clinical trials or quasi-experimental designs for homeless populations with mental illness. The "critical time intervention" by Susser and colleagues [40, 96] demonstrated significant gains in housing stability relative to usual services; Assertive Community Treatment demonstrated superior housing and mental health outcomes to case management [21, 59]; a psychiatric rehabilitation model demonstrated a wide variety of housing and psychiatric outcomes relative to standard treatment [86]; and intensive case management demonstrated moderate effect sizes relative to case management

[19]. Examining costs associated with outcomes, [78] noted that innovative programs tend to be more expensive than usual services, but challenged his readers to examine his findings in light of the value that society places on these marginalized members.

In the literature on services for homeless populations, addiction treatment is often not the primary focus of the intervention. As we have already noted, housing first is eponymous—it aims to get individuals into housing first regardless of other behaviors (primarily addiction-related ones). Thus, the findings from these type of interventions generally focuses extensively on housing outcomes, often concluding that housing-first approaches do equally well as their comparison groups in addiction-related outcomes (cf. [99]). Generally, research on services for addiction in homeless populations focuses on either "dually diagnosed" populations [36] or on including substances in integrated models [25]. One effective model for homelessness that incorporates a contingency management intervention paired with abstinence-based housing demonstrated positive and housing-related outcomes [56, 84].

Conclusions

In summing up knowledge on homelessness, substance use and abuse, other psychiatric and medical illness, and available services, some very broad conclusions can be made. First, the homeless population is a substantial one in terms of size, particularly with consideration of longer assessment periods. Although spells of homelessness for a majority of the population identified are relatively short-term, the substantial minority of individual spells that are chronic present complex challenges in service provision.

In terms of substance use and abuse, all psychiatric disorders have a disproportionate prevalence in the homeless population, regardless of sampling or assessment methods. The primary drugs of abuse are cocaine (in various forms, but especially crack cocaine), alcohol, and marijuana; and the proportion of the homeless population with addictions appears to be increasing in recent decades. However, despite popular assumptions, addiction does not appear to have a simple direct causal relationship with homelessness, rather it appears to have indirect effects contributing to the likelihood of becoming homeless. Further, it appears that homelessness has a similar indirect effect on the likelihood of substance use and abuse.

There appears to be a disproportionate prevalence of psychiatric (especially substance use disorders) and other medical illness in this population. However, even including the disproportionate prevalence of psychiatric and medical illness among the homeless, the majority do not have a non-substance-related psychiatric diagnosis, and the most common category of psychiatric malady (outside of the highly prevalent substance abuse) is not severe and persistent mental illness such as schizophrenia, but rather major depression or some homelessness-related phenotypic variant of depression related to the miseries of homelessness. Further, these psychiatric and other medical disorders in homeless populations appear to occur almost exclusively as comorbidities with addictive disorders.

Generally effective services for homeless populations must be intensive in nature, matched closely with assessed and perceived needs, effectively addressing barriers to care (especially lack of coordination across providers), and providing intensive services at key transitional times. A number of effective models have been demonstrated to yield favorable housing outcomes relative to comparison conditions, including Housing First, Assertive Community Treatment, Intensive Case Management, Critical Time interventions, and psychiatric rehabilitation.

In concluding this review, we return to the ongoing methodological issues that have consistently plagued the field and, therefore, complicated this chapter. At best, the research applied to discuss this population has limited consistency, in large part due to difficulties in methodological designs of existing research studies. Important issues such as changes to the population over time, differences among locations such

as cities (particularly around transience), and the interrelationship of the individual-level risk factors with economic and policy factors all remain understudied and may significantly impact our understanding of homeless individuals. What is required to address these issues is methodologically sophisticated, longitudinal research that incorporates multiple sites, consistent sampling and multiple levels of data (individual, social, environmental), and complex modeling congruent with the data sophistication.

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Part XIII
New Vistas

To Open Up New Vistas in Basic and Preclinical Addiction Research

Rainer Spanagel

Contents

A Retrospective View on the Hallmarks of Neurobiological Alcohol and Drug Abuse Research

What were the major achievements in the past in neurobiologically oriented alcohol and drug abuse research? This can only be answered by a very personal view. I would like to illustrate this in terms of the hallmarks of alcohol research. In 1940, Curd Paul Richter [80] reported that laboratory rats voluntarily consume alcohol, though with high individual variability. This discovery marked the beginning of animal research in the study of alcohol. Furthermore, this observed variability in alcohol intake provided the basis for the generation of alcohol-preferring and non-preferring rat and mouse lines, 8 of which have been genetically selected since 1960 [26]. Thousands of studies on alcohol drinking in rodents have been conducted subsequently, permitting the deciphering of the genetic and neurochemical basis of alcohol reinforcement. Studies of alcohol self-administration in laboratory animals remain crucial to the development of medication in the field of alcohol research, and the predictive value of these models is demonstrated by the fact that all available pharmacotherapies, e.g., naltrexone and acamprosate [98], have been based on animal work of this nature. The same is true for any other drug of abuse—without appropriate animal models only little progress would have been made in the field of addiction research. In fact, most of the animal models, e.g., intravenous self-administration of heroin and cocaine, provide excellent face and construct validity [86].

In terms of construct validity the discovery of the brain reinforcement system by James Olds in 1954 [70]—one of the outstanding experimental psychologists of the last century—ultimately provided the key to understanding the neuroanatomical correlates underlying alcohol and drug reinforcement. Again, knowledge derived from animal work on the neuroanatomical and functional aspects of alcohol and drug reinforcement has been systematically translated to

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_75,

humans by means of neuroimaging techniques [116].

The foundation for understanding the neurochemical substrates of alcohol and drug reward[1] was laid by the three research teams in 1973 responsible for identifying the first opioid receptors [74, 93, 104]. In the hunt for the endogenous ligands, John Hughes and Hans Kosterlitz [40] then identified the first opioids in the brain only two years later, and called them enkephalins. However, it took almost two decades until the molecular cloning of the first opioid receptors was achieved [27, 49]. These studies not only promoted opioid research in general, but also represented key discoveries for subsequent alcohol and drug abuse research. Similarly, the isolation of Δ^9tetrahydrocannabinol in 1964 by the group of Ralph Mechoulam [29] marked the beginning of cannabinoid research. The brain targets of tetrahydrocannabinol remained unidentified until 1988, when a seminal paper by the group of Allyn Howlet [16] identified a G-protein-coupled receptor as the target of natural cannabinoids. It was followed immediately by the molecular cloning of the cannabinoid receptor 1 [60] and by the identification of the first endogenous ligand of the cannabinoid receptor, an arachidonic acid derivative termed anandamide [17]. These key discoveries led to one of the most active fields of research in neurobiology. But the real surprise came from the discovery of the role of the endocannabinoid system in reward processes and in the neurobiology of addictive behavior. Both the endocannabinoids and the cannabinoid receptor appear to be crucial in opioid, alcohol, psychostimulant and nicotine addiction and it can be foreseen that within the next 10 years we will have effective treatments on the market targeting various components of the endocannabinoid system [82].

Besides endocannabinoids, endogenous opioid systems are thought to induce the pleasurable and rewarding effects of alcohol and other drugs of abuse, and thereby constitute ideal targets for treatment [96]. The first description of opioid receptor blockade by means of naltrexone, and the resultant reduction of voluntary alcohol consumption in rats [2] marked the starting point of the development of relapse medication in alcohol research. A decade later, the first reports on the clinical efficacy of naltrexone in alcohol-dependent individuals were published [71, 117] and a recent meta-analysis of 24 randomised controlled trials that included a total of 2,861 subjects demonstrates that naltrexone decreased the relative risk of relapse compared to placebo by a significant 36% [101]. A further milestone in medication development was the finding that a functional polymorphism of the μ-opioid receptor gene may predict response to naltrexone [72]. Although this finding has recently been replicated [3] no final judgement on this pharmacogenetic discovery will be possible for several years. Nevertheless given the fact that our century is dominated by the belief that personalised medicine will power further biomedical developments, the study of Oslin et al. has already marked this shift in paradigms. Despite the promise of pharmacogenetics to identify treatment responders, there have so far been very few success stories in all of medicine.

[1] It must be emphasized that primary drug reinforcement processes mediated by mesolimbic dopamine release do not necessarily reflect the emotional hedonic components of alcohol and drug reward; it seems more likely that an enhanced mesolimbic dopamine signal highlights important stimuli and functions as a neurochemical learning signal for reinforcing stimuli [100]. Whether mesolimbic dopamine plays also a role in mediating hedonic aspects of alcohol and drug self-administration is not known. However, the endocannabinoid and especially the endogenous opioid systems may well serve as neurochemical substrates involved in the mediation of these positive mood states [96].

New Vistas in Neurobiological Alcohol and Drug Abuse Research

Addictive behavior is the result of cumulative responses to drug exposure, the genetic make-up of an individual, and the environmental perturbations over time. This very complex

"drug × gene × environment" interaction, which has to be seen in a life-span perspective, cannot be studied by a reductionistic approach. Instead, a systems-oriented perspective in which the interactions and dynamics of all endogenous and environmental factors involved are centrally integrated, will lead to further progress in alcohol and drug abuse research [96]. My future perspective adheres to a systems biology approach such that the interaction of a drug with primary targets within the brain is fundamental for understanding the behavioral consequences. As a result of the interaction of a drug with these targets, alterations in gene expression and synaptic plasticity take place that either function as protective mechanisms or lead to long-lasting alteration in neuronal network activity. As a subsequent consequence, drug-seeking responses ensue that can finally lead via complex environmental interactions to an addictive behavior (Fig. 1). This systems biology approach, opens up new vistas in addiction research on the genetic (see Section "New Vistas on the Genetic Level"), molecular (see Section "New Vistas on the Molecular Level"), synaptic (see Section "New Vistas in Alcohol- and Drug-Induced Synaptic Plasticity"), neuronal network (see Section "New Vistas on Neuronal Network Activity"), and finally on the behavioral level (see Section "New Vistas on Studying Alcohol- and Drug-Related Behaviors").

New Vistas on the Genetic Level

Genetics of Addictive Behavior

A large body of genetic epidemiological data strongly implicates genetic factors in the etiology of addictive behavior. In the following I will mainly focus on smoking behavior as progress in genetics are most pronounced in the field of nicotine addiction. The data from family, adoption and twin studies strongly support a genetic influence on the initiation and maintenance of smoking [102, 103]. Two general scientific human approaches to identify candidate genes are genetic linkage analysis and genetic association studies including genome-wide association studies. Despite the success of linkage approaches in unravelling the genetic antecedents of disease, the findings with respect to smoking behavior have been disappointingly inconsistent. However, a variety of plausible candidate genes have been examined for associations with smoking behavior. The vast majority of these studies have focused on genetic variations in relevant neurotransmitter pathways and/or nicotine metabolizing enzymes or neuronal nicotinic receptors. Despite the large number of studies published on the association between specific candidate genes and smoking behavior, one has to conclude from the existing literature that the evidence for a contribution

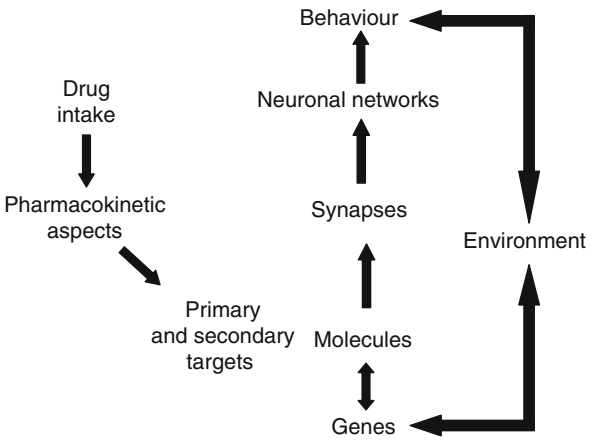

Fig. 1 This scheme shows a systems approach towards a better understanding of the acute and chronic effects of a drug. The here described future perspective follows exactly this approach. Thus, future advances on the genetic level, on drug/receptor interaction, on drug-induced synaptic plasticity, on neuronal network activity, and finally on the behavioral analysis are described

of a specific gene to smoking behavior is rather small.

Genome-Wide Association Studies in Addiction Research

Genome-wide association studies employing a high number (500,000+) of single nucleotide polymorphisms across the genome have now been conducted in a variety of complex disorders and have been shown to be a successful tool in identifying underlying susceptibility genes (for all published genome-wide association studies see: www.genome.gov/26525384). Several genome-wide association studies have recently also been conducted on smoking behavior phenotypes. These studies have used sample sizes up to 11,000 cases [106] and have implicated a number of novel genes in nicotine addiction[2] and smoking cessation, as well as known candidate genes [8, 10, 21, 106, 111]. Especially, in conjunction with several candidate gene studies [85, 87], evidence has been accumulated that genes encoding nicotinic acetylcholine receptor proteins are associated with multiple smoking phenotypes [1]. In particular, the nicotinic acetylcholine receptor subunit genes *CHRNA3*, *4* and *5,* as well as *CHRNB4* are associated with nicotine addiction. Although the robust association of the nicotinic acetylcholine receptor subunit genes investigated with smoking-related phenotypes is an apparent success story of genetic epidemiology, the respective variations seem to exert no relevant influence on smoking cessation probability in heavy smokers in the general population [11]. These data suggest that the corresponding nicotinic acetylcholine receptor single nucleotide polymorphisms are relevant to the development of chronic smoking behavior but might not influence abstinence and relapse behavior. Although this is somewhat discouraging regarding the usability of genetic determinants of susceptibility to nicotine addiction as predictors of smoking cessation, it highlights the importance of taking this highly interesting phenotype explicitly into account in future studies [11]. In conclusion, genome-wide association approaches as discussed here offer great promise for detecting candidate genes for the development of chronic smoking behavior and relapse, respectively. However, the demonstration of a causal relationship of a specific genotype with a pathological phenotype is difficult, if not impossible, to achieve in humans.

Forward Genetics in Preclinical Addiction Research

Animal Models Provide the Basis for Forward Genetic Approaches

Animal studies using intravenous self-administration in rodents represent a powerful method to functionally validate candidate genes deriving either from human genome-wide association study approaches or from gene expression profiling studies in animals. Intravenous self-administration is commonly used as an animal model for studying nicotine intake as it offers face validity from various perspectives, for example there is good concordance between the nicotine concentrations in plasma of human cigarette smokers and of rats in intravenous self-administration studies [92]. Furthermore, genetic differences have been reported since various strains of rats show different latencies to acquire nicotine self-administration behavior [91]. Thus, studies on the acquisition of intravenous self-administration will help to elucidate the genetic vulnerability of the development of chronic smoking behavior in humans.

[2] Note that the term "dependence" is avoided in this review. Addiction is a pathological behavioral syndrome that has to be strictly separated from physical dependence. Transient neuroadaptive processes underlie physical dependence to drugs of abuse whereas persistent changes within specific neuronal systems underlie addictive behavior. In order to avoid any confusion between clinicians, psychologists, and preclinicians, the term "dependence" should refer to a state of physical dependence—this terminology will most likely be also included in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders*.

Major progresses in animal models for addictive behavior also allow now to study compulsive nicotine-seeking behavior and relapse [97]. The most common procedure to study nicotine-seeking behavior—which can be considered as the motivational component of nicotine craving and relapse—is the reinstatement model [13]. In this model, intravenous self-administration of nicotine paired with conditioned cues has to be acquired at first. This is followed by a nicotine free period where the animals undergo extinction (i.e., allowing the animal to perform the operant response, without programmed consequences). Finally, in response to previously conditioned cues reinstatement can be tested. If instead of extinction training protracted abstinence is applied, responsiveness to conditioned cues progressively increases over the first weeks of abstinence (i.e., the animals remain in their home cage for at least one month without any further conditioning)—a phenomenon called incubation [35]. In summary, reinstatement of drug-seeking behavior as well as the incubation of this behavior following protracted abstinence has become the gold standard to measure craving and relapse in animals.

Alterations in Gene Expression in Drug-Exposed Animals

Microarray studies revealed that chronic exposure of nicotine increases expression of genes involved in regulation of food intake and energy expenditure as well as it co-regulates multiple neurotransmitter systems and pathways involved in protein modification/degradation in rat brain [45, 118]. Our knowledge on how these changes in gene expression contribute towards nicotine addiction is substantially limited because nicotine was administered passively in these studies which do not mimic the situation observed in smokers. No previous study has identified the effects of nicotine in active self-administering animals on brain regions and performed gene expression profiles of such regions. However, we know from a key publication by Jacobs et al. [42] that active drug consumption during intravenous self-administration is a crucial psychological factor directing long-term genomic responses in the brain, especially in the nucleus accumbens shell. Therefore, it will be crucial in the future to establish gene expression profiles in a triad design from animals that actively self-administer nicotine in direct comparison to yoked nicotine and saline control animals. This kind of studies usually result in a huge database on gene expression profiles in animals and it will be essential to combine this genomic information with datasets deriving from human genetic studies by a convergent translational genomics approach.

Convergent Translational Genomics Approach for Addictive Behavior

Convergent translational genomics approaches integrate genomic information (e.g., from microarrary analysis) from animal models with a candidate gene or genome-wide association study approach in humans. Especially, the explanatory power of genetic findings is enhanced by such a convergent approach [9] and as a result a priority gene list for functional validation is obtained. Very recently a convergent translational genomics approach was successfully applied to alcohol addiction [108]. In this study, genome-wide association study data from a huge case-control sample for alcoholism were combined with massive information from gene expression profiling in alcohol addicted rats. The genome-wide association studies produced approximately 100 single nucleotide polymorphisms with nominal $p < 10^{-4}$. These, together with 20 additional single nucleotide polymorphisms from genes showing differential expression in rats, were genotyped in a large replication sample. Fifteen single nucleotide polymorphisms showed significant association (two single nucleotide polymorphisms met genome-wide significance) with the same allele as in the genome-wide association studies. Eight out of the 15 genes derived from the animal data demonstrating that relevant genes would have been lost by a mere genome-wide

association study approach [108]. In response to this study, the Integrative Neuroscience Initiative on Alcoholism has now announced that one of their major aims is to integrate animal data into data obtained from studies in human alcoholics (www.scripps.edu/cnad/inia/structure.html). In summary, this novel translational tool results in a priority gene list that has to be functionally validated.

Reverse Genetic Approaches for the Functional Validation of Candidate Genes

Reverse genetics are used to assess the role of a candidate gene in a specific behavior, e.g., in nicotine self-administration. The most common reverse genetic approach is the generation of a conventional mouse knockout model and its subsequent behavioral analysis. However, the generation of a conventional knockout model is time consuming, cost-intensive, has no tissue specificity, and since the gene is ablated early in development numerous compensatory mechanisms may ensue. Through more advanced techniques such as Cre/loxP and tetracycline-inducible systems, a gene of interest can be expressed or inactivated in a tissue-specific and time-controlled manner [30]. Although those conditioned knockout models are of very high value for the neuroscience community they still do not provide a good rational for large scale functional validation of candidate genes because there is still an enormous effort to generate those model. As an alternative the use of viral vectors for gene delivery offer many advantages for rapid functional validation studies. In particular, the advent of adeno-associated virus vectors carrying cDNA for—or short hairpin RNA against—specific genes allows now for the first time the rapid bidirectional manipulation of gene function [51].

New Vistas on the Molecular Level

Hallmarks in drug abuse research were the discoveries of endogenous primary target systems. Thus, drugs of abuse act on specific receptors, channels, or transporters within the brain in order to produce their psychoactive and reinforcing effects; e.g., opiates act mainly on μ-opioid receptors [61], cannabis products such as Δ^9tetrahydrocannabinol act mainly on cannabinoid receptor 1 receptors [16], nicotine acts on the nicotinic acetylcholine receptor [1], psychostimulants such as cocaine act mainly via monoaminergic transporters [38], and hallucinogens such as lysergic acid diethylamide act via the serotonin-2A receptor [34]—to name the primary targets of the most important drug classes. However, how does alcohol affect the functions of the central nervous system—are there any primary sites of action?

What are the Primary Targets of Alcohol in the Central Nervous System?

It is only recently that a shift from the so-called lipid theory (i.e., the primary targets of ethanol are membrane lipids) to the protein theory (i.e., the primary targets of ethanol are membrane proteins, especially receptors) took place [73]. Into the 1990s, different lipid theories postulated that alcohol acts via some perturbation of the membrane lipids of central nervous system neurons. In particular, effects on membrane fluidity and disordering of the bulk lipid phase of membranes was originally an attractive hypothesis of alcohol action because it provided a possible mechanism by which alcohol could affect membrane proteins, such as ion channels, via an action on membrane lipids.

There are clear limitations to the lipid theory. First, effects of alcohol on membrane disorder are generally measurable only at alcohol levels well above the pharmacological range (>500 mg/dl blood alcohol levels); these levels are close to the LD_{50} of ethanol in humans.[3] Significant effects of membrane disordering on

[3] For historical reasons, blood alcohol concentrations are calculated as g/kg blood plasma given in %. Since the specific weight of plasma is 1.23, a blood alcohol level of 500 mg/dl corresponds to 4.06%.

protein function are even more difficult to envision at pharmacologically relevant alcohol concentrations. For example, at very high intoxicating blood alcohol levels associated with loss of consciousness (~ 300 mg/dl), there would be only one alcohol molecule per approximately 200 lipid molecules [73]. Second, membrane effects induced by alcohol concentrations exceeding the pharmacological range can be mimicked by an increase in temperature of just a few tenths of a degree Celsius [73], which clearly does not produce behavioral signs of alcohol intoxication or appreciably alter the function of membrane proteins such as neurotransmitter-gated ion channels. Therefore, the reported effects of alcohol on membrane fluidity and organisation seem to be a purely biophysical phenomenon without any relevance for the pharmacological central nervous system effects of alcohol. Taking even more refinements of the lipid theory into consideration [73] it remains very unlikely that membrane lipids are the primary targets of alcohol.

The protein theory predicts that alcohol acts specifically on membrane proteins such as receptors and ion channels. The main reason for a shift towards the protein theory comes from findings that alcohol—at concentrations in the 10–20 mM range—directly interferes with the function of several ion channels and receptors.[4] In a key publication, David Lovinger and colleagues [58] showed that *N*-methyl-*D*-aspartate function was inhibited by ethanol in a concentration-dependent manner over the range of 5–50 mM, a range that also produces intoxication. The amplitude of the *N*-methyl-*D*-aspartate-activated current was reduced 61 percent by 50 mM ethanol. What is more, the potency for inhibition of the *N*-methyl-*D*-aspartate-activated current by several alcohols is linearly related to their intoxicating potency. This suggests that ethanol-induced inhibition of responses to *N*-methyl-*D*-aspartate receptor activation may contribute to the neural and cognitive impairments associated with intoxication [58]. But how can ethanol directly interefere with *N*-methyl-*D*-aspartate receptor function?

The *N*-methyl-*D*-aspartate receptor is a ligand-gated ion channel with a heteromeric assembly of NR1, NR2 (A-D), and NR3 subunits. The NR1 subunit is crucial for channel function, the NR2 subunits contain the glutamate binding site, and the NR3 subunits have some modulatory function on channel activity, especially under pathological conditions. Electrophysiological studies show that ethanol interacts with domains that influence channel activity [120], suggesting that residues within transmembrane domains may be involved. In the search for a possible binding site of alcohol at the *N*-methyl-*D*-aspartate receptor, several site-directed mutagenesis studies were performed and putative binding sites in the transmembrane 3 and 4 of the NR1 and NR2A subunit, respectively, were identified [37, 78, 79, 83, 95].

It is not yet possible to directly measure the binding of an ethanol molecule to the *N*-methyl-*D*-aspartate receptor by means of physical methods. The reason for this is that ethanol is a small molecule with low binding energy being efficient only in the mid millimolar range. These pharmacological characteristics preclude a direct assessment of an ethanol protein binding site. However, with the discovery of the LUSH protein in the fruit fly *Drosophila melanogaster* it became possible to model how transmembrane residues can form a specific protein-binding pocket for ethanol. The high-resolution crystal structures of LUSH in complex with a series of short-chain alcohols were obtained by the team of David Jones in 2003 [53]. The structure of LUSH reveals a specific alcohol-binding site. LUSH exists in a partially molten globule state. The presence of ethanol at pharmacologically relevant concentrations less than 50 mM shifts the conformational equilibrium to a more compact state [12], demonstrating that ethanol induces a conformational change of the binding protein—an important requirement for a functional binding site. A group of amino acids form a network of concerted hydrogen bonds between

[4] For reference, a low intoxicating blood alcohol level of 50 mg/dl (0.4%) is equivalent to an ethanol concentration of 10.6 mM.

the protein and the ethanol molecules provide a structural motif to increase alcohol-binding affinity at this site. This motif seems to be conserved in a number of mammalian ligand-gated ion channels and it is therefore suggested that the alcohol-binding site in LUSH represents a general model for putative alcohol binding sites in proteins such as the *N*-methyl-*D*-aspartate receptors.

Taken together it has been demonstrated over the last 20 years that ethanol acts directly on the *N*-methyl-*D*-aspartate receptor. However, direct interactions have been also described with gamma-aminobutyric acid-A, serotonin-3, glycine and nicotinic acetylcholine receptors, as well as with several ion channels such as L-type Ca^{2+} channels, where concentrations as low as 1 mM produce alterations in the function of these receptors and ion channels [96, 115]. This modern view on selective primary targets of alcohol in the central nervous system has so far not well been implemented into the general knowledge of drug abuse researchers and neuroscientists. Actually, most researchers still consider alcohol as a "dirty drug" with an undefined mode of action. In the future it will therefore be important to better define the putative binding sites for ethanol in the central nervous system. In particular, the findings on LUSH have to be translated to the mammalian brain.

Agonist-Directed Trafficking of Receptor Stimulus—A Key for Understanding Drug Action

A gain of knowledge in structural biology will not only be essential to define the molecular mode of action of the ethanol molecule but also for other drugs of abuse. This is best exemplified by the mode of action of lysergic acid diethylamide on the serotonin-2A receptor. The demonstration that lysergic acid diethylamide and other hallucinogenic compounds elicit their psychoactive effects via serotonin-2A receptor activation has generated a fundamental paradox in a way that not all serotonin-2A receptor agonists exhibit hallucinogenic activity. Indeed, non-hallucinogenic compounds such as lisuride and ergotamine share significant structural similarities and comparable agonist activities at this receptor [24], but lack psychoactive properties. This pharmacological paradox has recently been resolved by demonstrating that hallucinogenic *vs.* non-hallucinogenic compounds, while acting at the same binding site, elicit different patterns of signalling that are responsible for their different behavioral activities [34]. But how can such a divergent effect been explained in view of the standard pharmacological model of G-protein-coupled receptor activation. The ternary complex model postulates a conformational change from an inactive to an active state following agonistic activation [48]. However, both theory and experimental evidence suggest that G-protein-coupled receptors adopt multiple conformations when activated by different agonists [6, 32]. Thus, an advanced model of "agonist-directed trafficking of receptor stimulus" has recently been proposed by Kenakin [48]. This expanded version of the ternary complex model posits that different receptor agonists stabilize distinct conformations that preferentially recruit and activate specific signalling pathways [48, 113]. The fact that serotonin-2A agonists can activate different signalling pathways is consistent with such an expanded version of the ternary complex model as it explains how distinct cellular responses could be produced by agonists acting at the same binding sites. Paradoxical effects on the receptor level have been also observed with other drugs of abuse (e.g., opioids); progress in structural biology and the application of the new concept of "agonist-directed trafficking of receptor stimulus" will not only be helpful for a better understanding of the molecular action of alcohol and drugs of abuse but will be also important for getting a better insight into the molecular processes underlying drug-induced synaptic plasticity.

New Vistas in Alcohol- and Drug-Induced Synaptic Plasticity

A ubiquitous property of all synapses is their ability to undergo activity-dependent changes

in synaptic plasticity that can be studied most effectively using electrophysiological methods in brain slices. Since these slices only remain viable for several hours, the cellular mechanisms underlying the first few hours of long-term potentiation and long-term depression are the best understood. It has been suggested that synaptic plasticity within the mesolimbic dopaminergic system and associated limbic structures, including the extended amygdala, becomes manifest following drug exposure [46]. Some key publications on drug-induced adaptations in the mesolimbic system have revealed that glutamatergic synapses on dopamine neurons in the ventral tegmental area in particular undergo plastic changes following administration of drugs of abuse including ethanol [84, 112].

By increasing synaptic strength [112], facilitating long-term potentiation [57], or blocking long-term depression [44], drugs of abuse augment the responsiveness of dopamine neurons to glutamate and ultimately promote enhanced dopamine release in brain areas such as the nucleus accumbens and the prefrontal cortex [33]. Drug-induced synaptic strengthening in dopamine neurons in the ventral tegmental area is associated with changes in alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subunit composition [5]. Incorporation of the AMPA receptor subunit GluR1 promotes drug-induced synaptic strengthening, probably through the formation of highly conductive, Ca^{2+} permeable GluR1 homomeric AMPA receptors [20], while insertion of GluR2 containing receptors reverts it [59]. Synaptic recruitment of GluR1 subunits and the resultant synaptic potentiation requires the activation of *N*-methyl-*D*-aspartate receptors [20]. These synaptic changes in dopamine neurons are thought to be related to the development of drug-induced reinforcement processes ([46]; see also [25]).

In conclusion, drug-induced synaptic plasticity has been found in the ventral tegmental area—nucleus accumbens projection as well as in other brain areas of the extended amygdala. However, the generally held view that these cellular adaptations underlie drug reinforcement is based on purely associative findings. Direct experimental evidence for the behavioral significance of these drug-induced synaptic changes involving glutamate receptors is still lacking. Only in vivo electrophysiology in conditional mouse models that selectively lack, for example, *N*-methyl-*D*-aspartate receptors in dopaminergic neurons will provide a clear answer as to whether AMPA/*N*-methyl-*D*-aspartate receptor induced synaptic strengthening of dopamine neurons within the ventral tegmental area serves as a cellular model for the induction of drug reinforcement. It will be also important to know whether these drug-induced synaptic changes modulate neuronal network activity. For answering this question multielectrode recording and ultra high-field imaging in rodents will be useful.

New Vistas on Neuronal Network Activity

Multielectrode Recording to Reveal Neuronal Network Activity Underlying Alcohol- and Drug-Related Behavior

An increasing number of laboratories now have the capability to simultaneously monitor the extracellular activity of more than 100 single neurons in freely moving animals. This paradigm, known as multielectrode recording, is revolutionising systems neuroscience by enabling the visualization of the function of entire neural circuits [69].

So far, only a few studies have used this technique in freely moving animals in order to correlate drug-related behavior with neuronal activity. Janak et al. [43] used multielectrode recording within the shell of the nucleus accumbens during operant alcohol self-administration, and found that different, but overlapping, populations of neurons in the nucleus accumbens mediate each event occurring along the temporal dimension of a single trial performed to obtain ethanol reward. These data suggest that the nucleus accumbens

plays a crucial role in linking conditioned and unconditioned internal and external stimuli with motor plans in order to allow ethanol-seeking behavior to occur. In a recent study, multielectrode recording was used to determine the effects of ethanol on neuronal firing and network patterns of persistent activity in prefrontal cortex neurons [110]. The results of this study show that ethanol inhibits persistent activity and spike firing of prefrontal cortex neurons, and that the degree of ethanol inhibition may be influenced by dopamine D1 receptor tone. Ethanol-induced alterations in the activity of deep-layer cortical neurons may therefore underlie the disruptive effects of alcohol on cognitive functions supported by these neurons.

These few examples demonstrate that multielectrode recording in freely moving animals may prove a powerful future approach in understanding alterations of neural network activity during the course of long-term alcohol consumption. Application of this technique to investigate the transition from drug-seeking behavior to more compulsive behavior would be particularly valuable [86, 119]. Such studies would need to be performed over a long-time period; however, with repeated measures being taken over several weeks or even months, and data handling and analysis would be further limiting factors.

Animal Brain Imaging to Identify the Neuroanatomical and Neurochemical Substrates of Addictive Behavior

Brain imaging in small laboratory animals such as mice and rats is restricted, since the brain sites of interest are very small compared to those of the human brain and measurements can only be performed in anesthetized animals. Use of a comfortable head restraint device in well trained conscious monkeys; however, enables the performance of imaging and the assessment of conditioned drug responses [39]. Recent progress in ultra high-field imaging up to 17 T now allows brain imaging in rodents with a good resolution (<100 μm). Spectroscopy and pharmacological magnetic resonance imaging provide particularly powerful tools for the study of the progression of alcohol and drug consumption towards addictive behavior. The advantage of animal neuroimaging is that a subject can be studied repeatedly over a long period, allowing the investigation of neuronal network activity in the transition phase from controlled to compulsive behavior.

One important application for future studies in laboratory animals is glutamate spectroscopy. Pfeuffer and colleagues [75] demonstrated as long ago as 1999 that at least 18 metabolites, including glutamate and gamma-aminobutyric acid, can be quantified in the adult rat brain using [^{1}H] nuclear magnetic resonance spectroscopy at 9.4 T. In vivo detection and quantification of glutamate in the rat brain, as well as regional differences in signal intensities, have been also demonstrated by others [62]. High-field spectroscopy provides superior peak separation, allowing the direct measurement of glutamate in different brain areas of small laboratory animals, providing an ideal tool for non-invasive longitudinal tracking of neurometabolic plasticity within the glutamatergic systems accompanying alcohol and drug withdrawal, abstinence, and relapse.

The most promising approach however, is the in vivo mapping of functional connectivity in neurotransmitter systems using pharmacological magnetic resonance imaging. Schwarz and colleagues [88, 89] have pioneered the application of functional connectivity studies to pharmacological challenges. In their studies, analysis of the pharmacological magnetic resonance imaging responses to various drugs revealed specific structures for functionally connected brain regions that closely reflect known pathways in the neurotransmitter systems targeted by these drugs [88, 89]. These studies therefore demonstrate that the hemodynamic responses observed following a pharmacological challenge are closely related to drug-specific changes in neurotransmission. This novel approach can now be used to study the impact of pharmacological or genetic manipulation on functional connectivity. This application has already been used to study the disruption of drug-induced

functional connectivity by a dopamine D3 antagonist. The strongest modifications of functional connectivity by dopamine D3 blockade occurred in nigrostriatal connections [90]. This approach is also being applied to current alcohol research. The progression of alcohol drinking towards a habit-like behavior, as studied in terms of alteration in nigrostriatal connectivity of brain sites, is being studied in a long-term alcohol self-administration paradigm using a 9.4 T scanner. The working hypothesis is that the nigrostriatal pathway may be involved in the habit forming properties of alcohol and other drugs of abuse [18, 28, 31, 97]. More precisely, a neuroanatomical principle of striatal organization is that ventral domains, including the nucleus accumbens, exert control over dorsal striatal processes that are mediated by so-called "spiraling, striato-nigro-striatal" circuitry. Chronic administration of drugs of abuse may lead to alterations in this serial connectivity, and drug-seeking habits—a key characteristic of addictive behavior—are triggered as a result [4]. Functional connectivity studies with good resolution conducted in a high-field scanner provide a tool for proving this attractive hypothesis of alcohol/drug-induced alterations of striato-midbrain-striatal serial connectivity and will be very helpful to understand the neurobiology of drug-related behaviors such as drug-seeking and relapse.

New Vistas on Studying Alcohol- and Drug-Related Behaviors

Reconsolidation of Alcohol- and Drug-Related Memories

Relapses contribute considerably to the maintenance of addiction and are a major challenge in the treatment of addictive diseases. One fundamental problem in the treatment of drug addiction is the ability of drug-associated environmental cues to evoke drug-seeking behavior leading to relapse even after years of abstinence. Consistent with the long-lasting risk of relapse several recent studies indicate that long-term memory formation and development of drug addiction are sharing common neural circuitries and molecular mechanisms [41, 47]. Thus, understanding learning and memory processes in the addicted brain is an important key for understanding the persistence of addiction and it is reasonable to hypothesize that selective disruption of drug-related memories might help to prevent relapses.

Several earlier studies have shown that newly-acquired memories are initially labile but then are stabilized through a process called memory consolidation [22, 64]. Within the first minutes to hours this process is susceptible to interference. Following this stabilization period the consolidation theory proposes that memories, once stored, are resistant to interference [64]. In contrast to this idea Misanin and colleagues [66] proposed that reactivation of a consolidated memory trace returns it to an unstable state again. More than 30 years later, Nader et al. [67, 68] confirmed this assumption in a fear-conditioning paradigm with targeted infusions of the protein synthesis inhibitor anisomycin into the lateral and basal nuclei of the amygdala—sites known to play an important role in fear learning—after retrieving previously conditioned fear memories. This study demonstrated that infusion of anisomycin shortly after memory reactivation produced amnesia on later tests, while anisomycin application in the absence of re-exposure to the conditioned cue left the memory intact [68]. Thus, reactivation of a consolidated memory can return into a labile state in which the memory trace has to undergo reconsolidation for which, like consolidation, new protein synthesis is required. Subsequently, further evidence for the reconsolidation theory and its dependence on renewed protein synthesis has been provided [15, 23, 67]. In particular, antagonism of the *N*-methyl-*D*-aspartate subtype of glutamate receptor has been shown to be effective in disruption of memory reconsolidation [55, 77, 107, 109], likely because of the crucial role of these receptors in learning and memory. Furthermore, given the fact that adrenal stress hormones activate adrenergic receptors in the amygdala and that the basolateral amygdala is

essential for fear memory [64] it is suggested that the release of norepinephrine within the amygdala is of importance for reconsolidation processes. Indeed, infusion of the non-selective beta-adrenergic antagonist propranolol into the amygdala of rats shortly after the reactivation period of a previously acquired fear association impaired the fear expression on a long-term test [14]. Very recently, this finding was translated to humans in a randomized and double-blind placebo controlled design. In volunteers oral administration of propranolol before memory reactivation erased the behavioral expression of the fear memory 24 h later and prevented the return of fear [50]. This key finding has important implications for the treatment of persistent and self-perpetuating memories in individuals suffering not only from anxiety disorders but also from drug addiction.

The reconsolidation hypothesis was also tested in regard to drugs of abuse. In the laboratory of Barry Everitt, rats were examined in a cocaine self-administration paradigm in which a conditioned stimulus was presented during each self-administered cocaine infusion. The conditioned reinforcing properties of the conditioned stimulus were tested subsequently by measuring its ability to support the acquisition of a new instrumental drug-seeking response of lever pressing in the absence of the primary drug reinforcer. Thus, the rats were exposed to a brief test session in which a nose-poke resulted in presentation of the conditioned stimulus, but an infusion of saline instead of cocaine. This session was sufficient to reactivate the previously formed conditioned stimulus-drug association and render it sensitive to disruption since an infusion of anisomycin into the basolateral amygdala immediately after reactivation subsequently impaired the acquisition of the new response [56]. Furthermore, a single reactivation-dependent infusion of an antisense oligonucleotide targeting Zif268—an immediate-early gene (also known as EGR1, NGFI-A, and Krox24) that is significantly upregulated in the basolateral amygdala following self-administered cocaine [105]—into the amygdala, 24 h prior to testing resulted in a long-lasting disruption of the ability of a drug-associated stimulus to act as a conditioned reinforcer [54]. These results demonstrate that addictive drug memories undergo reconsolidation in a manner similar to fear memories. This key publication was followed by several other studies demonstrating disruption of the reconsolidation of cocaine-, heroin-, and morphine-related memories with various pharmacological manipulations and behavioral paradigms [7, 36, 56, 65, 81, 114]. Disruption of alcohol-associated memories was also very recently tested in animals trained to self-administer orally alcohol during which each self-administered alcohol drop a conditioned stimulus was presented. The protein synthesis inhibitor anisomycin and the non-competitive *N*-methyl-*D*-aspartate receptor antagonist MK-801 were given after retrieval of alcohol-related memories to test whether these memories undergo a protein synthesis- and *N*-methyl-*D*-aspartate receptor-dependent reconsolidation. Additionally, acamprosate as an abstinence-promoting agent that is widely used in the treatment of alcohol addiction was administered. Although the primary site of action is still not known it has been demonstrated that acamprosate dampens a hyper-glutamatergic state in the alcohol dependent brain and thereby reduces the risk of relapse [97, 98]. Due to this interference with the glutamatergic system it is hypothesized that acamprosate may also have an impact on the memory reconsolidation processes. With these experiments evidence was provided that alcohol-associated memories can also become unstable and liable to disruption after their reactivation. Thus, both the protein synthesis blocker anisomycin as well as the *N*-methyl-*D*-aspartate receptor antagonist MK-801 given immediately after re-exposure of animals to alcohol-paired conditioned stimuli impaired the ability of the conditioned stimuli to induce alcohol-seeking behavior in subsequent test-sessions whereas acamprosate had no impact on reconsolidation processes [von der Goltz et al., unpublished results]. These findings demonstrate that the administration of anisomycin and MK-801 specifically disrupted reconsolidation, as the administration of these agents without the reactivation of the

conditioned stimulus-alcohol-related memory had no effect on the responsiveness of the animals to the alcohol-paired conditioned stimulus during alcohol-seeking tests. Finally, reactivated alcohol-related memories as well as other reactivated reward-related memories are also susceptible to interference with beta-adrenergic blockade by propranolol [19].

In conclusion, it was shown that alcohol- and drug-associated memories can be disrupted pharmacologically after their reactivation by both protein synthesis inhibition and *N*-methyl-*D*-aspartate receptor antagonism. These findings have important clinical implications, because they show that it is possible to selectively reduce long-lasting drug-associated memories. Hence, the disruption of drug-related memory reconsolidation may be an effective treatment strategy for the reduction of relapse. These findings should be rapidly translated into alcoholics, smokers and illicit drug users as pharmacological manipulations before memory reactivation was shown to prevent the return of fear [50]. Either propranolol or ketamine treatment before memory reactivation in addicted individuals would be a promising starting point.

Summary

In this chapter I have given a personal retrospective view on the hallmarks of neurobiological alcohol and drug abuse research and have then discussed new approaches and challenges in the addiction field.

In terms of future genetic work I have highlighted the application of convergent translational genomics approaches. This novel bioinformatic tool has already been successfully applied to alcohol addiction [108]. It allows the integration of genetic information from animal and human studies thereby enhancing the explanatory power of genetic findings and will be essential to define candidate genes for alcohol- and drug-related phenotypes. Most importantly, candidate genes have to be functionally validated. Two reverse genetic strategies for the functional validation of candidate genes have been proposed here: the use of conditional mouse models and the application of virus-mediated gene transfer. Following this validation process genetic risk profiles can be defined for alcohol- and drug-taking behavior.

On the molecular level, the interaction of a drug with primary targets (e.g., receptors) within the brain has been discussed. In this context the concept of "agonist-directed trafficking of receptor stimulus" was highlighted for a future key to understand the consequences of drug/receptor interactions and subsequent signalling transduction.

On the synaptic level, new concepts were discussed in regard to drug-induced synaptic plasticity. Alterations on the synaptic level can modulate neuronal network activity which can be studied by means of multi-electrode recording or ultra high-field imaging in small rodents. A systems biology approach will then be helpful to integrate data sets obtained on the genetic, molecular, synaptic, and neuronal network level in order to understand addictive behavior.

Finally, the most burning question relates to new options for the treatment of addictive behavior? Instead of having discussed new potential anti-relapse compounds (for review see [52, 76, 94, 98]), I have highlighted the possibility of disrupting reconsolidation of alcohol- or drug-related memories as a new approach to treat our clients.

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Opportunities, Challenges, and Successes in the Development of Medicines for the Treatment of Addiction

Bankole A. Johnson

Contents

Animal Studies

Animal models have formed the foundation for understanding the neurobiology of abused substances and the mechanistic processes associated with the acquisition and maintenance of substance dependence. Our knowledge of the neuroscientific basis by which abused substances exert their reinforcing effects associated with their abuse liability is greater than our understanding of the biological determinants of disease in any other field of psychiatry. Predicated on this understanding, these pathways associated with the reinforcing effects of abused drugs have formed the molecular targets for the discovery of new medicines to treat substance dependence.

An important challenge in the discovery of new medicines is to find animal models that mimic accurately the human condition of alcohol or drug dependence. Prevailing in the demonstration of self-administration of abused substances has been the core element of the cortico-mesolimbic dopamine theory of addiction [49]. Basically, this theory proposed that most abused drugs—and, more recently, other addictive behaviors such as gambling (see Chapter "The Biology and Treatment of Pathological Gambling") and overeating [46] (see also Chapter "An Addiction Model of Binge Eating Disorder")—probably exert their reinforcing effects through activation of cortico-mesolimbic dopamine neurons and down-regulation of dopamine-2 receptors [47]. Plausibly, other more recently recognized addictive behaviors such as instant messaging also might be shown to activate the same circuit (see Chapter "Instant Messaging Addiction Among Teenagers: Abstracting from the Chinese Experience").

Furthering the cortico-mesolimbic dopamine theory, it has been demonstrated that substances with abuse liability have higher reinforcement value than natural reinforcers (e.g., food, water, and sex), and this primes and maintains the salience of substance-abusing behavior [6]. Clearly, this points to the teaching that medicines to treat dependence on abused substances are unlikely to be generally successful by simple ablation, destruction, or direct opposition of these cortico-mesolimbic pathways. Indeed, it is now accepted widely that direct dopaminergic antagonism, probably as a result of counter-regulatory neuroadaptive mechanisms, either has little effect or actually can

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9_76,

be a trigger for further substance use [15, 17]. Agonist theories, specific to dopamine enhancement, also have had little success, presumably because these also act as surrogate reinforcers. In gainsay, however, non-dopaminergic agonists have been useful treatment for some disorders (e.g., methadone for morphine or heroin dependence or the nicotine patch to treat nicotine dependence). Nevertheless, there is a continuing search even in these areas for treatments that have lower addictive potential. Contemporary avenues in medications development have, therefore, focused primarily on medicines that provide neuromodulation of these brain circuits.

Extension of the cortico-mesolimbic dopamine theory has necessitated greater understanding of not only how midbrain circuits modulate addictive behavior but also cortical processes. Some of these intriguing interactions have been amply demonstrated in studies that have examined dopamine function contemporaneously at various brain sites and in moving rather than yoked animals [12]. This should be linked with multiple electrode recordings to ensure higher concordance between neuronal activity and behavior. Emerging from these studies is that the cortico-mesolimbic system does not act in isolation to express reinforcing behavior but does so through its interaction with other neurotransmitter systems. Some of the complexity of these potential inter-neuronal interactions is shown in the conceptual model provided in Fig. 4 of Chapter "Pharmacotherapy for Alcoholism and Some Related Psychiatric and Addictive Disorders: Scientific Basis and Clinical Findings".

Addicted humans can retain strong memories and affect for the situations in which substances are abused. A useful elaboration of the cortico-mesolimbic dopamine theory has, therefore, been greater understanding of the role of the extended amygdala and associated stress hormones (e.g., corticotrophin-releasing factor), neurotransmitters (e.g., gamma-aminobutyric acid, glutamate, and the cannabinoid-1 receptor), orexins, and small molecules (e.g., neurokinins) in developing these enmeshed emotions that can trigger substance taking after a period of abstinence [31]. This has led to the development of reinstatement models of addiction, which are appealing as a relatively close cross-species estimate of relapse in animals and humans. Advances in this model are, however, needed to better segregate motoric response from actual drug-seeking behavior in animals so as to develop paradigms more analogous to alcohol or drug dependence in humans [7, 45]. Nevertheless, an important avenue for medications development using this paradigm might be to study agents that modulate activity in the extended amygdala. One notable example has been the demonstration of topiramate—a sulfamate-substituted fructopyranose derivative and gamma-aminobutyric acid-A/glutamate neuromodulator—as a treatment for alcohol dependence [22, 28] and possibly cocaine dependence [29]. Another includes the development of the neurokinin-1 antagonist, LY686017, for the treatment of alcohol dependence [11]. Other ideas for medications development in the alcoholism field include the targeting of neuropeptide Y.

Humans use substances with abuse liability repeatedly, not acutely, once the addiction is entrenched. Repeated dosing paradigms are, therefore, common in testing the efficacy of putative therapeutic medications in animals. The contrast between acute and repeated dosing models can lead to an incorrect estimate of the anti-reinforcing effects of putative therapeutic agents. For instance, compared with the acute dosing model, where a large pharmacological effect of naltrexone to diminish alcohol self-administration in nonhuman primates was seen, chronic naltrexone administration resulted in a modest anti-drinking effect [5]—a closer approximation to the magnitude of response seen in clinical studies [18, 41]. To extend this paradigm, repeated dosing schedules in animals have to be adjusted to examine behavioral effects over extended periods rather than just a few days. Often, this has necessitated the experimental use of nonhuman primates rather than rodents or smaller animals in such studies.

Arguably, the more striking examples of new medicines to treat addiction have been

seen in the alcohol field. Examples of these medicines include those that have been approved by the Food and Drug Administration (e.g., naltrexone and its analogs, and acamprosate) and experimental but promising medications such as baclofen, ondansetron, and topiramate [17]. Nevertheless, even with these promising medicines, the picture of their pharmacological effects in the array of animal models (i.e., craving, reinforcement, and reinstatement) is incomplete.

Continuing with the alcohol field as an example, no medication has been developed directly from animals to humans. Most of these medications—apart from topiramate, which was developed from basic conceptual theory and applied directly to the clinic [14]—have been found by secondary explorations, usually from clinical observations. Therefore, the general direction of development has been from humans with further testing to elucidate mechanisms in animals. As such, an important knowledge gap exists with respect to the pharmacobehavioral effects of these medicines on alcohol-seeking behavior.

An important realization of the process that has taken place in the alcoholism field is that medications development must be bi-directional—not only from animals to humans but from humans back to animals—to gain a greater understanding of how to identify other putative therapeutic compounds. For example, in a clinical trial testing a hypothesized conceptual framework [14], topiramate was found to be efficacious for treating alcohol dependence although there were almost no preclinical data available [22]. Implementing a bi-directional scientific approach to medications development means that it would now be necessary to test topiramate in an array of preclinical models to characterize fully and validate the mechanism of action that might underlie its therapeutic effect [22]. This strategy yields another scientific opportunity with important practical implications. Since preclinical testing of clinically promising medications for treating alcohol dependence is likely to exhibit a differential set of findings across the array of animal paradigms, especially if the medication's mechanism of action is relatively specific, it might be possible to construct a response pattern or "fingerprint" of such medication effects. Not only does this approach circumvent the thorny problem of defining the response to medication in a single animal model that translates best to efficacy in clinical testing, it suggests that animal models should be conducted in an array of paradigms, and that the response "fingerprint" from these studies should be used as the comparator to predict clinical efficacy between putative therapeutic medications. This reverse-engineering approach has been successful in bioengineering. In the substance abuse field, this approach has the attraction of enabling researchers to screen an array of agents efficiently in animals to yield a high likelihood of finding candidate medications with similar therapeutic profiles. A theoretical stumbling block also is bridged by this approach. These medications need not even be pharmacologically similar in structure in exact modes of action, but only to be capable of eliciting comparable therapeutic response. Indeed, these models to "fingerprint" response need not be confined to anthropomorphic approaches but should develop into those that provide the highest construct validity. Computational methods from systems biology can be applied usefully to increase the efficiency of this medication-finding process (see Chapter "In Silico Models of Alcohol Dependence Treatment: Stochastic Approach"). Furthermore, since each of the different animal models that exist have been pioneered or favored for study by particular laboratories, a practical and efficient method for conducting these experiments might be to develop and use a national network of preclinical laboratories. Apart from the obvious efficiency of this approach, a process also will be established to develop other additive and informative models and paradigms.

Animal studies examining molecular genetic paradigms on the pathophysiology of substance abuse and response to putative therapeutic agents should be expanded to consider a more diverse range of environmental and rearing conditions that also take into account gender differences across various species. Animal experiments that

vary the interaction between genetic and environmental factors would facilitate the development of preclinical models translating to special human populations, e.g., children and adolescents or individuals with comorbid disorders. Gene-by-environment approaches in animal studies might serve as models for understanding therapeutic response in special situations, conditions, or environments. These models might provide better characterization of the important determinants of individual response and the "elasticity" of the treatment effect across various subpopulations.

Integrating genomic studies in animals with humans appears to be a powerful approach for identifying a priority list of genes to understand the pathophysiology of addictive behavior. An example from the alcohol field is that this method allowed for the identification of 15 single nucleotide polymorphisms from gene-expression studies in rodents that could be associated with the same allele in the genome-wide association studies in humans [43]. A non-integrative approach, based solely on genome-wide association studies in humans, would have failed to identify 8 of these 15 genes. Thus, this integrative approach is essential to capture the spectrum of genetic influences on addictive behavior (see also Chapter "To Open Up New Vistas in Basic and Preclinical Addiction Research").

Advances in our understanding of synaptic plasticity due to abused drugs, especially alcohol [40, 44], have brought into prominence the role of the glutamate system and its interactions with calcium channels as modulators of cortico-mesolimbic dopamine-induced reinforcement. With respect to alcohol, the important role of the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, perhaps through the formation of Ca^{2+}-permeable glutamate receptor type 1 homomeric AMPA receptors [8] and other signaling pathways, has been elaborated into a hypothesis for the therapeutic mode of action of topiramate [14]. These ideas can be developed further into identifying other therapeutic compounds that might be efficacious in treating not only alcohol dependence but also a wider range of addictive disorders and behaviors.

As a bridge to the future in this field, animal models need to be developed that inform the possibility to define stages in the development and progression of substance-seeking behavior. Disease staging in humans is not well understood from a neurobiological perspective, presumably because it is difficult to segregate the manifest phenotype from endophenotypes of the disease process. Animal studies that combine molecular genetic techniques with variable exposures to the abused substance, under different conditions and stages of development (e.g., adolescence or adulthood), should provide important clues as to the pathophysiological steps in disease development. Clearly, these stages might define varying susceptibility to disease at specific points in development, as well as the direction and magnitude of response to putative therapeutic agents. These experiments should have useful parallels and insights with which to inform the human condition.

Greater emphasis on cross-species experiments in humans is needed to better validate pharmacobehavioral models. Experimentation with nonhuman primates should facilitate the development of models closer to mimicking the variety of responses to situation, set, and characteristics that form the variation in response to pharmacotherapy in the clinical treatment of substance dependence. Nonhuman primates might also be especially useful in the development of vaccines. Finally, nonhuman primates afford the possibility of studying the impact of disease states that have parallels with those that can occur in humans (e.g., hepatitis or HIV) on the pathophysiology of substance dependence.

Bridging the Gap: Human Laboratory Studies

In the development of medicines to treat addictive behaviors, human laboratory studies offer an important method to bridge the scientific

gap between animal studies and clinical trials. Human laboratory studies are typically conducted in either an inpatient or outpatient setting in a highly monitored (for medical safety) and controlled (i.e., for both set and setting, and the administration of experimental manipulations and measures) environment. Human laboratory studies are essential because, as yet, there are no animal paradigms that are directly predictive of therapeutic response to candidate medicines in humans. Also, human laboratory studies can include the examination of actual or surrogate experimental drug taking and the measurement of response to putative therapeutic agents, and can enable the characterization of adverse events, toxicology, and dose profiling [24] and, sometimes, the initial determination of efficacy [26, 36, 42] for candidate therapeutic medications.

Human laboratory procedures usually are split into those that measure conditioned craving, and others that ascertain self-administration of alcohol or other drugs. An important problem with studying one or the other of these procedures is that human drug-taking behavior incorporates both of these components.

In the human laboratory, there are three important challenges that can limit the utility of direct self-administration procedures to quantify alcohol or drug reinforcement, and any interactive effects with a candidate therapeutic medication. First, self-administration of alcohol or drugs in the human laboratory can have limited parametric validity in humans since the number of administrations is restricted by the need to avoid intoxication or toxicity in combination with candidate medications. Although there have been attempts to overcome such issues by providing small amounts of alcohol or drugs under scheduled responding paradigms, the lack of context within these settings (i.e., humans do not in natural settings self-administer alcohol or drugs on completion of fixed operant tasks such as lever-pressing) makes extrapolation to the clinical condition difficult. Second, with respect to alcohol self-administration, the scaling of pharmacobehavioral response to small amounts of alcohol is not entirely linear as a break point is reached between its stimulant and sedative effects, which can vary considerably among individuals. Thus, because of this biphasic pharmacological effect of alcohol, the timing of experimental procedures needs to be relatively precise, and the trend has been to concentrate efficacy testing of candidate therapeutic medications within the narrow time band of the ascending part of the alcohol effects dose curve. Third, experiments using stimulant drugs that are administered intravenously or intranasally can only be done with small, pharmacologically relevant doses, and repeated dosing in the same day, or even over several days, is constrained by safety concerns to limit exposure. Thus, human laboratory studies are not designed to be "real world" studies or truncated clinical trials but a mechanism for establishing safety and determining initial efficacy.

A relatively under-utilized but stronger strategy in the design of human laboratory studies is to combine conditioned craving response with behavioral measurement of reinforcement through choice procedures over monetary reward and delayed discounting (e.g., see [26]). The use of delayed discounting measures also enables avoidance of the restriction posed by self-administrating alcohol or drugs during the experiment, which can itself be a confounder of contemporaneous measurement of other parameters such as mood and cognition, but postpones this to afterwards. Recently, our group developed a further enhancement of this technique by providing serial exposures to this combined paradigm over several days rather than at a single time point. This allows the acute effects to be measured on the first day, which can then be compared with the serial measurements of repeated exposures over several days. The repeated-exposure component of this paradigm tests the ability of the candidate therapeutic medication to decrease alcohol or drug taking over time, and is hypothesized to be more predictive of results that would be expected from a clinical trial.

Human laboratory studies can couple the measurement of pharmacobehavioral aspects with other methods of segregating individual

response, such as molecular genetics [1] (including genome-wide association studies) and functional neuroimaging. Indeed, there are now well-established human laboratory paradigms for conducting pharmacobehavioral studies whilst performing simultaneous neuroimaging [35]. These additional techniques bolster the information from human laboratory studies by providing a greater understanding of the relationship between behavior and the site-specific effects of candidate medications.

As proposed in animals, a national network of human laboratory researchers should be established to "fingerprint" the pharmacobehavioral response of the interaction between the abused substance and the candidate therapeutic medication.

In recent years, there has been a decline in neuro-hormonal studies examining the impact of stress on pharmacobehavioral response to abused substances and their interaction with candidate medications. Neuro-hormonal probes for examining the monoamine system are used infrequently, and the delineation of effects by menstrual cycle and other hormonal changes across the life span needs greater study.

Future human laboratory studies and designs will have to address the issue of testing medication combinations for the treatment of substance dependence. The unique capabilities of human laboratory studies to examine contemporaneously both pharmacodynamic and pharmacokinetic effects [19] of abused drugs and their potential interactions with candidate medications will need to be harnessed further.

Clinical Trials

Randomized, double-blind, placebo-controlled clinical trials are the "gold standard" for determining the efficacy of candidate medications for the treatment of substance dependence. Nonetheless, this is not a perfect technology in the substance dependence field, and certain challenges and controversies remain. Some of these challenges are unique as to whether the field of study relates to treatment for alcohol or drug dependence. The alcohol field will be used as the illustrative example to highlight these challenges, with some additional references provided in the area of drug dependence.

It has become increasingly obvious that alcohol dependence is a heterogeneous disorder [20]; yet, this is not captured by diagnostic criteria including the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [2] or the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [50]. There is, therefore, a wide variation in pathophysiology and response to candidate therapeutic medications among individuals who meet the diagnostic criteria for alcohol dependence. For instance, it has been shown that medications with different actions on the serotonergic system are not efficacious within the same subtype of alcoholic. Serotonin reuptake inhibitors appear to be efficacious among alcohol-dependent individuals with a late-onset or Type A-like disease characterized by an onset of problem drinking after the age of 25 years, low familial loading for disease, and a range of anxiety- and mood-related symptoms [38]. In contrast, Johnson and colleagues have shown that the serotonin-3 receptor antagonist, ondansetron, is efficacious in treating early-onset or Type B-like alcoholism characterized by an onset of problem drinking before the age of 25, high familial loading for disease, and a range of impulse-dyscontrol behaviors [21]. These observations have now been developed into a conceptual understanding by which alcoholic subtypes can be segregated by allelic variation at the serotonin transporter that is differentially responsive to serotonergic medications [13]. Indeed, the results of the first large prospective pharmacogenetic study in the alcoholism field based on this serotonin transporter hypothesis are awaited eagerly. Conceptually, another approach would be to determine whether alcohol-dependent individuals can be additionally characterized through intermediate behavioral or pharmacological phenotypes, or both [9]; then, it might be possible to understand more accurately the basis of individual response to

drinking, and to increase the likelihood that we can tailor treatment to the subpopulation most likely to respond to that strategy.

Retrospective pharmacogenetic analyses have been done in the alcoholism field, particularly with respect to whether allelic variation in the OPRM1 gene predicts treatment response to naltrexone. Whilst some have found an association between allelic variation at the OPRM1 gene and therapeutic response to naltrexone [4], others have not [10]. Further studies are, therefore, needed to determine whether there is a relationship between polymorphisms of the OPRM1 gene and therapeutic response to naltrexone.

Other promising compounds are being studied in the treatment of alcohol dependence. Notably, these include baclofen, the neurokinin-1 receptor antagonist LY686017, and corticotrophin-releasing factor antagonists—all of which can be envisioned as modulators of stress response to alcohol dependence and its cessation (for a review, see Chapter "Pharmacotherapy for Alcoholism and Some Related Psychiatric and Addictive Disorders: Scientific Basis and Clinical Findings"). These medications expand the concept that the extended amygdala has an important role in the modulation of alcohol reinforcement in the cortico-mesolimbic dopamine system [30]. The results of phase II clinical trials with these medicines are awaited eagerly.

An important conundrum in the alcoholism field that appears to be resolving is the place of adjunctive psychotherapy in medication trials. Primarily in the United States, but also in other countries, there has been great effort in standardizing psychosocial treatment with respect to both its content and its delivery. While there is growing acceptance that psychosocial treatment should be viewed in terms of dose response, in much the same way as pharmacotherapy [18], it is curious that this concept is often considered as a unipolar paradigm—more psychosocial treatment being associated with greater or more prolonged therapeutic effect, or both. An important and seemingly forgotten lesson of Project MATCH is that there might be a "ceiling" of psychosocial treatment response [39]. For instance, it has not been proven in pharmacotherapy studies involving different intensities of psychosocial treatment that the maximum therapeutic response is always seen when the maximum level of the medication is combined with the most intensive psychosocial treatment. Additionally, if both the psychosocial and pharmacological treatments have a dose-response function that can interact, is it not reasonable to predict that some combinations might be not only ineffective but, actually, counter-therapeutic? What is emerging is that the "dose" of psychosocial treatment needed as an adjunct to a candidate therapeutic medication appears to be modest. This was demonstrated clearly in the COMBINE study, where the briefer medication management, compared with the high-intensity cognitive behavioral intervention, was more efficacious in combination with naltrexone [3]. Strikingly, in the COMBINE study, those assigned to no medication but just the high-intensity cognitive behavioral intervention had a worse outcome than those who received placebo plus medication management [48]. Furthermore, the pivotal studies that demonstrated the efficacy of topiramate for the treatment of alcohol dependence were all done using an even briefer intervention that maximizes participation and pill-taking compliance—brief behavioral compliance enhancement treatment [22, 28]. An important advantage of brief interventions like brief behavioral compliance enhancement treatment is that they can be delivered in about 10–15 min, which might make the findings from controlled trials more generalizable to clinical practice [23] (see also Chapter "Brief Interventions for the Treatment of Alcohol or Other Drug Addiction"). Hence, there is no current support for using intensive psychotherapy rather than a brief intervention as an adjunct in a pharmacotherapy trial.

Other conundrums remain in the development of medications for the treatment of alcohol dependence, some of which also are nearing a resolution. For example, there is growing acceptance that abstinence is an important, but not the only, valid endpoint in the treatment of alcoholism. Advocating the harm reduction model,

the present author has demonstrated the utility of entering individuals into clinical trials not after a brief period of abstinence, which was the traditional model, but whilst drinking actively [25]. Naturally, the most appropriate endpoint from such a paradigm would be a reduction in heavy drinking. This endpoint is now accepted as valid by the Food and Drug Administration, which is at present working collaboratively with academia and industry to refine exactly how this should be quantified. Hence, this approach promises to expand the array of potential medicines that can be used in the treatment of alcoholism beyond those that are simply designed to prevent relapse following a period of abstinence.

Pressure to deliver more efficacious medications for treating alcohol dependence has rekindled debate about whether there are proxies for large and time-intensive clinical trials. Such suggestions have included conducting smaller studies, often of inadequate sample size, to determine a "signal" that would encourage more elaborate clinical testing. Such approaches have more generally been used in testing candidate medications to treat drug rather than alcohol dependence and, to date, have proved fruitless and perhaps even more time-consuming. This is because positive "signals" from smaller studies frequently fail to be confirmed by larger clinical trials. Perhaps a more powerful strategy for the alcoholism field would be to develop a national network of clinical trials investigators such that the individual obligation to each site for testing a medication is lessened by dividing the workload across multiple sites, thereby increasing the scientific and practical efficiency of the medications development process. The National Institute on Alcohol Abuse and Alcoholism is, at present, using such a network to develop new medicines for the treatment of alcoholism.

Challenges remain in understanding the role of the placebo response in developing medicines to treat alcohol dependence. For instance, it is evident from most clinical trials that there is a high placebo response. Although this high placebo response is usually considered the "nuisance" that can mask the differential effect of active medication over placebo treatment against a platform of psychosocial intervention, the real problem associated with the failure to find clinical efficacy with most existing medications has been their small therapeutic effect size. Hence, even with current clinical trial paradigms, a "floor" effect in terms of the reduction in heavy drinking or abstinence rates is typically not reached, and there is ample room for moderately to highly efficacious medication treatments in adequately powered trials to demonstrate clinical efficacy. Nevertheless, two prevailing ideas that are currently being studied to reduce the placebo effect in clinical trials are to recruit individuals with much higher levels of alcohol consumption or to decrease the high degree of "reactivity" in clinical trials due to the many non-specific factors such as the high amount of personal attention and intensive questioning through experimental measures incorporated into their design. Future contemporary clinical trials in the alcoholism field will need to use more focused and economical clinical trial designs. Further study of the factors that determine the magnitude of the placebo response in clinical trials for alcohol dependence is needed to determine how these benefits can be harnessed to improve the effectiveness of candidate medicines in clinical practice [37].

Perhaps the most difficult challenges in the development of new medicines for the treatment of alcoholism are not entirely academic. An important roadblock occurs with the transfer of basic science discoveries into human testing. Conducting the studies required for an Investigational New Drug Application for promising preclinical compounds can be problematic for academic researchers and small companies because of the high cost that is involved and the level of expertise needed. Another important challenge lies in establishing public–private partnerships that will allow for a more comprehensive effort to discover and develop safe, effective medications. If successful, these partnerships will create more opportunities and choices for medications development. Networking among academia, industry, and governmental bodies (including the Food and Drug

Administration) needs to be coordinated more efficiently and focused to streamline the development process. Indeed, the Food and Drug Administration should be encouraged to play a more active role in not only the development of endpoints but also laying out clearly the essential benchmarks for registration trials. Important strides need to be made in the development of biomarkers, and surrogate endpoints that objectively indicate clinical success for candidate compounds would make the medications development process more predictable. Although progress has been made in identifying biomarkers of alcohol consumption, there are no ideal biomarkers (or surrogate endpoints) currently available [32]. Recently, advances in high-throughput technologies in genomics, proteomics, and metabolomics have created new, exciting opportunities for discovering and developing novel biomarkers. Exploring multiple genes, RNAs, proteins, and metabolites as well as a combination of markers might provide a characteristic pattern that indicates alcohol consumption, alcohol-induced organ damage, or both, and can be used subsequently to predict the efficacy of candidate compounds during clinical trials. Finally, an important hurdle has been the difficulty in broadly disseminating and implementing medications proved to be effective in clinical trials. Currently, only a small percentage of individuals receiving alcoholism treatment are prescribed medications for the disorder [33]. This is a serious problem that needs a concerted effort to educate health providers and the general public to increase the demand and utilization of efficacious medicines to treat alcoholism.

In the field of drug dependence, progress in identifying efficacious medicines has met with mixed success. In recent years, perhaps the most successful program has been the development of smoking cessation agents. Building upon the success of the nicotine patch and analogous compounds, there has been the development of bupropion and, more recently, varenicline as efficacious anti-smoking agents. Indeed, a recent editorial concluded that the medication-based treatments for smoking cessation had become so well established that there was no longer an excuse not to seek treatment [16]. A potentially important advance is the development of vaccines that will sequester nicotine in the bloodstream and prevent it from reaching the brain; however, these compounds are still a few years from reaching the market, and important technical problems remain to be solved (see Chapters "Nicotine" and "Nicotine").

Despite decades of scientific effort, no medications have been approved by the Food and Drug Administration for the treatment of either cocaine or methamphetamine dependence. The search for medicines to treat cocaine dependence has been particularly frustrating, especially as it appeared somewhat tantalizing that the solution would be to develop anti-dopaminergic agents. As detailed earlier, this approach of using direct anti-dopaminergic agents has failed, as have programs that have attempted the opposite—developing agonists of catecholamine function to provide a less stimulating or reinforcing "substitute" [15]. One avenue that appears promising in the cocaine dependence field has been the success of topiramate in an early clinical trial [29]. Results of large-scale phase II-type studies are, however, awaited to determine whether topiramate's efficacy in treating cocaine dependence can be established. Also, there is an intriguing signal for ondansetron as a possible therapeutic agent for treating cocaine dependence [27], and this lead is currently being followed up in an ongoing National Institutes of Health–funded study. Unfortunately, the initial promise of modafinil and disulfiram is unlikely to be realized on account of their failure due to a lack of efficacy and concerns related to toxicity, respectively, for this indication. There is some promise that a vaccine approach might yield some success; however, much needs to be done to improve its efficacy (for a review, see Chapter "Pharmacotherapy of Cocaine Addiction").

Many challenges remain in the development of medications to treat cocaine or methamphetamine dependence. Promising findings regarding the ability of candidate medications to decrease cocaine or methamphetamine intake or related behaviors in animals have not led to successful efficacy studies in clinical trials. Indeed, over 50 different candidate medications have been tested without a clear "signal"

predictive of efficacy for these indications (for a review, see Chapters "Pharmacotherapy of Cocaine Addiction" and "Methamphetamine").

The lack of concordance between animal studies and human trials is rather puzzling since preclinical studies have formed the backbone for understanding the neuropharmacological basis of addiction to stimulants and the basis for the selection of candidate medications. Most authorities have interpreted this lack of concordance as evidence that animal studies need to mimic the human condition more closely to have greater predictive value. Included in this argument is the proposal to validate studies done in lower animals (e.g., rodents) with experiments conducted in nonhuman primates. In gainsay, others have proposed that despite its face validity, the greater anthropomorphization of animal behaviors is the reason for the lack of concordance, and more useful models would be those that encompass greater construct validity. New animal models that enhance both the face and construct validity of cocaine- or methamphetamine-taking behavior as compared with the human condition continue to be developed.

One idea toward model building in the development of medications to treat cocaine or methamphetamine dependence would be to perform contemporaneous pharmacobehavioral studies in a variety of animal models and humans, once the toxicity profile of the candidate medication is known. Computational mathematical methods can then be used to determine the salient factors predictive of different "fingerprints" of response to the candidate medications.

Another approach toward finding an efficacious medicine to treat cocaine or methamphetamine dependence has been to embark on a search for candidate medications in the hope of finding an agent with a strong therapeutic effect. Critics of this approach have argued that this has led to an interminable search for a "magic bullet", which has failed to yield any tangible results. Also, such a process does not allow for the systematic accumulation of new knowledge upon which to obtain better clues as to why an agent might have failed in the clinic. Remarkably, this strategy has not enabled model building that could be achieved by testing medication combinations. Medication combinations have the potential advantage of at least a summation of therapeutic effects, and a more sustained duration of action, especially for compounds that act through ion channels [15].

Plausibly, individuals dependent on cocaine or methamphetamine, like alcohol, also might constitute a heterogeneous group. Few clinical studies have explored the possibility of phenomenological subtypes of the disease or an examination of response by molecular genetic or other biological differences. Future studies that explore the possibility of differential response to different subtypes of cocaine or methamphetamine taking are needed urgently.

An intriguing possibility for the treatment of cocaine dependence is the development of a potential vaccine. This vaccine is designed to tag succinylnorcocaine covalently with cholera toxin-B-subunit protein, to which the individual develops an antigenic response and the formation of antibodies. These antibodies bind to the antigenic complex in the bloodstream, thereby causing their sequestration and blockade from entering the brain. In a recent study, a clinical trial with the cocaine vaccine showed promising results in those with high antibody titres [34]. More work is, however, needed to develop a more robustly effective vaccine and to overcome the complexity by which it needs to be administered, especially to a population of poorly motivated, cocaine-dependent individuals (for a review, see Chapter "Pharmacotherapy of Cocaine Addiction"). Nevertheless, this is an approach that appears to be worth pursuing.

In the field of opiate dependence (including those opiates initially prescribed to treat a painful disorder), the agonist replacement or "substitution" approach has had much success with developing efficacious medicines. Notable examples include the use of methadone, levacetylmethadol, and suboxone (a combination of buprenorphine and naloxone). Since these medications are weak opiates, they do have to be used with care under strictly regulated schedules for their administration as they also have the potential to be habit forming or addictive. Hence, there is presently a search for non-opiate-based medications that can act as

pharmacological modulators of the neurotransmitters involved with the expression of opiate reinforcement. Furthermore, there is a need to widen access to treatment for opiate dependence, especially in semi-urban or rural communities in the United States.

Summary

The field of medications development for addictions has had many successes, and there are both important opportunities and challenges that lie ahead. Undoubtedly, these scientific advances have occurred against a background of exploding knowledge in cellular and structural biology, the neurosciences, neuroimaging, molecular genetics, and the behavioral sciences. Integrating these fields of knowledge to develop viable targets for medications development has been successful in several areas, including those that improve drinking outcomes and aid smoking cessation. Although no medication has been approved for the treatment of cocaine dependence, there are promising leads with newer agents, and a potentially useful vaccine remains in development. Developing better predictive models in animals, and in the human laboratory, that can predict therapeutic response in the clinic remains the vista that we all seek.

Acknowledgments I thank the National Institute on Alcohol Abuse and Alcoholism for its support through grants 5 R01 AA010522-14, 5 R01 AA012964-06, 5 R01 AA014628-04, and 5 R01 AA013964-05; the National Institutes of Health for its support through University of Virginia General Clinical Research Center Grant M01 RR00847, and Robert H. Cormier, Jr. and Ann Richards for their assistance with manuscript preparation.

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B.A. Johnson (ed.), *Addiction Medicine*, DOI 10.1007/978-1-4419-0338-9,

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