Addiction Special Offer

Expires July 31, 2018

This Special Offer includes:

Methamphetamine Use Disorder
Cannabis Use, Abuse, and Dependence
Cocaine Use Disorder

NetCE
Continuing Education

Methamphetamine Use Disorder

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty
Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners Disclosure
The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use methamphetamine.

Accreditations & Approvals

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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NetCE is recognized by the New York State Education Department's State Board for Social Work as an approved provider of continuing education for licensed social workers #SW-0033.

This course is considered self-study, as defined by the New York State Board for Social Work. Materials that are included in this course may include interventions and modalities that are beyond the authorized practice of licensed master social work and licensed clinical social work in New York. As a licensed professional, you are responsible for reviewing the scope of practice, including activities that are defined in law as beyond the boundaries of practice for an LMSW and LCSW. A licensee who practices beyond the authorized scope of practice could be charged with unprofessional conduct under the Education Law and Regents Rules.

NetCE is recognized by the New York State Education Department's State Board for Mental Health Practitioners as an approved provider of continuing education for licensed mental health counselors. #MHC-0021.

This course is considered self-study by the New York State Board of Mental Health Counseling.

NetCE is recognized by the New York State Education Department's State Board for Mental Health Practitioners as an approved provider of continuing education for licensed marriage and family therapists. #MFT-0015.

This course is considered self-study by the New York State Board of Marriage and Family Therapy.

This course has been approved by NetCE, as a NAADAC Approved Education Provider, for educational credits, NAADAC Provider #97847. NetCE is responsible for all aspects of their programming.

A complete Works Cited list begins on page 28.

Mention of commercial products does not indicate endorsement.

NetCE is approved as a provider of continuing education by the California Consortium of Addiction Programs and Professionals (CCAPP). Provider Number 5-08-151-0618.

NetCE is approved as a provider of continuing education by the California Association for Alcohol/Drug Educators. Provider Number CP10 889 H 0620.

Designations of Credit

NetCE designates this enduring material for a maximum of 5 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 5 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

NetCE designates this continuing education activity for 5 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 1 pharmacotherapeutic/pharmacology contact hour.

AACN Synergy CERP Category A.

Social Workers participating in this intermediate to advanced course will receive 5 Clinical continuing education clock hours.

NetCE designates this continuing education activity for 2 NBCC clock hours.

NetCE designates this continuing education activity for 5 continuing education hours for addiction professionals.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 11/21/2021); California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Iowa, Provider #295; Kentucky, Provider #7-0054 (valid through 12/31/2019); South Carolina, Provider #50-2405.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

Methamphetamine use has risen alarmingly, reaching epidemic proportions in some regions. The purpose of this course is to provide a current, evidence-based overview of methamphetamine abuse and dependence and its treatment in order to allow healthcare professionals to more effectively identify, treat, or refer patients who use methamphetamine.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the history and background of amphetamine use.
2. Discuss the epidemiology and demographics of methamphetamine use, including risk factors.
3. Describe the pharmacology of methamphetamine and the neurobiology of stimulant addiction.
4. Discuss the use characteristics of methamphetamine abuse.
5. Review the acute and chronic effects of methamphetamine use, including effects on cognitive and neurobiologic function in abstinent users.
6. Describe comorbid conditions associated with methamphetamine abuse and dependence.
7. Identify signs and symptoms of methamphetamine withdrawal syndrome.
8. Outline possible treatment modalities for methamphetamine dependence and comorbid conditions, detailing implications for special populations, the importance of 12-step programs, and interventions for non-English-proficient patients.
9. Review the prognosis for those dependent on methamphetamine.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

In the past few decades, the manufacture and abuse of methamphetamine in the United States has gained increased attention. The admissions rates for treatment of methamphetamine-related disorders have ballooned alarmingly in some areas, particularly in rural or frontier areas, causing public health concerns. As a result, it is important that healthcare professionals have a solid knowledge of the effects and appropriate treatment of methamphetamine abuse and dependence. Research regarding effective treatment modalities for methamphetamine-dependent patients has generally been limited to those used in the treatment of dependence to other stimulants, such as cocaine. Because the use characteristics and demographics associated with methamphetamine use are unique, these special populations' needs should be taken into consideration in both the evaluation and treatment processes.

HISTORY AND BACKGROUND OF AMPHETAMINES AND METHAMPHETAMINE

Amphetamines are a group of central nervous system (CNS)-stimulating drugs that include dextroamphetamine (Dexedrine), methamphetamine (Methedrine, Desoxyn), mixed amphetamine salts (Adderall), and amphetamine (Benzedrine) [1]. Amphetamine and methamphetamine are structurally related and very similar; both act by stimulating the release of central and peripheral monoamines, such as dopamine, serotonin, and norepinephrine, and both exhibit psychomotor, cardiovascular, anorexigenic, and hyperthermic properties. However, methamphetamine has greater CNS action than peripheral nervous system action and is more potent and longer lasting in its subjective effect [2]. Methamphetamine rapidly and efficiently crosses the blood-brain barrier because it is highly lipid-soluble [3].

Amphetamine and methamphetamine were originally synthesized in Japan in 1893 for use as substitutes for the plant-derived ephedrine, which has been used for centuries in Asia to treat respiratory conditions [1; 4]. Widespread use began in World War II (WWII), when American, German, and Japanese soldiers utilized the drugs to increase endurance and performance and to counter fatigue and hunger [4]. In addition to its military use, methamphetamine was given to Japanese factory workers to increase productivity and diminish the need for sleep and was sold over-the-counter. Immediately following WWII, the Japanese army and pharmaceutical industry made its surplus methamphetamine widely available, flooding the civilian market and resulting in the first methamphetamine epidemic (1945–1957). By 1954, an estimated 2 million Japanese were addicted to intravenously administered methamphetamine, with roughly 10% exhibiting symptoms of methamphetamine-induced psychosis [1; 5]. In response to the increase in crime and homicides linked to methamphetamine use, the Japanese government enacted the Stimulants Control Law and the Mental Health Act, enacting strict laws and permitting the involuntary treatment of methamphetamine abusers. During the second Japanese methamphetamine epidemic (1970–present), use spread to a wider cross-section of Japanese society, including blue-collar workers, students, housewives, and office workers. The demographics of Japanese methamphetamine abusers are somewhat different from those in other regions in that persons 35 years of age and older comprise the majority of users [5]. Widespread methamphetamine use persists in Japan, with methamphetamine-related crime accounting for 86% of all drug arrests in 2011 [6]. However, methamphetamine abuse in Japan is modest compared to Western countries [140].

In the United States, medical use of amphetamines began in 1932, when the American Medical Association approved amphetamine (marketed as Benzedrine) as a treatment for asthma and a variety of other medical and psychiatric conditions, including alcoholism, narcolepsy, attention deficit hyperactivity disorder (ADHD), appetite suppression, schizophrenia, morphine addiction, smoking cessation, low blood pressure, radiation sickness, and even intractable hiccups [1; 5]. Amphetamines were available over-the-counter in the United States as tablets until 1951 and as inhaler ingredients until 1959. Prescriptions for amphetamines peaked in 1967, when 31 million prescriptions were written for amphetamines for indications such as obesity and depression [5]. Until this period, the illicit market was comprised mainly of drugs diverted from pharmaceutical companies, distributors, and physicians. In 1962, amid growing concern over the abuse of amphetamine/methamphetamine, the U.S. Food and Drug Administration (FDA) launched an education campaign [1].

Until the 1960s, methamphetamine was widely available in the United States under the brand names Desoxyn and Methedrine. A liquid formulation became widely popular in the 1960s as a treatment for heroin addiction, leading to an emerging pattern of abuse among intravenous (IV) users. Motorcycle gangs in the San Francisco Bay area exploited the void created by stricter regulation and the ultimate withdrawal from the market of prescription methamphetamine preparations in the early to mid-1960s, quickly spreading and controlling methamphetamine use on the West Coast [5]. The term "crank" stems from biker gangs' storage of methamphetamine in the crank cases of their motorcycles during transportation and distribution [4].

In the 1980s, law enforcement focus on the biker groups, coupled with tighter precursor restriction and the emergence of a simpler, ephedrine reduction-based recipe, shifted the center of methamphetamine distribution to San Diego and induced greater involvement of Mexican criminal elements. During the same period, Hawaii began to see an epidemic of highly potent dextromethamphetamine hydrochloride ("ice") supplied by illicit labs in Southeast Asia, spread by the extended kinship networks comprised of families, co-workers, and neighborhoods [5].

Before the current methamphetamine epidemic, which began in the late 1980s, the chemical phenyl-2-propanone (P2P) was the primary precursor for domestically produced methamphetamine [1]. The subsequent use of ephedrine and pseudoephedrine was simpler, more efficient, and yielded a higher concentration of the psychoactive D-isomer (dextromethamphetamine). By the mid-1990s, domestic and Mexican "superlabs," producing 10-plus pounds of high-purity methamphetamine within a 24-hour period, began competing with the more numerous small-scale labs [3]. Many of the precursor substances for these operations, such as pseudoephedrine, originate from Southeast Asia and Central Europe and are supplied through international trafficking organizations. The massive amount of money generated from such distribution and sales leaves the United States and is laundered by criminal organizations [1].

The methamphetamine market has been observed to adapt to manufacturing and distribution disruptions, most notably precursor regulation, at every stage of the epidemic. Likewise, quantifications of the costs of such policy interventions are needed, including regulatory burdens and limits on the availability of legitimate products. Supply-side expenditures may not be worth the benefits over time if regulatory costs remain constant while drug sellers adjust to precursor control with relative ease [7].

EPIDEMIOLOGY AND DEMOGRAPHICS OF USE

The widespread use of methamphetamine stems largely from its potential to produce euphoria, reduce fatigue, enhance performance, suppress appetite, and induce weight loss, coupled with multiple interacting social, biologic, cultural, and psychologic factors [8]. Unlike cocaine and heroin, which are plant-derived and whose synthesis is complex, methamphetamine is easily prepared from simple chemical precursors. The more recently available and highly potent "ice" is created from ephedrine by reduction of its beta-hydroxyl group to form methamphetamine hydrochloride [9].

While national trends are showing declines, regional use of methamphetamine continues to vary widely, with the strongest effects felt in Alaska, the West, the Southwest, and parts of the Midwest (particularly Iowa, Oklahoma, Missouri, and Nebraska), with rural areas being the most severely impacted [10; 12; 13]. During the first half of 2012, treatment admissions for methamphetamine use were highest in Hawaii and San Diego, second highest in San Francisco, and third highest in Denver and Phoenix [11]. The higher use of methamphetamine in Western states is also reflected by the number of persons under its influence who come into contact with law enforcement. According to the 2016 National Drug Threat Assessment compiled by the U.S. Drug Enforcement Administration (DEA), methamphetamine was reported as the greatest drug threat in the Southwest region (71%), followed by West Central (56%), Pacific (50%), and Southeast (43%). The percentages declined in areas further east [12].

The number of current users 12 years or older increased 61% between 2010 and 2014, while the number of new users 12 years or older increased 71% over the same period [12]. A 2014 survey found that approximately 1.3 million individuals 12 years of age or older had used the drug in the past year and that 569,000 were current users, and although this number is a 61% increase from 2010, it is near average for the past two decades [12]. According to data from the 2016 Monitoring the Future (MTF) survey, which examines adolescent drug use and attitudes, approximately 0.5% of 8th, 10th, and 12th graders had used methamphetamine in the past year [17]. This indicates that high school-age students are using methamphetamine less than they did five years ago. Overall, use of methamphetamine by adolescents has declined significantly since 1999, when the drug was first added to the MTF survey [17]. However, illicit use of other amphetamines is significantly higher among 8th, 10th, and 12th graders, with 3.5%, 6.1%, and 6.7% annual prevalence, respectively.

Data from the Drug Abuse Warning Network (DAWN), which collects nationwide information on drug-related episodes from hospital emergency departments, indicates that methamphetamine accounted for nearly 103,000 emergency visits in 2011, a decrease from 132,576 visits reported in 2004 [11]. Nationwide, admissions to treatment programs for any methamphetamine abuse have fluctuated but averaged approximately 130,000 between 2003 and 2013 [12].

Lower prices, higher purity, increased production, and increased flow of methamphetamine across the southwest border has contributed to rising domestic availability. Nevertheless, methamphetamine demand and use has stabilized and the number of new and current users has overall remained statistically similar from 2003 to 2013 [12]. Final DEA data from 2016 indicates that methamphetamine lab seizures decreased from 10,522 in 2010 to 4,595 in 2015; the majority were small-scale "laboratories" [12]. Between 2008 and 2012, the seizures of methamphetamine crossing the southwest border of the United States increased nearly five-fold (from 2,282.6 kg to 10,636.5 kg), as Mexican superlabs produced the preponderance of the drug [12]. The gram price of methamphetamine continues to fall and the average purity remains high [12].

The epidemic of methamphetamine use in Hawaii has received considerable attention. Use of methamphetamine in Hawaii is characterized by several aspects that contribute to the rather unique quality of the epidemic. Highly pure "ice" constitutes almost all of the available methamphetamine, and the Hawaiian epidemic is among the longest in duration of any region in the United States. Young, single mothers make up a large proportion of methamphetamine users; it is reported that 85% of child abuse cases in the state involved methamphetamine use in one or both parents [14]. Probably more than with any other population, methamphetamine is distributed through the extended kinship network, with multiple generations of methamphetamine users within the same family not uncommon [15]. Approximately 14% of teens 12 to 17 years of age and 15% of young adults 18 to 24 years of age report having a family member who has been treated for methamphetamine use [16]. Due to law enforcement and awareness campaign efforts, such as the Hawaii Meth Project, there is some indication that the epidemic in the state is stabilizing [16].

Although traditionally used by college students and white, working-class males 18 to 34 years of age on the West Coast, the demographics are now much broader. Native American and Hispanic persons constitute a growing population of methamphetamine users; however, relatively few African Americans are regular users of methamphetamine [1]. Additionally, the 2015 Youth Risk Behavior Surveillance found that more Hispanic students (4.4%) had ever used methamphetamine one or more times compared to white (2.1%) or black (2.6%) students [18]. Female students (2.3%) are slightly less likely to have used methamphetamine than male students (3.6%), which follows other national statistics showing slightly less prevalent use among women. However, the total number of students ever having used methamphetamine has decreased from 1999 (9.1%) to 2015 (3.0%), which corresponds with information showing the latest spike of increased use occurring primarily among individuals older than 25 years of age.

RISK FACTORS FOR METHAMPHETAMINE USE DISORDER

Data from a large community survey of drug abuse conducted from 1995 to 1998 found the factors most robustly associated with progression from stimulant use to stimulant dependence were early onset of stimulant use, multiple-substance abuse, and daily cigarette smoking between 13 and 17 years of age [19]. Contributory and risk factors for methamphetamine abuse include the presence of depression, ADHD, a desire to enhance sexual pleasure, the manic phase of bipolar disorder, obesity, childhood conduct disorder, and adult antisocial personality disorder [20].

Several motivational factors for methamphetamine use have been identified. In comparison to other stimulants (i.e., cocaine), methamphetamine carries the perception of producing a better, cheaper, and more satisfying drug effect. Users are also initially attracted to methamphetamine out of a desire to cope with mental illness, emotional trauma, and/or mental distress; stay awake longer; enhance sexual experience and performance; or reduce weight [21].

PHARMACOLOGY

Methamphetamine stimulates the release and blocks the presynaptic reuptake of serotonin, dopamine, and norepinephrine [4; 22]. It is metabolized at a much slower rate than some other stimulants, such as cocaine [5]. As a result of methamphetamine's 12-hour half-life, inexpensive synthesis, and abundant supply, abusers spend 25% to 30% as much as cocaine-dependent persons on their drug of choice [23].

Purity of methamphetamine is typically very high, at 60% to 90%. It is predominantly d-methamphetamine, which has greater CNS potency than the l-isomer. Common doses of abuse are 100 to 1,000 mg/day, and chronic users on a binge may take up to 5,000 mg/day [24].

Single doses of amphetamines, including methamphetamine, improve performance across several dimensions of cognitive function in humans [4]. Behaviorally, an acute dose of methamphetamine acts by stimulating the release of newly synthesized catecholamines, including serotonin, dopamine, and norepinephrine, brain chemicals that mediate pleasure and reward, mood, sleep, and appetite, and that block their presynaptic re-uptake [9]. Dopamine transmission levels in the synaptic cleft are primarily increased through inhibition of the dopamine transporter, essentially reversing the direction of these transporters [4]. Methamphetamine also acts on other presynaptic sites, including storage vesicles and monoamine oxidase (MAO), the enzyme that breaks down dopamine and norepinephrine to inactive metabolites [9].

Methamphetamine is rapidly absorbed from the gastrointestinal tract. The drug is metabolized by aromatic hydroxylation, *N*-dealkylation, and deamination, primarily in the liver. For the most part, methamphetamine is excreted in urine and is dependent on urine pH; alkaline urine will significantly increase the drug half-life. The majority (62%) of an oral dose is eliminated in the urine within the first 24 hours, with about one-third as intact drug and the remainder as metabolites [24]. Seven metabolites specific to methamphetamine use have been identified in users' urine.

Inhibitors of the 2D6 isoenzyme can decrease the rate of methamphetamine elimination, while potential inducers could increase the rate of elimination [24]. Approximately 10% of white individuals are deficient of this isoenzyme, making them ultrasensitive to the effects of methamphetamine because they lack the ability to metabolize and excrete the drug efficiently [9]. Following oral administration, peak methamphetamine concentrations are seen in 2.6 to 3.6 hours, and the mean elimination half-life is 10.1 hours (range: 6.4 to 15 hours). The amphetamine metabolite peaks at 12 hours, or slightly longer following IV injection. Methamphetamine is metabolized to amphetamine (active) and p-OH-amphetamine and norephedrine (both inactive) [24].

NEUROBIOLOGY OF STIMULANT ADDICTION

Use of stimulant drugs, such as methamphetamine, has the potential to create profound dependence and a seeming inability to remain abstinent, in part because these drugs trigger brain mechanisms that reinforce and reward the basic behaviors of human survival (e.g., food, water, sexual activity) [25]. Reward and reinforcement are essentially synonymous terms that refer to "the quality of drugs to produce effects that make the user wish to take them again," a concept of central importance in the context of the development and maintenance of drug dependence (i.e., addiction) [26].

Dopamine is the neurotransmitter responsible for mediating motor movement, reward, motivation, and cognition. Dysregulation in brain dopamine systems can result in addictive disorders, Parkinson disease, and schizophrenia [27]. Psychostimulant drugs, or stimulants, are powerful modulators of dopamine activity that share the common mechanism of increasing synaptic dopamine concentration. However, stimulants are grouped into two distinct classes based on mechanism of action. The first group consists of the uptake blockers, which include cocaine and methylphenidate (MPD; Ritalin). The second group is the releasers, which include the amphetamine analogs methamphetamine, dextroamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") [27].

The different mode of action of these two classes of drugs on monoamine transporters influence dopaminergic signaling and result in important differences in physiologic and functional impact [27]. Generally speaking, the uptake blockers bind and inhibit dopamine transport through the dopamine transporter (DAT); inhibited DAT activity results in elevated extracellular dopamine levels, which in turn stimulates dopamine receptors, causing vesicles to move to the cytosol [27]. In contrast, the releasers elevate extracellular dopamine levels through the disruption of vesicular pH gradients,

redistributing vesicular dopamine into the cytoplasm and releasing dopamine through reverse transport and/or channel-like DAT activity [28; 29].

Four structurally and functionally distinct dopamine neuronal pathways exist in the adult brain [30]:

- The neostriatal pathway, which originates in the substantia nigra and extends to the neostriatum, mediates motor movement.
- The mesolimbic pathway originates from the ventral tegmentum and travels to the nucleus accumbens. It is involved in mediating mood and reward.
- The mesocortical pathway projects from the ventral tegmentum to the anterior cingulate gyrus and mediates cognitive functioning.
- The tuberohypophysial pathway initiates in the arcuate nucleus and innervates the pituitary system, which mediates prolactin release.

Dopamine neurons originating in the ventral tegmental area of the midbrain innervate numerous limbic and cortical regions including the nucleus accumbens, amygdala, and prefrontal cortex, which collectively form the mesocorticolimbic dopamine system. Increased dopamine activation in this neuronal pathway mediates the reinforcing properties of drugs of abuse, including methamphetamine [31].

USE CHARACTERISTICS OF METHAMPHETAMINE ABUSE

Illicit methamphetamine is also referred to as "speed," "meth," "ice," "crystal," and "crank" and can be ingested through several routes of administration, depending on the specific preparation [32]. Methamphetamine is primarily available as [2]:

- "Speed," a low-grade, locally manufactured powder that is snorted or injected
- Pills that are often combined with other drugs, such as ketamine
- "Base" or "paste," an often locally manufactured, glue-like substance
- "Crystal meth" and "ice," which are highly pure, crystalline forms that are smoked or injected

Binge use of methamphetamine is a frequently reported pattern of use and is characterized by frequent ingestion of the drug, generally 8 to 10 times per day for 3 to 10 days. High doses (0.3 to 1 or more grams per day) are used because tolerance to the desired subjective drug effects develops quickly. Users who initially snorted or smoked methamphetamine often find they need to administer the drug intravenously to achieve the desired effects [33].

Compared to other stimulants, the progression to methamphetamine addiction is accelerated, particularly the time from initial use to regular use and regular use to first treatment. This is likely mediated by the synergistic interaction of the pharmacologic properties with the behavioral, social, and psychologic effects of the drug [34; 35]. Although treatments designed and validated for cocaine abusers have constituted the mainstay of treatment for methamphetamine, two important distinctions in patient characteristics may limit treatment generalizability: the long-term drug effects on cognitive and emotional functioning, and lifestyle and background differences associated with methamphetamine-addicted patients.

Differences in neurotoxicity between methamphetamine and other stimulants have also been identified. Methamphetamine damages neurons that inhibit dopamine and serotonin brain pathways, while cocaine is not toxic to these neurons [35]. The anergia, dysphoria, and lack of mental energy seen in postacute withdrawal from methamphetamine are much more severe and protracted than that observed among cocaine-dependent patients. Persistent paranoia is also unusual in abstinent cocaine addicts, whereas methamphetamine abuse can predispose the patient to paranoia several years into abstinence. Withdrawal from methamphetamine is likely the manifestation of both the short-term stimulant withdrawal syndrome (anergia and psychasthenia) experienced and the expression of long-term functional changes and/or neurotoxicity unique to this drug [33]. Users of methamphetamine exhibit cognitive impairment distinct from that induced by other stimulant drugs, with impairment of perceptual speed, information manipulation, and tasks combining these skills with visuomotor scanning [4]. Methamphetamine abusers continue to display deficiencies in these neuropsychologic dimensions three years into abstinence [36; 37].

User characteristics also tend to vary among methamphetamine and other stimulant abusers. According to one study, methamphetamine abusers are more likely than cocaine abusers to be unemployed and never married; to use on a daily basis and begin use at a younger age; and to currently experience depression, suicidal thinking, hallucinations, and paranoia [1]. Compared with cocaine users, methamphetamine abusers exhibit greater family strife, more friends who shared their drug of choice, a stronger relationship between their drug of choice and sex, and increased concurrent cannabis and hallucinogen use. Interestingly, little crossover from cocaine to methamphetamine abuse or vice versa was found, indicating that users do not readily substitute one for the other [1]. Another study found outpatient methamphetamine users more likely than outpatient cocaine users to be human immunodeficiency virus (HIV) positive, to engage in needle sharing, to be gay or bisexual, and to be on psychiatric medication [38].

EFFECTS OF METHAMPHETAMINE USE

ACUTE EFFECTS

In addition to euphoria, hyperactivity, and energy, other acute effects of methamphetamine use can include increased confidence and self-esteem, grandiosity, feeling of well-being, heightened attentiveness, elevated body temperature, profuse sweating, restlessness, tremors, aggressive behavior, and uncontrollable jaw clenching (***Table 1***) [3; 10; 20; 39; 40; 41; 42]. As noted, single doses of amphetamines, including methamphetamine, improve performance across several dimensions [4]. By stimulating serotonin, dopamine, and norepinephrine and blocking their presynaptic re-uptake, pleasure, mood, sleep, and appetite mediators are increased. The immediate cognitive effects are a heightened sense of awareness and attention [1; 9].

Acute methamphetamine ingestion can both exacerbate pre-existing psychopathology and generate comorbidity [43]. Fatalities associated with methamphetamine use stem from homicide; suicide; motor vehicle accidents; manufacturing, distribution, and sales of the drug; and the direct toxic effects of the drug [20]. Biologically based causes of methamphetamine-induced mortality include stroke and cerebral hemorrhage, cardiovascular collapse, pulmonary edema, myocardial infarction, hyperpyrexia, and renal failure [4; 42].

SIGNS AND SYMPTOMS OF ACUTE METHAMPHETAMINE USE	
Psychologic symptoms	Increased confidence and self-esteem Grandiosity Feeling of well-being Heightened attentiveness Sexual arousal Paranoia Psychosis Hallucinations, including delusions of parasitosis (a belief one is infested with parasites) Depression Acute anxiety Unprovoked aggressive/violent behavior Irritability
Physiologic signs	Increased heart rate Elevated body temperature Insomnia Increased blood pressure Increased respiration rate Profuse sweating Tremors Neurologic symptoms, such as headaches Vision loss
Behavioral signs	Excessive talkativeness Excitation Agitation Aggressive behavior Uncontrollable jaw clenching Restlessness Performance of repetitive, meaningless tasks
Source: [3; 10; 20; 39; 40; 41; 42]	*Table 1*

CHRONIC EFFECTS

Chronic effects from methamphetamine use can include paranoia, insomnia, psychotic or violent behavior, pronounced fatigue, poor coping abilities, sexual dysfunction, and dermatologic conditions (***Table 2***) [3; 10; 20; 39; 40; 41; 42]. Other methamphetamine-related effects include malaise, fatigue, nausea, headache, and dizziness from toxic fumes associated with methamphetamine production, burn injuries from lab accidents and explosions during production, and chemical burns from contact with precursors or byproducts of production [40].

Dental Effects

"Meth mouth" is widespread among certain populations of methamphetamine users, particularly those incarcerated for methamphetamine-related offenses [40]. "Meth mouth" (dental deterioration) is a constellation of signs and symptoms associated with chronic use of methamphetamine and is caused by methamphetamine-induced vasoconstriction and reduced salivary flow, methamphetamine-induced vomiting, jaw clenching, the high intake of sugary beverages often seen with methamphetamine users, and abandonment of oral hygiene. This condition is characterized by widespread tooth decay and tooth loss, advanced tooth wear and fracture, and oral soft tissue inflammation and breakdown [40].

SIGNS AND SYMPTOMS OF CHRONIC METHAMPHETAMINE USE	
Psychologic symptoms	Persistent anxiety Paranoia Insomnia Auditory hallucinations Delusions Psychotic or violent behavior Homicidal or suicidal thinking
Physiologic signs	Hypertension Pronounced fatigue Malnutrition Neglected hygiene Hair loss Cardiovascular and renal damage from toxic byproducts of methamphetamine production Choreoathetoid (involuntary movement) disorders Sexual dysfunction Cerebrovascular damage Weight loss (possibly substantial) Nose bleed from intranasal ingestion Dental problems, such as cracked teeth and excessive caries Muscle cramping from dehydration and depleted electrolytes Dermatitis around the mouth from smoking Smell of stale urine stemming from ammonia (a manufacturing component) Dermatologic conditions, such as excorciated skin lesions Constipation from dehydration and lack of dietary fiber Dyspnea and coughing up blood from smoking
Behavioral signs	Unprovoked violent behavior Poor coping abilities Disorganized lifestyle Unemployment Relationship estrangement
Source: [3; 10; 20; 39; 40; 41; 42]	*Table 2*

The American Dental Association recommends that practitioners be particularly aware of the following signs, which may indicate that dental deterioration is linked to methamphetamine use [44]:

- Unaccounted for and accelerated decay in adolescents and young adults
- Distinctive pattern of decay on the buccal smooth surface of the teeth and the interproximal surfaces of the anterior teeth
- Malnourished appearance of heavy users

Cognitive and Neurobiologic Effects

Prolonged use of methamphetamine is associated with changes to the brain and CNS through several general mechanisms, including depletion of presynaptic monoamine reserves, down-regulation of neurotransmitter transporters and receptors, and neurotoxicity through reactive metabolic byproducts of dopamine and serotonin. Neurotoxicity can occur from as little as several days of methamphetamine exposure and may persist for months and even years [33]. Even a sub-neurotoxic reduction of dopamine activity can produce the lingering motivational difficulties often encountered by patients in early to intermediate recovery [33]. Another

mechanism of methamphetamine-induced neurotoxicity is the substantial and prolonged release of the excitatory neurotransmitter glutamate triggered by acute ingestion [3].

Cognitive and Neurobiologic Dysfunction in Abstinent Methamphetamine Users

During the first several weeks of abstinence, methamphetamine abusers have been found to display functional and structural changes to key brain regions that are associated with attention deficits, impaired visual pattern recognition, and impaired decision-making speed and accuracy [45; 46]. Abnormalities consistent with frontal lobe vascular damage are related to the amount and duration of methamphetamine use and may underlie the dysfunction in craving and compulsive behavior seen in methamphetamine addicts [47]. Substantial impairment in attention/psychomotor speed, verbal learning and memory, and fluency-based measures of executive systems functioning have been reported [48]. Metabolic brain abnormalities in the limbic and paralimbic regions observed in methamphetamine addicts may underlie the affective dysregulation often experienced in early recovery [49].

Cognitive performance in methamphetamine-dependent patients may actually worsen during the first three months of abstinence. Simon et al. found that abstinent patients with a recent lapse scored worse on neuropsychologic testing than patients with ongoing methamphetamine use, indicating that abstinent patients may encounter difficulties in treatment when attention, understanding, and memory are needed [50].

Functional and structural deficits associated with methamphetamine use have been observed 6 to 12 months into continuous abstinence. Chang et al. found significant impairment in reaction time, working memory, and mental concentration [51]. This symptom constellation mimics subclinical Parkinson disease, another neurologic condition characterized by substantial dopamine transporter loss. Neuronal damage associated with metabolic abnormalities in frontal lobe regions was also found, which may explain the persistence of violence, paranoia, and personality changes well into intermediate-term abstinence [52]. Ongoing dysfunction in executive control of verbal encoding and retrieval consistent with neurologic damage to the prefrontal cortex was observed by Woods et al. [53]. Significant correlations between aggression severity, extent of serotonin transporter density reduction, and duration of methamphetamine use have been observed [54]. Moreover, the reduction in serotonin transporter density persisted well into abstinence, suggesting the decrease remains long after methamphetamine use stops. This finding is consistent with several other studies that have linked decreased serotonin function with increased aggression and violence [55; 56; 57; 58].

Many studies have examined the impact of chronic methamphetamine use on the persistence of dopamine transporter density reduction beyond one year of abstinence. Severity of methamphetamine use, dopamine transporter reduction, and residual psychiatric symptoms (e.g., paranoia, anxiety, irritability and depressed mood, auditory hallucinations, disordered thinking) were found to be highly correlated, but no association between dopamine transporter density and duration of methamphetamine abstinence was observed [59]. In another study, degraded dopamine transporter activity was correlated with deficits in motor and memory performance, and duration of methamphetamine use was highly correlated with the severity of the effects [60]. No significant improvement beyond one year of abstinence was found. Together, these studies suggest that persisting dopamine transporter depletion underlies the pathophysiology of the ongoing psychiatric and neuropsychologic disturbances in methamphetamine users with intermediate-length abstinence [59]. Significantly diminished activation in brain pathways has also been observed and was associated with reduced decision-making speed and impaired decision-making strategies, with the magnitude of activation deficit predictive of methamphetamine abuse duration. Long-term changes in dopamine transporter density were implicated in these findings [61].

Despite abundant evidence of durable changes in brain structure and function as a result of chronic methamphetamine abuse, several studies have documented improved functioning with abstinence from methamphetamine. Neuronal recovery with extended abstinence from methamphetamine was noted by Nordahl et al., who observed partial anterior cingulated cortex normalization that positively correlated with duration of methamphetamine abstinence [62]. Volkow et al. found significant increases in striatum and putamen dopamine transporter density, with the degree of putamen increase inversely correlated with the amount and duration of methamphetamine use [60]. Another study demonstrated that metabolic activity in the thalamus improved between early and protracted abstinence and was correlated with improved motor skill and verbal memory [63].

The absence of longitudinal studies on methamphetamine users makes drawing a causal relationship between methamphetamine use and depression, paranoia, and reduced dopamine transporter density difficult. In the absence of such data, it remains unknown if users selectively chose methamphetamine to counter baseline anergia, depression, or impaired cognition if a vulnerability to psychoses predated the methamphetamine use or if these symptoms/neuronal changes arose as a consequence of the methamphetamine use itself.

Neonatal Effects

Methamphetamine is potentially neurotoxic to the developing fetus, and the lifestyle of methamphetamine-addicted mothers, who typically engage in poor prenatal care (e.g., neglect proper nutrient intake or consume cigarettes, alcohol, or cannabis), is a contributory factor. Infants born to methamphetamine-addicted mothers may exhibit methamphetamine withdrawal upon birth, with one study finding 49% of 134 methamphetamine-exposed infants exhibiting withdrawal symptoms [64]. Neonates exposed to methamphetamine tend to exhibit lower birth weight, decreased head circumference, and overall decreased growth, as well as subsequent increased aggressive behavior, impaired social adjustment, deficits in the acquisition of mathematics and language skills, and poor visual recognition memory relative to non-methamphetamine-exposed infants [4; 64]. These infants also display reduced hippocampal and striatal nuclei volume associated with long-term emotional and behavioral dysfunction [4]. Abnormalities in brain microstructure that persist into childhood and adolescence have been observed in children with prenatal exposure to methamphetamine [65]. Methamphetamine-exposed children often exhibit deficits in brain development, including significantly smaller subcortical brain volume corresponding with significantly worse scores on measures of visual motor integration, attention, verbal memory, and long-term spatial memory compared with healthy infants [51]. However, a study using magnetic resonance spectroscopy and magnetic resonance imaging found no evidence of neuronal damage or loss in selected brain regions [66].

COMORBID CONDITIONS ASSOCIATED WITH METHAMPHETAMINE USE

Comorbid conditions associated with methamphetamine use include CNS depressant (e.g., alcohol, benzodiazepine, sedative) abuse or dependence, psychoses, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, social phobia, and major depression [67].

Patients entering treatment for stimulant dependence display a high prevalence of Axis I disorders (clinical syndromes), such as depression, schizophrenia, and ADHD, and high rates of suicide attempts, anxiety, rage, violence, and impulsivity [68; 69; 70]. High rates of previous and current suicidal ideation are found in incarcerated methamphetamine abusers, who are also likely in need of psychiatric assistance [71]. The high rates of depression among methamphetamine-dependent persons may, however, be attributed to baseline depression, situational aspects of the individual's life, or the methamphetamine withdrawal process itself [72].

PSYCHOSES

Any stimulant drug can induce psychotic symptoms if used in high doses over several days. However, methamphetamine use is associated with more severe and protracted delusions and paranoia than cocaine and other stimulants, and this is the main focus of the following section.

Psychotic symptoms are associated with both methamphetamine use and methamphetamine withdrawal. Most users of methamphetamine develop psychoses, typically auditory hallucinations, persecutory delusions, and delusions of reference, within one week of continuous use [72]. Continued use results in further loss of insight, increased psychoses, and possible violent behavior. Although psychotic symptoms resolve within 96 hours following cessation for many users, a sizeable percentage of patients remain psychotic for months or even years after they stop using the drug [72].

Methamphetamine-induced psychoses are believed to be due, in part, to the level of methamphetamine metabolites in the bloodstream and excess synaptic dopamine. The condition is usually indistinguishable from paranoid schizophrenia. Compared with nonpsychotic methamphetamine addicts, patients with methamphetamine-induced psychoses are more likely to be diagnosed with major depression, alcohol dependence, and antisocial personality disorder, with earlier and heavier use of methamphetamine positively correlated with the development of psychoses [72]. Neurologic morbidity, such as traumatic brain injury, birth trauma, learning disabilities, and soft neurologic signs (e.g., poor balance and coordination), is associated with treatment-resistant methamphetamine psychoses [4].

Psychoses and paranoia can develop from stimulant abuse in persons without pre-existing psychotic symptoms. However, patients with a psychotic disorder are most vulnerable to stimulant-induced psychoses, with 50% to 70% of patients diagnosed with schizophrenia or psychoses exhibiting a psychotic response to a single dose of a stimulant drug, even with antipsychotic pretreatment [73].

AGGRESSIVE AND VIOLENT BEHAVIOR

The acute effects of methamphetamine can include irritability, agitation, hypervigilance, and possibly violent outbursts, and chronic use of methamphetamine has a greater association with violent behavior than any other psychoactive drug [74]. Biologic factors play a role in methamphetamine-induced violent behavior, with alteration in serotonin, dopamine, and norepinephrine levels being implicated. A study of more than 1,000 methamphetamine outpatients found that 11.7% experienced difficulty in controlling violent behavior in the past month, with no significant gender differences [74]. Violence is also associated with methamphetamine-induced psychoses [22]. A longitudinal study of 278 methamphetamine users 16 years of age or older found a dose-related increase in violent behavior during active methamphetamine use. Although methamphetamine use creates the clear potential for violent behavior, it is important to remember that violent behavior is not an inevitable outcome of even heavy, long-term methamphetamine use [75].

Users of methamphetamine are also at high risk for being recipients of violence. A study of 1,016 methamphetamine outpatients found that 85.4% of women and 69.6% of men reported physical abuse [76]. Women were significantly more likely to have been physically assaulted by a partner, while men were significantly more likely to have been assaulted by a friend or stranger. Violence associated with methamphetamine is also related to the protection of illegal production sites, distribution and trafficking operations, and territories in the black market drug business [32]. Among paroled inmates, methamphetamine use is associated with violent crime and recidivism, even after controlling for demographic variables, indicating the need for greater treatment engagement and parole supervision among parolees with a history of methamphetamine dependence [32].

WITHDRAWAL FROM METHAMPHETAMINE

The 5th edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) does not distinguish symptoms of methamphetamine withdrawal from that of cocaine or other stimulant drug withdrawal [77]. Withdrawal from methamphetamine is generally characterized more by psychiatric symptoms than physical symptoms [4]. Catecholamine depletion is believed to underlie the withdrawal/protracted abstinence syndrome, which may persist for more than 12 months beyond complete cessation of methamphetamine use [4]. The associated withdrawal syndrome consists of several symptom clusters [68; 78]:

- Hyperarousal (agitation, severe craving for methamphetamine, disturbing dreams)
- Vegetative symptoms (decreased energy, craving sleep, increased appetite)
- Anxiety-related symptoms (anxiety, loss of interest or pleasure, psychomotor retardation)
- Severe dysphoria, mood volatility, irritability, and sleep pattern disruption

The prominence and duration of the anhedonia, irritability, and poor concentration associated with methamphetamine withdrawal has been characterized as an apathy syndrome rather than a depression-mediated syndrome. This symptom cluster is also observed in neuropsychiatric disorders associated with dysregulated brain dopamine systems, such as Parkinson disease, Huntington disease, and progressive supranuclear palsy. The treatment implications for this are compelling, as pharmacotherapy for apathy syndromes involves dopaminergic agents that are generally distinct from antidepressant agents [79].

TREATMENT OF METHAMPHETAMINE USE DISORDER

Although amphetamines and methamphetamine have been abused for more than 70 years, effective treatment approaches have only recently emerged and are in the early stages of development and evaluation. Most have been borrowed from approaches effective in treating cocaine dependence, including cognitive-behavioral therapy (CBT), contingency management (CM), and the Matrix Model. Treatment of methamphetamine dependence is typified by the Matrix Model, which combines cognitive, behavioral, and psychologic approaches and is delivered to the patient immediately following acute withdrawal [80].

Effective treatment of methamphetamine-dependent patients poses many challenges, some of which are unique. For instance, poor treatment engagement and high treatment dropout rates, severe or ongoing paranoia or psychotic symptoms, high relapse rates, and intense protracted cravings, dysphoria, and anhedonia are among the commonly cited obstacles to success in this population [39]. In addition to the medical, dental, relationship, occupational, child welfare, financial, and legal consequences associated with addiction to methamphetamine, this drug produces psychiatric and neurologic consequences that are relatively unique, as well as a heightened risk of sexually transmitted infections (STIs), including HIV infection [2].

Enhancing motivation for abstinence, improving strategies for avoiding use, and facilitating relapse prevention require the patient's attendance, comprehension, and effective memory recall [81]. However, as discussed, chronic methamphetamine abuse results in cognitive impairment in the form of deficits in attention, impulse control, and task performance. Methamphetamine users who are cognitively impaired will not be able to benefit from such treatment programming [3; 50]. Understanding the effects of methamphetamine use on

mood, neuropsychologic functioning, capacity for motivation and drive, and the recovery process is essential in devising and implementing effective treatment approaches.

Determining the most effective treatment components for methamphetamine addiction is complicated by the special needs of methamphetamine-using subgroups. Each special population has unique needs that should be addressed to optimize therapeutic outcome [15]. This is illustrated by the culturally sensitive approach tailored for gay and bisexual men, termed gay-tailored cognitive-behavioral therapy (GCBT) [82].

PSYCHOSOCIAL THERAPY

The Matrix Model

The Matrix Model was first conceptualized and developed during the 1980s in response to the overwhelming need for cocaine treatment programs, following evidence that the traditional private sector 28-day inpatient treatment programs for alcohol- and opioid-dependent patients were ineffective for patients with stimulant dependence [83; 84]. This model integrates several empirically validated interventions into a single treatment model, with pragmatics given priority and programs based on theory and ideology being avoided [82; 84]. The goals of the Matrix Model include stopping drug use, transmitting knowledge of issues critical to addiction and relapse to the patient, educating family members impacted by addiction and recovery, familiarizing patients with 12-step programs, and implementing drug and alcohol testing [80; 85].

Elements of the Matrix Model include [82]:

- Engagement and retention: Emphasizing the patient-therapist relationship
- Structure: Planning and scheduling to help patients eliminate blocks of free time
- Information: Helping patients connect psychologic, cognitive, and external consequences with drug use
- Relapse prevention: Providing coping skills for urges and high-risk situations, increasing self-efficacy
- Family involvement: Engaging and educating family members
- Self-help involvement: Orientation and encouragement of attendance and involvement in 12-step programs
- Urinalysis/breath testing: Weekly random drug testing and alcohol breath testing

These elements are incorporated into several treatment protocols, including individual sessions, early recovery groups, relapse prevention groups, family education sessions, 12-step meetings, social support groups, relapse analysis, and urine tests [80].

A convenience sample of 114 patients out of an original population of 500 patients receiving the Matrix Model was analyzed for follow-up two to five years after treatment initiation [39]. A combination of self-report and urine screen revealed that in the 30 days preceding the follow-up interview, 82.5% reported no methamphetamine use, 11.4% reported some use, and 6.1% reported daily use. This is compared with 13.2% no use, 38.6% some use, and 47.4% daily use in the 30 days prior to treatment intake. Other drug use also decreased from intake to follow-up, and full-time employment increased from 26% at baseline to 62% at follow-up. Interestingly, the frequency of depression, headache, and hallucinations were statistically unchanged from baseline to follow-up. Although these results indicate decreased methamphetamine and other substance use and increased psychosocial function associated with Matrix Model-based treatment, 77% of the sample was lost to follow-up, and there was evidence that the subjects in the sample utilized treatment services significantly more than the pooled population of patients, hampering the generalizability of this data.

In a multisite study across eight different communities, 978 methamphetamine-dependent outpatients were randomized to either the Matrix Model or conventional outpatient treatment [86]. Conventional treatment was considered the best available option in the eight communities in which the study took place. Significant variation existed in the conventional outpatient conditions. Although subjects receiving the Matrix Model exhibited significantly better treatment retention, program completion, treatment engagement, more methamphetamine-free urine samples, and longer periods of abstinence during treatment than conventional treatment recipients, these differences did not persist into the post-treatment follow-up period. No differences were noted in methamphetamine-free urine after six months (69% of total urine samples methamphetamine-free in both groups). The authors state that although the Matrix model resulted in a more rapid reduction in methamphetamine use and increased treatment utilization, comparing the Matrix Model to eight different types of comparison treatment conditions increased within-group variance and obscured differences among the groups.

Cognitive-Behavioral Therapy (CBT)

CBT is one of the most studied psychosocial approaches in the treatment of substance abuse disorders in general and non-methamphetamine stimulant abuse in particular. This approach integrates behavioral theory, cognitive social learning theory, and cognitive therapy. The rationale for CBT is the finding that craving for methamphetamine is triggered by exposure to conditioned cues and that the strength of cue response is a factor in relapse. CBT is delivered by a clinical psychologist or other licensed mental health professional in either an inpatient or outpatient setting. Most treatment programs for substance abuse in the United States, and even 12-step programs such as Alcoholics Anonymous (AA), incorporate elements of CBT [82].

A 2005 study suggests that CBT can improve the psychologic well-being of outpatient methamphetamine users [87]. Specifically, a four-week, one hour per week CBT intervention was delivered to 507 outpatients (87.2% amphetamine-dependent), consisting of well-defined cognitive, behavioral, and motivational interviewing methods focused on five core areas [87]:

- Amphetamine refusal self-efficacy skills
- Developing more effective coping strategies
- Teaching problem-solving skills
- Treating needle fixation, if necessary
- Relapse prevention planning

According to self-report, 33% of participants completed the treatment protocol and remained abstinent. Treatment completers experienced significant improvement from baseline on measures of somatic symptoms, anxiety, social dysfunction, and depression, as well as significant improvement in amphetamine refusal self-efficacy, all of which remained significant following intention-to-treat analysis. The authors noted that patients with more severe dependence and general health concerns displayed the greatest improvements. Self-reported drug use reduction or abstinence was not verified with drug screening, and the high attrition rate hampers conclusions on efficacy.

The effectiveness of brief CBT in transmitting the skills and confidence to minimize relapse was also evaluated by Yen et al. [88]. In a sample of newly incarcerated inmates residing in a residential detoxification facility, 30 methamphetamine users were randomized to receive five sessions of CBT that emphasized skill acquisition in managing interpersonal and intrapersonal situations related to drug use, and 37 were randomized to a control treatment group consisting of no CBT. Subjects receiving CBT exhibited greater confidence in resisting using situations than control subjects; however, actual changes in drug use were not evaluated.

Gay-Tailored Cognitive-Behavioral Therapy (GCBT)

Developed and first evaluated in 2005 to address the dual concern of methamphetamine abuse and HIV-risk behavior, GCBT integrates the core features of CBT with an emphasis on behavioral and cultural aspects that are relevant to gay and bisexual men. Topics are gay-referent, and discussion of relapse triggers includes gay cultural events and environments. Group sessions cover topics such as sexual risk reduction, sexual behavior on and off of methamphetamine, and recognition of characteristics of sexual partners and significant others who do and do not use methamphetamine [82].

Shoptaw et al. randomized 162 methamphetamine-dependent gay and bisexual men (52.2% of whom were HIV positive) to 16 weeks of CBT, CM, CBT plus CM, or GCBT to determine efficacy in reducing drug use and sexual risk behavior [82]. Immediately post-treatment, GCBT group participants exhibited a significant reduction in unprotected receptive anal intercourse, and participants in the CM and CBT plus CM groups showed the greatest mean duration of methamphetamine-negative urine and the greatest total methamphetamine-negative urine samples. At one-year follow-up, all four groups displayed significant reductions in unprotected receptive anal intercourse relative to baseline, and there were no significant between-groups differences for methamphetamine use, with all groups reporting significant reductions from baseline levels. Interestingly, employment and legal problems increased from baseline to end of treatment and follow-up. The data suggest that the culturally sensitive GCBT leads to the most rapid reduction in sexual risk behavior, while treatments containing CM result in the most rapid reduction in methamphetamine use, although reductions in sexual risk behavior and drug use were eventually achieved with all treatment approaches studied.

Contingency Management (CM)

CM is based on the behavioral theory that both desired and undesired behavior increase when they are reinforced. CM manipulates reinforcers to shape behavior in the desired direction. This type of therapy is used in outpatient settings and is provided by conventional chemical dependency treatment personnel. Patients are rewarded for submitting drug-free urine samples by receiving vouchers with progressively increasing value. The vouchers are ultimately exchanged for goods and services that promote a drug-free lifestyle, such as groceries, clothing, electronic equipment, or plane fare, but are not exchanged for cash [82; 89]. Studies comparing the effectiveness of different reinforcement schedules in promoting abstinence from methamphetamine found that an escalating schedule, whereby the reinforcement vouchers are progressively greater for each successive negative drug test with a reset contingency that reduces voucher value with evidence of drug use, is most effective [90].

CM in the form of prize-based vouchers was added to usual care and compared with usual care only in a mixed sample of 415 cocaine- and methamphetamine-dependent outpatients [91]. Subjects randomized to CM exhibited significantly greater treatment retention, increased counseling session attendance, and more frequent alcohol and drug-free urine tests. These individuals were also more likely to achieve 4, 8, and 12 weeks of continuous abstinence than control subjects. Although the authors state that CM increased treatment retention and improved drug-free outcomes, it remains unknown if these short-term benefits persisted when reinforcement was withdrawn [91].

Conventional Treatment

The efficacy of conventional residential treatment with methamphetamine-dependent patients was studied by Gunter, Black, Zwick, and Arndt [92]. A sample of 199 methamphetamine abusers was admitted to an inpatient residential treatment setting for a mean stay of 86 days. Treatment consisted of group therapy, individual case management, and psychiatric assessment and referral in a semi-structured environment. The therapy was performed by trained chemical dependency counselors with knowledge of methamphetamine addiction. At 60 days following admission, significant reductions were observed on measures of anxiety (e.g., compulsions, obsessions, social phobia, generalized anxiety) and major depression. Approximately 25% of the sample was available for six-month follow-up, with significant reductions in methamphetamine use noted through self-report. Conclusions of efficacy are severely limited by subject attrition and subjective, nonverifiable outcome measures [92].

Coercive Interventions

Although many patients with methamphetamine addiction are coerced into treatment through criminal justice or child protection services pressure, little research has been completed about the outcome of such patients. Brecht, Anglin, and Dylan evaluated the treatment outcomes of 350 outpatient methamphetamine abusers randomly selected from a large database of outpatient and residential treatment patients in Los Angeles County [93]. Approximately 50% of the sample reported legal coercion as the motivation to enter treatment. Coerced clients remained in treatment longer but did not significantly differ from noncoerced clients in abstinence rates at six-month follow-up (59% coerced versus 49% noncoerced). Although there were no significant differences between the groups in percentage of days of methamphetamine use or percentage of patients reporting complete abstinence at 24-month follow-up, the number of months in treatment was associated with a more positive outcome, suggesting a benefit of longer treatment programs for methamphetamine-dependent patients.

PHARMACOTHERAPY AND BIOLOGIC THERAPY

The substantial cognitive dysfunction in many methamphetamine-dependent patients early in recovery makes engagement and participation in psychosocial-based treatment difficult. Effective pharmacotherapy has the potential to substantially improve patient comprehension and engagement in treatment, as well as improve treatment retention and reduce relapse to methamphetamine use [4]. There are currently no FDA-approved medications for the treatment of methamphetamine dependence. However, several potential strategies for pharmacotherapy of methamphetamine addiction have been identified. These strategies include targeting the depressed mood and drug craving associated with withdrawal, using drugs that elicit an aversive response when methamphetamine is ingested, using agents that block the positive effects of methamphetamine, treating the co-occurring conditions pharmacologically, and providing agonist therapy, in which a safer pharmaceutical amphetamine-type compound is substituted for methamphetamine [94].

Although several pharmacologic agents have demonstrated modest degrees of efficacy in reducing cravings and methamphetamine use, evidence supporting the widespread clinical application of each agent is tentative and preliminary and requires replication. Thus, psychosocial therapy remains the backbone of treatment for these patients [95].

According to the Department of Veterans Affairs, there is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of methamphetamine use disorder.

(https://www.guideline.gov/summaries/summary/49968. Last accessed June 22, 2017.)

Level of Evidence: Expert Opinion/Consensus Statement

Serotonergic Agents

Many methamphetamine withdrawal symptoms (e.g., fatigue, anhedonia, depressed mood, hypersomnia) simulate a major depressive episode, providing the rationale for the use of the selective serotonin reuptake inhibitor (SSRI) sertraline in methamphetamine patients. However, Shoptaw et al. found that outpatients receiving sertraline exhibited significantly worse outcomes in tested urine samples, group attendance, and ability to achieve three consecutive weeks of methamphetamine abstinence, with no reduction in depressive symptoms or cravings [89]. These findings suggest that sertraline should not be given to methamphetamine users complaining of depression or depressive-like symptoms. It is possible that depressive symptoms in early methamphetamine abstinence may be a syndrome distinct from primary, non-methamphetamine-induced depression. Additionally, a subsequent study found that a poor response to treatment with sertraline resulted in sustained craving and increased propensity to relapse during treatment among research participants dependent on methamphetamine [96].

Another trial using the SSRI paroxetine to treat methamphetamine dependence was reported by researchers who randomized 20 methamphetamine-dependent patients to either paroxetine 20 mg/day or placebo for eight weeks [97]. The substantial attrition rate (85%) prohibited any conclusions regarding efficacy to be drawn. However, the authors stated that the weight gain, sexual side effects, and sedation often induced by paroxetine and other SSRIs are opposite of the desired effects of methamphetamine, possibly heightening problems with patient acceptance and compliance with this class of medications.

A randomized, placebo-controlled trial of mirtazapine, an antidepressant with presynaptic alpha2-adrenergic antagonist, serotonin 5-HT1 agonist, serotonin 5-HT2 and 5-HT3 antagonist, and histamine H1 antagonist properties, was performed to assess its impact on amphetamine withdrawal [8]. Twenty amphetamine-dependent subjects detained in a short-term correctional facility received either mirtazapine (15–60 mg/day) or placebo for 14 days and were evaluated on days 3 and 14. Active treatment subjects exhibited significantly lower hyperarousal, anxiety, and total withdrawal scores compared with subjects receiving placebo, with no significant differences in depression between the groups. These results may indicate specificity for amphetamine withdrawal symptom reduction distinct from depression reduction with mirtazapine.

Norepinephrine and Dopamine Reuptake Blockers

As noted, chronic methamphetamine use can result in neuroadaptation in presynaptic dopamine neurons, manifesting as dysphoria, drug craving, and cognitive impairment in early abstinence. This indicates the possible utility of the dopamine and norepinephrine reuptake blocker bupropion. In a randomized, single-blind, placebo-controlled trial, 26 non-treatment-seeking subjects meeting the criteria for methamphetamine abuse or dependence received either a placebo two times per day or 150 mg extended-release bupropion two times per day for six days in addition to IV methamphetamine or placebo [98]. Subjects were housed in a clinical research unit during the study. Compared with placebo, bupropion treatment was associated with reduced ratings of "drug effect," "high," and "desire to use," as well as reduced cue-elicited cravings. The sample was small, however, and the results require replication. A Cochrane Review that included 11 studies (791 participants) evaluated the safety and efficacy of psychostimulants (including bupropion) for amphetamine abuse or dependence. Results of the review found no significant differences between the drugs and placebo in their ability to reduce amphetamine use or craving or to increase sustained abstinence [99].

Agonist Replacement Therapy

An approach consistent with the harm reduction model has been proposed by Shearer, Sherman, Wodak, and van Beek and involves prescribing dextroamphetamine to patients addicted to methamphetamine [42]. The basis for this treatment is the success seen with agonist replacement therapy (methadone) treatment of heroin addiction and nicotine replacement therapy for smoking cessation. However, ideologic and regulatory obstacles exist in the United States to the implementation of such a treatment regimen.

Preliminary data from an investigation utilizing methylphenidate to treat withdrawal symptoms in non-ADHD, long-term prescription amphetamine abusers appears promising [100]. Specifically, severe and protracted depression following amphetamine cessation was resolved with ongoing methylphenidate treatment at long-term (two- to four-year) follow-up assessment.

The efficacy of extended-release dextroamphetamine (d-AMP) 60 mg/day as a replacement therapy for methamphetamine dependence was evaluated in a randomized, placebo-controlled trial [101]. Although d-AMP did not significantly reduce methamphetamine use, reductions in withdrawal and craving scores were observed among subjects receiving d-AMP. The authors state that further investigation of d-AMP using higher doses is warranted. Another randomized placebo-controlled trial evaluating extended-release d-AMP was performed in 2010 [102]. In this study, subjects were randomized to d-AMP up to 110 mg/day for a maximum of 12 weeks, which was gradually reduced over a 4-week period. Subjects receiving d-AMP remained in treatment significantly longer than those receiving placebo (86.3 days versus 48.6 days), showed a non-significant reduction in methamphetamine use, and had a lower extent of methamphetamine dependence at follow-up.

Modafinil

Modafinil is a drug indicated for use in patients with excessive daytime sleepiness secondary to narcolepsy and other conditions. Initially believed to work through CNS histamine activation, more recent research has identified the dopamine agonist properties of modafinil. The hypothesis that the dopamine agonist properties of modafinil may help normalize brain dopamine function in methamphetamine-dependent patients and improve abstinence rates in the process has been evaluated in several studies [103]. In a randomized, double-blind trial comparing modafinil (200 mg/day) with placebo, researchers found non-significant trends in reduced methamphetamine use among subjects who remained engaged in counseling, had no other substance dependencies, and who adhered with medication [104]. A randomized, double-blind study of modafinil 400 mg/day found no statistically significant effects on methamphetamine use or craving, treatment retention, or depressive symptoms [105]. A subgroup of patients with high-frequency methamphetamine use showed a non-significant trend toward reduced use. A study comparing the effect of modafinil 400 mg/day and mirtazapine 60 mg/day on methamphetamine withdrawal among inpatients found that subjects treated with modafinil demonstrated a milder withdrawal syndrome as measured by the Amphetamine Cessation Symptom Assessment and less sleep disturbance compared with mirtazapine [106].

GABA Receptor Agonists

Gamma-aminobutyric acid (GABA) neurons decrease dopamine transmission in the nucleus accumbens and ventral tegmental mesolimbic regions, possibly decreasing the reinforcing effects of methamphetamine and providing the basis for trials of GABA agonists with methamphetamine-abusing patients. Heinzerling et al. reported the results of two GABA agonists, baclofen (20 mg three times per day) and gabapentin (800 mg three times per day), in a double-blind, randomized, placebo-controlled trial of 16 weeks duration [107]. A total of 88 methamphetamine-dependent

outpatients were randomized to either baclofen, gabapentin, or placebo, and all subjects attended clinic three times a week for assessment, counseling, and urine drug testing. There were no statistically significant differences in completion of the 16-week trial, reduction in depressive symptoms, craving of methamphetamine, or reduction in methamphetamine-positive urine samples between the groups. However, when patients with high protocol adherence were compared, baclofen recipients exhibited greater numbers of methamphetamine-negative urine samples relative to gabapentin and placebo subjects, suggesting a small but positive effect of baclofen in reducing methamphetamine use. Greater attendance of psychosocial therapy groups was also associated with decreased methamphetamine use across all three groups, underscoring the importance of psychosocial therapy augmentation of pharmacotherapy for methamphetamine addiction.

Observations of dysregulated brain GABA(A) function during and immediately following the active abuse of substances, including methamphetamine, provides the rationale for combining two agents with GABA action in the treatment of methamphetamine dependence. A randomized, double-blind study comparing flumazenil (a benzodiazepine antagonist) plus gabapentin with placebo found significant reductions in craving and decreased methamphetamine use among subjects receiving the study drugs relative to those receiving placebo [108].

The safety and efficacy of another GABA agonist, gamma vinyl-GABA (GVG), was evaluated in a nine-week, open-label, pilot study involving 10 methamphetamine-dependent, 17 methamphetamine- and cocaine-dependent, and 3 cocaine-dependent subjects [109]. Because GVG has not received FDA clearance in the United States due to concerns over concentric visual field defects associated with its use, the study was carried out in Mexico. A total of 18 subjects completed the trial. Of those 18, 16 subjects tested negative for methamphetamine and cocaine during the last six weeks, with a median of 42 days drug free for this group during the 63-day study period. Visual field defects were not observed during the study period. Although unblended and lacking a control group, these results are promising, especially in light of the absence of effective pharmacotherapy for methamphetamine addiction. However, more rigorous testing must be completed before any conclusions regarding efficacy and safety can be drawn.

Tricyclic Antidepressants

The possible efficacy of the tricyclic antidepressant imipramine in improving treatment retention and drug use-related outcomes was tested in a randomized controlled trial of 32 methamphetamine-dependent outpatients [110]. Participants received either 10 mg/day or 150 mg/day imipramine for 180 days in addition to counseling, medical care, and psychiatric support. Although patients receiving the 150 mg dose remained in treatment longer, no differences in craving, depression, percentage of methamphetamine-positive urine, days since last methamphetamine use, or study visit attendance were noted between the groups. These results suggest that imipramine may be ineffective as a treatment for methamphetamine dependence.

Dopamine Antagonists

Mesolimbic dopamine pathways are believed to play a large role in the reinforcing properties of stimulant drugs, including methamphetamine, and serotonin (5-HT) may also contribute to the subjective effects of amphetamines. Based on the observation that dopamine-blocking agents attenuate the reinforcing properties of stimulant drugs in animal studies, the dopamine D2 blocker haloperidol and the D2 and 5-HT2 receptor antagonist risperidone were given to nonaddicted human subjects in a placebo-controlled trial to examine their possible efficacy in blocking the rewarding effects of methamphetamine [111]. Neither drug was found to block the euphoric effects of methamphetamine, suggesting that the pleasurable and rewarding properties of methamphetamine are not mediated through dopamine D2 or 5-HT2 activation.

Ondansetron is a 5-HT3 receptor antagonist and modulator of cortico-mesolimbic dopamine function. Results of a reduction in the rewarding effects of d-amphetamine in animal and human laboratory studies have prompted the investigation of ondansetron in the treatment of methamphetamine dependence. However, the results of a randomized, double-blind trial comparing ondansetron 0.25 mg, 1 mg, or 4 mg twice daily with placebo did not find an advantage in decreased methamphetamine use, withdrawal, craving, or clinical severity of methamphetamine dependence compared with placebo [112].

Opioid Antagonists

As discussed, the cortico-mesolimbic dopamine system is the primary reinforcing or reward pathway involved with methamphetamine use; however, other neurotransmitter systems modulate brain dopamine [113]. For example, mesolimbic dopamine neurons contain μ-opioid receptors and the ventral tegmental area and the substantia nigra contain neurons in which dopamine and opioids coexist. These regions of the brain are known to play a role in adaptive behaviors related to methamphetamine addiction. It is hypothesized that opioid antagonist agents may reduce the subjective effects of methamphetamine and modulate the dopamine-opioid interaction.

The opioid receptor antagonist naltrexone, commonly used to treat alcohol and opiate dependence, has been demonstrated to reduce cravings and relapse in methamphetamine addicts in a small-scale Swedish study [113]. The participants in the treatment group reported significantly reduced craving levels and amphetamine use and had a greater number of amphetamine-negative urine samples (65.2%) compared to the placebo group (47.7%). The length of time until a relapse was longer in the treatment group (six weeks) compared to the control (three weeks). An earlier animal study found that naltrexone reduced drug-seeking behavior following administration of conditioned environmental cues in rats that had exhibited extinction behavior in response to a sudden switch from an amphetamine solution to saline solution; however, when primed with methamphetamine, naltrexone had no effect on cue induced drug-seeking [114]. These researchers also concluded that naltrexone may be helpful in preventing relapse.

TREATMENT OF METHAMPHETAMINE USE IN SPECIAL POPULATIONS

Women

Although the number of female methamphetamine users seeking treatment is nearly comparable in number to men, women often display special needs, including high frequencies of personal and social disadvantage, psychiatric illness, sexual risk behavior, and history of sexual and/or physical abuse [20; 76; 115]. It is imperative that these special needs be assessed and addressed by treatment providers. Failure to address physical and sexual abuse issues and associated psychiatric disorders, such as post-traumatic stress disorder, may contribute to resumption of chemical use [76]. Gender differences in the motivation to use methamphetamine have also been found, with women more likely to use methamphetamine for weight loss and energy enhancement and men more likely to use methamphetamine for increased work productivity and sexual enhancement [34].

Women who are pregnant or have small children necessitate a higher level of care than other patients, with attention to proper prenatal care. Treatment staff may need special training in managing their negative emotions toward the patient(s) while working with pregnant women who relapse to methamphetamine use. Women with small children may require sober living arrangements or day treatment that can accommodate their children [85].

Gay, Bisexual, and HIV-Positive Patients

In the United States, methamphetamine abuse by gay and bisexual men is endemic in urban settings, where its use is profoundly intertwined with sexual and social behavior. Rates of use in this population are as high as 20 times that of the general population [116]. It has been hypothesized that methamphetamine's effects of stimulating energy, confidence, and libido may be particularly effective in counteracting depression or fatigue [117]. This, coupled with the drug's relative inexpensiveness, may make methamphetamine particularly attractive to gay and bisexual men and/or persons with HIV [117]. Methamphetamine use can also increase the frequency and duration of sexual encounters and result in the abandonment of safe sex practices [118]. Consequently, methamphetamine-dependent gay and bisexual men are at heightened risk of STIs, in particular HIV transmission [15]. The issues surrounding concurrent methamphetamine use and hypersexuality among gay and bisexual men does not lend itself to discussion in a mixed group setting with heterosexual men, which could increase the likelihood of poor treatment engagement and early dropout [85].

The profound connection of methamphetamine use with HIV infection in gay and bisexual men in urban settings has been documented by Peck et al., who found that 61% of a sample of 162 methamphetamine-dependent, treatment-seeking outpatients in Los Angeles were HIV-positive [119]. In another study, Shoptaw et al. found that 77.6% of their sample of 143 outpatients in San Francisco were HIV-positive [120]. Although unprotected sex, particularly receptive anal intercourse, is highly correlated with HIV infection, other factors are also associated with infection, including prior treatment for methamphetamine dependence, history of STI, and negative health insurance status [119]. Among inmates in the California state correctional system, methamphetamine use was strongly associated with sex-related HIV risk, indicating the importance in addressing this risk with methamphetamine users enrolled in prison-based drug treatment programs [121].

Treatment of gay or bisexual methamphetamine users can be complicated by the presence of HIV infection. In these patients, the onset and severity of the medical, neurologic, and neurocognitive consequences of methamphetamine use can be accelerated. In addition, increased viral load and decreased compliance with antiretroviral therapy, possibly resulting in rebound of viral replication and the development of resistance to antiretroviral drugs, is common [122; 123]. However, abstinent methamphetamine abusers who adhere to antiretroviral therapy can suppress HIV replication, underscoring the need to properly engage HIV-positive methamphetamine abusers in treatment [124]. Many methamphetamine abusers are also afflicted with hepatitis C virus, and the negative effects of hepatitis, HIV, and methamphetamine abuse on neurocognitive functioning are synergistic [125].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Male Training Center for Family Planning and Reproductive Health asserts that men who have sex with men (MSM) in conjunction with illicit drug use (particularly methamphetamine use) should be screened more frequently for sexually transmitted infections, including gonorrhea and syphilis.

(https://www.guideline.gov/summaries/summary/48456. Last accessed June 22, 2017.)

Level of Evidence: Expert Opinion/Consensus Statement

Rural Populations

Methamphetamine use is particularly prevalent in rural areas, where the relative privacy allows the operation of manufacturing labs to go undetected [13; 126]. The demographics and use trends are different, with equal numbers of male and female users and a higher number of injection drug users than urban counterparts [13]. Methamphetamine users in rural areas, especially areas designated as frontier regions (defined as six persons or less per

square mile) are likely to experience great difficulty in accessing medical, psychiatric, or substance abuse services. Even self-help groups are likely to be nonexistent in these areas, and when they are available, the degree of anonymity in a 12-step group in a small town may be compromised. The nearest available small city often serves as the population center for the region. Social services in these cities may be overwhelmed by numbers of transient persons from the surrounding rural areas needing services in addition to the inhabitants of the city [15].

Substance abuse treatment approaches should be tailored to meet the needs of this rural population. One such approach, Structured Behavioral Outpatient Rural Therapy, is designed around the use of storytelling activities, a more culturally acceptable form of therapy than the traditional role-playing techniques [127]. Case management and behavioral contracting have also been identified as useful approaches to engage and maintain rural residents in therapy [126]. It is also important that healthcare professionals in rural settings receive the training necessary to effectively diagnose and treat methamphetamine-dependent patients. Kentucky and North Carolina have implemented a system by which specialists in substance abuse are available at welfare or social services offices [126]. Other possible approaches in the treatment of rural methamphetamine abuse include treatment of jail and prison inmates and the use of drug courts [126].

TREATMENT OF AGITATION ASSOCIATED WITH METHAMPHETAMINE USE

Paranoid, psychotic, and depressive symptoms can be present during active methamphetamine use, persist into abstinence, and/or emerge during abstinence among methamphetamine patients. Therefore, it is important to frequently assess for and/or actively monitor these symptoms over the course of treatment [128]. Patients with either severe psychiatric comorbidity or severe methamphetamine-induced psychiatric symptoms are unable to safely and effectively function as outpatients and should be admitted to an inpatient facility to undergo medical evaluation, treatment, and observation. Some patients require only 48 to 72 hours of observation for agitation, paranoia, anxiety, or psychotic symptoms to be properly evaluated and managed, while others exhibit symptoms that are not readily alleviated, even with optimal pharmacotherapy. Antipsychotic medications such as olanzapine may be necessary on a long-term basis [85; 129].

Many patients who use methamphetamine have difficulty controlling angry and violent impulses, reflecting the importance in addressing these issues in treatment. The high rates of anger and violence in female methamphetamine abusers also underscore the importance of avoiding gender stereotypes and questioning female patients as thoroughly as male patients about these issues [69]. Management strategies for aggressive and violent patients include [130]:

- Keeping the patient grounded in reality
- Placing the patient in a quiet, subdued environment with sufficient personal space
- Conveying an awareness of patient distress
- Remaining nonjudgmental
- Attentive listening
- Reinforcement of progress
- Removing objects that could be used as weapons
- Being prepared to show force with chemical or physical restraints if behavior escalates

Users in a state of methamphetamine-induced agitation or psychoses often present to the emergency department and require rapid sedation. In these cases, lorazepam IV or droperidol IV produce a similar magnitude of sedation within five minutes, with droperidol producing faster and more pronounced sedation and requiring fewer repeat dosings than lorazepam [131].

ALTERNATIVE/COMPLEMENTARY TREATMENT OF METHAMPHETAMINE USE DISORDER

Self-Help and 12-Step Therapy

Twelve-step programs for stimulant and other drug abuse and dependence include Narcotics Anonymous (NA) and Crystal Meth Anonymous (CMA) and are modeled after AA, an abstinence-based support and self-improvement program that is based on the 12-step model of recovery. AA is widely considered the most successful treatment for alcoholism and has helped hundreds of thousands of alcoholics achieve sobriety [132]. The 12-step model emphasizes acceptance of addiction as a chronic progressive disease that can be arrested through abstinence but not cured. Additional elements of the AA model include spiritual growth, personal responsibility, and helping other addicted persons. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution and are a resource for emotional support [132].

Part of the effectiveness of AA, NA, and CMA is rooted in their ability to provide a competing and alternative reinforcer to drug use. Involvement in a 12-step program can enhance the quality of social support and the social network of the member, a potentially highly reinforcing aspect that would be forfeited if drug use is resumed. Other reinforcing elements of 12-step involvement include recognition for increasingly durable periods of abstinence and frequent awareness of the consequences of drug and alcohol use through attendance of meetings [133]. Research shows that establishing a pattern of 12-step program attendance early in treatment predicts the level of ongoing involvement. Thus, healthcare providers should emphasize and facilitate early engagement in a 12-step program [134]. Twelve-step programs are not considered substitutes for treatment. Instead, they are organizations that provide ongoing support in maintenance of abstinence, personal growth, and character development.

Crystal Meth Anonymous (CMA)

Although a fairly new organization, CMA meetings can be found in over 114 metropolitan areas throughout the United States, Canada, New Zealand, and Australia. Only a few studies involving members of CMA have been published; not surprising considering it is a relatively new organization. Lyons et al. primarily focused on the role of CMA on sexual behavior in a subpopulation of methamphetamine- and cocaine-abusing gay and bisexual men attempting to abstain from sex through 12-step program involvement [135]. The qualitative study noted that many methamphetamine users have difficulty with sex in recovery because sex is so intimately associated with methamphetamine use. Although the reductions in stimulant use were not explicitly measured, data gathered from this study indicate that CMA involvement led to dramatic reductions in the number of sexual partners (reduced from seven per month to one per month) and the frequency of unprotected anal intercourse (declined from 70% to 24%). The authors concluded that although the reductions in HIV risk behavior may not be entirely due to the teachings of CMA, the program appears to be a valuable forum to help methamphetamine- and cocaine-addicted persons work through issues, such as sex, that are intimately associated with their stimulant abuse [135]. For additional information, please visit the CMA website at https://www.crystalmeth.org.

INTERVENTIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding the risks associated with the use of methamphetamine and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners.

Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

PROGNOSIS

Unrelenting dysphoria and impaired motivation and cognition, common in methamphetamine patients, can complicate or derail the best available treatment [39]. Poor prognosis and relapse are associated with [98; 136; 137; 138]:

- The severity and duration of protracted withdrawal
- Lack of a supportive environment and pressure from friends and associates to use methamphetamine
- Deficits in coping skills
- Drug craving
- Impaired decision-making capacity
- Frequent exposure to conditioned environmental cues

For patients being treated for methamphetamine abuse in outpatient settings, the abundant supply of illicit methamphetamine and the enticement of rapid relief from protracted withdrawal symptoms can result in resumption of methamphetamine use in the early stages of treatment. Treatment dropout often follows, before any benefit from psychotherapy or pharmacotherapy can be achieved. This is unfortunate because treatment retention is the single most robust predictor of positive treatment outcome in methamphetamine dependence [50; 139].

Neurobiologic factors associated with prognosis have been identified [136]. Specifically, a significant correlation was found between vulnerability to methamphetamine relapse and the severity of degraded brain function in the region mediating decision-making capacity, autonomic arousal processes, guessing, selective attention, and distinguishing task-relevant from task-irrelevant events. Additionally, patients with more severe dopamine transporter depletion have been found to exhibit higher rates of relapse and treatment dropout [60].

CONCLUSION

The current epidemic of methamphetamine abuse has become more widespread than previous periods and has resulted in substantial medical, public health, social service, and criminal justice concerns. This wave of methamphetamine addiction has primarily afflicted persons who are white, rural inhabitants of Western and Midwestern states but now may be shifting to include a wider spectrum of individuals, particularly Native American and Hispanic youths. This shift may reflect America's changing demographics. In addition, urban-dwelling gay and bisexual males have experienced an alarming increase in methamphetamine abuse, resulting in rapid spread of HIV infection fueled by unsafe sexual practices. Thus, medical, mental health, and other healthcare professionals working in a variety of settings with a variety of patient populations are likely to encounter patients with a methamphetamine use disorder. However, devising and implementing effective treatments for patients addicted to these substances has posed a challenge, as the methamphetamine abuser generally differs from the typical patient for whom the 28-day inpatient model was designed in terms of demographics, disease characteristics, and resources. The knowledge gained from this course can greatly assist healthcare professionals in identifying, treating, and providing an appropriate referral to patients with methamphetamine use disorders.

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Evidence-Based Practice Recommendations Citations

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Cannabis and Cannabis Use Disorders

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
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Faculty
Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners Disclosure
The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cannabis, either illicitly or as an adjunct to medical treatment.

Accreditation
NetCE is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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This program is approved by the National Association of Social Workers (Approval #886531582-6972) for Substance Use Disorders continuing education contact hours.

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This course is approved by the Association of Social Work Boards - ASWB NJ CE Course Approval Program Provider #14 Course #50. Social workers will receive the following type and number of credit(s): Clinical Social Work Practice 2, and General Social Work Practice 3 for the approval period starting 09/09/2014 and ending 09/09/2016.

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NetCE designates this enduring material for a maximum of 5 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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AACN Synergy CERP Category A.

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NetCE designates this continuing education activity for 5 continuing education hours for addiction professionals.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through December 12, 2017); California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; Florida, Provider #50-2405; Iowa, Provider #295; Kentucky, Provider #7-0054 through 12/31/2017.

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Special Approval

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to allow healthcare professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients with cannabis use disorders.

Learning Objectives

Upon completion of this course, you should be able to:

1. Review the history of cannabis use and define the concepts of cannabis use disorder and withdrawal.
2. Discuss the epidemiology of cannabis use in the United States, including treatment utilization and risk factors for cannabis use disorders.
3. Outline the pharmacology of cannabis.
4. Review the established and investigational therapeutic uses of cannabis and delta-9-THC.
5. Identify acute effects of cannabis ingestion on both physical and psychological systems.
6. Describe long-term effects of cannabis ingestion and conditions associated with cannabis use, including the associated withdrawal syndrome.
7. Discuss the prognosis and treatment approaches for individuals who misuse cannabis, including considerations for non-English-proficient patients.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Cannabis products such as marijuana and hashish comprise the most widely used recreational drugs both in the United States and worldwide [55]. Although, with a few exceptions, these drugs lack the liability of abuse and dependence seen with other illicit drugs, such as cocaine, methamphetamine, and heroin, physical and psychological withdrawal symptoms can occur with cannabis products, posing an additional consideration in the management of these patients. This course will provide the most pertinent, up-to-date information regarding the demographics and characteristics of cannabis users, the history of therapeutic and recreational use of the drug, the pharmacology and clinical effects, adverse effects and conditions, and the management and treatment of overdose, toxicity, and use disorders.

HISTORY OF CANNABIS USE

Although the later part of the 20th century saw a rise in the use of cannabis for recreational, religious/spiritual, and medicinal purposes, humans have been consuming cannabis since prehistory. Cannabis, native to Central Asia, is one of the oldest known psychotropic drugs. Cultivated and consumed long before recorded history, archeological discovery indicates that it was used in China since around 4000 B.C.E. There are several species of cannabis, including *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. *Cannabis sativa* is the most widely used variety and can be cultivated in a variety of climates [1; 13].

The two main derivatives of cannabis are marijuana and hashish. The term marijuana originated in Mexico to describe cheap tobacco; today, it refers to the dried leaves and flowers of the *Cannabis* plant. Hashish, an Arabic term, is the viscous resin of the plant [1; 13].

The Chinese emperor Shen Nung is believed to be the first to describe the properties and therapeutic uses of cannabis, which appeared in his compendium of Chinese medicinal herbs written in 2737 B.C.E. Following this, cannabis was cultivated for its fiber, seeds, medicinal use, and recreational consumption, which then spread to India from China [1].

In 1839, William O'Shaughnessy, a British physician and surgeon working in India, was the first individual in Western medicine to discover the use of cannabis as an analgesic, appetite stimulant, antiemetic, muscle relaxant, or anticonvulsant. In 1854, cannabis was listed in the United States Dispensatory; however, after prohibition was repealed, American authorities condemned the use of cannabis, claiming it responsible for insanity, intellectual deterioration, violence, and various crimes. In 1937, the U.S. Government introduced the *Marihuana Tax Act*. According to this legislation, a tax of $1 per ounce was collected when cannabis was used for medical purposes and $100 per ounce when it was used for unapproved purposes [13]. Cannabis was removed from the U.S. Pharmacopoeia in 1942 [1].

DEFINITION OF CANNABIS USE DISORDERS

Although severe problems associated with abuse and dependence are less common among cannabis users than among other drug users, they do occur. Furthermore, cannabis had the highest rate of past year use or dependence in 2013 of all illicit drugs [5]. (Please note that laws passed in Alaska, Washington, Oregon, Colorado, and the District of Columbia have decriminalized recreational use of cannabis.

Cannabis use disorder is best described as a chronic relapsing disease characterized by compulsive seeking and use of cannabis, accompanied by functional and molecular changes to the brain [84]. The single most defining aspect of cannabis use disorder is the salience of the relationship with the drug. The stronger the relationship, the more likely the patient will continue problematic use despite internal and external consequences. Individuals who use cannabis often believe it is necessary to get through daily activities, alleviate stress, and cope with problems. Physiological adaptation, evidenced by tolerance and withdrawal, is often present but may not be sufficient for diagnosis. Cannabis use disorder is diagnosed behaviorally and is evidenced by cravings for cannabis, preoccupation with use of the drug, sneaking and concealing ingestion, loss of the ability to control cannabis use, and continued use despite significant physical, psychological, social, or occupational consequences [84]. Cannabis use disorder may be further qualified as mild, moderate, or severe based on the number of diagnostic criteria fulfilled.

Cannabis withdrawal is a condition that occurs following cessation or substantial reduction in use in previously heavy and chronic users [84]. Withdrawal symptoms (e.g., depression/mood changes, anxiety, sleep difficulties, anorexia, physical symptoms) must result in significant distress and/or affect the patient's social, occupational, or other important areas of functioning.

Identifying patients with a cannabis-related disorder can be difficult, as use disorders and associated problems are typically slow to develop. Patients frequently do not recognize they have a problem or do not want to give up their drug use. They may also be attempting to conceal their drug use from parents, physicians, and other authority figures. Unexplained deterioration in academic or work performance, problems with or changes in social relationships, and changes in recreational activities are signs of a possible problem [4].

EPIDEMIOLOGY OF CANNABIS USE

The 2013 National Survey on Drug Use and Health found that 43.7% of Americans 12 years of age and older had tried cannabis at least once in their lifetimes, and 19.8 million (7.5%) had used cannabis in the past month [5; 57]. Adolescent boys in all age groups are more likely than girls to have used cannabis in the last 30 days [5]. Among ethnic groups, non-Hispanic/Latino mixed race (16%) and Native Hawaiian/other Pacific Islander (13.4%) individuals 12 years of age and older are the most likely to have used cannabis within the last month, followed by American Indian/Alaska Native (10.8%), black/African American (8.7%), and white (7.7%) [57]. Hispanic or Latino (6.5%) and Asian (2.2%) adults and adolescents are the least likely to have used cannabis in the past month [57].

Of the 24.6 million illicit drug users in the United States, 80.6% were current (past month) users of cannabis, with the majority (64.7%) using cannabis exclusively [5]. In 2013, the National Survey on Drug Use and Health found that 4.3 million Americans met the criteria for cannabis dependence [5]. Approximately 3.4% of adolescents and 1.5% of adults who have used cannabis in the past year meet the *Diagnostic and Statistical Manual of Mental Disorders* 4th edition (DSM-IV) criteria for cannabis use disorder; as of 2015, no prevalence data are available for the DSM-5 criteria [84]. Analysis of data from 1992 to 2002 by researchers at the National Institutes of Health revealed that while dependence/abuse rates (using DSM-IV criteria) grew only slightly overall during that decade (from 1.2% to 1.5%), a sharp increase was noted among particular subgroups (e.g., black men/women and Hispanic men 18 to 29 years of age; white men and black women 45 to 64 years of age) [61]. The researchers noted that the increase in use disorders was unrelated to a substantial overall increase in frequency or quantity of use and was possibly associated with higher cannabis

potency, decreased cost, and various societal factors [5; 57]. The 2013 National Survey on Drug Use and Health noted a similar rate (1.6%) [57].

It is estimated that there are 6,600 cannabis initiates (12 years of age and older) every day [5]. Approximately 17.4% of persons who use cannabis are daily or nearly daily users, and as noted, cannabis use disorder affects 1.8% of the population, a higher rate than any other illicit drug [5; 9]. This rate is mainly attributable to the greater numbers of cannabis users relative to users of other substances [8]. When examining the risk of dependence among those who have ever used a particular substance (referred to as conditional dependence), the rates for alcohol (22.7%), cocaine (20.9%), and tobacco (67.5%) are significantly higher than for cannabis (8.9%) [8]. However, the risk of developing dependence is increased in those who begin using cannabis in adolescence (16.7%) and among those who are daily users (25% to 50%) [62].

The rate of cannabis use by children and adolescents doubled during the 1990s [9]. After a slight decline and leveling off from 2000 to 2007, the rate again began (and continues) to climb [5]. Occasional cannabis experimentation during adolescence, while illegal, is often considered normative behavior and is not strongly correlated with behavioral or emotional disorders in the general population [9]. Although the exact number is unclear, approximately one-half of "very young" individuals who use cannabis more than monthly exhibit behavioral or emotional difficulties. It is unclear if these difficulties exist before or are an effect of cannabis use or of overlapping factors. Genetic behavior disorders, parents who use cannabis, family disintegration, and "loss of trusting attachments to key adults" have been implicated as both causes of adversity leading to cannabis use and of anxiety, depression, and risk-taking behaviors in pre-adolescents [9]. The perceived impact that cannabis has on physical and psychological health, along with other negative factors, strongly predicts use patterns; past-month use rates were 0.6% among adolescents who saw "great risk" versus 9.3% among those who perceived lesser or no risks [5].

TREATMENT UTILIZATION

Increases in both the prevalence of cannabis use and the potency of cannabis have contributed to the 381% increase in cannabis- and other cannabinoid-related emergency department episodes reported from 2002 to 2011 [62; 63]. Cannabis-related conditions that may be seen in an emergency department include chronic addiction to cannabis, acute cannabis psychosis, and cannabis-related schizophrenia [10].

Utilization of treatment services for cannabis dependence has also increased. Adults entering substance abuse treatment programs with cannabis-related problems doubled in the 1990s, and primary admissions for cannabis rose from 13% in 1999 to 17.5% in 2012 [64]. The 2012 percentage of cannabis treatment admissions has surpassed those for cocaine (6.9%) and heroin (16.3%) and is second only to admissions for alcohol treatment (38.9%) [64].

However, these statistics are dramatically higher among adolescents. Nearly 30% of all treatment admission for substance use disorders among adolescents 12 to 17 years of age cite cannabis as either the primary or secondary reason for admission [64]. As was witnessed with adults in the 1990s, the number of adolescents receiving treatment at public treatment centers for cannabis abuse or dependence also doubled during this period [12].

Overall, the proportion of those seeking treatment for cannabis dependence is relatively low in the United States. This may be partially due to the perception of cannabis as a relatively innocuous drug [13]. In a sample of 311 cannabis-dependent users (according to the DSM-IV criteria), the leading reasons for failure to seek treatment included a desire for self-reliance (36.7%), perceived treatment ineffectiveness (16.7%), and avoiding stigma (13.3%) [3].

RISK FACTORS FOR CANNABIS USE DISORDERS

Cannabis use typically begins in early to middle adolescence, and use tends to peak during late adolescence and young adulthood [13]. Many people first use cannabis out of curiosity, peer pressure, or both, and continue to use it for the desired effects of euphoria, relaxation, heightened sensations and perceptions, and socialization with other users. Factors that contribute to chronic use include easy access, the expectation of few or no legal consequences for use, and attempts to self-medicate physical and emotional problems.

A major risk factor for adolescent substance abuse, including cannabis use, is the presence of conduct problems in childhood. This may be because family conflict, poor parental monitoring, parental substance use, academic problems, and association with deviant peers are all risk factors for both substance abuse and conduct problems. More than one-half of adolescents with substance abuse problems also exhibit conduct problems [12]. Co-occurrence of these problems is a strong predictor of poor outcome following substance abuse treatment [12]. Factors associated with cannabis dependence include male gender, adolescent aggression/delinquency, childhood abuse (particularly sexual abuse), and evidence of adolescent risk-taking behaviors, such as cigarette smoking, conduct problems, and involvement in a delinquent peer group [88; 89]. One study found that externalizing disorders (e.g., antisocial personality disorder) from proximal developmental periods were a significant risk factor for future cannabis use disorders in adolescents and young adults; internalizing disorders were not [91]. Exposure to multiple risk factors is associated with poorer prognosis.

Early subjective response to cannabis is associated with later risk of misuse [16; 90]. Participants in a survey reporting five positive reactions to the drug had 20 times greater risk of later use disorder than those who did not experience positive reactions, even after controlling for confounding factors. These findings suggest that early subjective and physiological reactions to cannabis are predictive of later misuse and possibly reflect underlying genetic differences in vulnerability to use disorders. These possible genetic predispositions are likely mediated by individual differences in the responsiveness of the mesolimbic dopamine system to substance use [16].

Several factors associated with successful cessation of cannabis use have been identified. These factors include older age, female gender, married marital status, infrequent cannabis use, absence of delinquent behavior, exposure to formal treatment, higher socioeconomic status, high school completion, and non-using friends [17; 92; 93].

Genetic Vulnerability Theory

Analyses of several adoption, family, and twin studies that examined the relationship between cannabis use and heritable factors determined that the use of cannabis (and other licit and illicit substances) is due in part to genetic vulnerability and an overlap of environmental influences [18; 94]. There appear to be substantial genetic influences on measures of cannabis involvement that correlate with progression to greater levels of addiction, and an individual's vulnerability to cannabis abuse/dependence is shaped by a common susceptibility to multiple substance abuse and also by risk factors unique to cannabis. Researchers in one twin study clarified the basics of this theory in their conclusion, stating that genetic factors predispose individuals to substance use/abuse whereas environmental experiences determine which class of psychoactive substances a predisposed individual will prefer over another [65].In a meta-analysis evaluating the relative magnitude of the influence of genetic and environmental factors on problematic cannabis

use, researchers estimated that proportion of the total variance attributable to genetics was 51% in men/boys and 59% in women/girls [94].

ESCALATION OF CANNABIS USE TO OTHER ILLICIT DRUGS

Early onset and frequency of cannabis use are strong predictors of escalation in other illicit drug use across sexes, populations, ethnicities, and socioeconomic strata. Frequent cannabis use during young adulthood significantly increases the risk of polysubstance abuse, earlier onset of substance dependence, poorer educational and occupational outcomes, multiple health and psychiatric problems, and criminal justice system involvement [15].

Cannabis and other illicit drug use may be correlated. Studies have shown that cannabis is a potential "gateway drug," leading to the use and abuse of more dangerous drugs, such as cocaine and heroin [18]. However, it should be noted that evidence of a causal relationship between cannabis use and progression to other drug use has not been clearly proven [18]. A report from the National Center on Addiction and Substance Abuse at Columbia University found that cannabis's "gateway" effect (if any) is far less important than that of cigarettes and alcohol, and teens who use alcohol and nicotine are 30 times more likely to try cannabis [66]. Analysis of data from the National Epidemiological Survey on Alcohol and Related Conditions found that 44.7% of individuals who try cannabis progress to another illicit drug in their lifetimes, although the researchers in this study did not control for lifetime alcohol or nicotine use [95]. One theory is that dopaminergic effects of alcohol, cannabis, and nicotine lead users to seek similar effects from other, more potent drugs.

PHARMACOLOGY

Cannabis contains more than 480 known chemicals, more than 100 of which are grouped under the category of cannabinoids [1; 96]. The primary psychoactive ingredient is delta-9-tetrahydrocannabinol (delta-9-THC), which accounts for up to 25% of the total dry weight of high-potency strains [69]. Other cannabinoids, including delta-8-THC, cannabinol, cannabicyclol, cannabichromene, and cannabigerol, are present in small quantities (typically less than 5% dry weight) and have no significant psychotropic effects compared to THC. It is unknown whether these compounds may have an impact on the overall effect of cannabis [1].

One notable exception is cannabidiol (CBD), which in some cannabis strains can account for up to 5% dry weight and has demonstrated therapeutic efficacy for psychosis, anxiety, and other disorders in small-scale studies [69; 70; 71]. The psychotomimetic and anxiogenic effects of THC itself are thought to be attenuated by CBD [72]. In a 2011 study, cannabis users who ingested high-CBD-content cannabis experienced significantly lower degrees of psychotic symptoms compared to those who ingested high-THC-content cannabis [70]. Cannabinoid receptor type 2 (CB2) activity accounts for some anti-inflammatory and antinociceptive effects, while the anxiolytic effects of CBD probably result from $5HT_{1\text{-}A}$ (serotonin) receptor agonist activity [72; 73]. CBD also exhibits significant anti-inflammatory and analgesic effects [74].

Cannabis is ingested in many forms, but it is most often smoked in the form of a cigarette ("joint") or out of a pipe, water pipe (e.g., "bong"), or improvised vessel (e.g., sawn-off plastic bottle). It may also be added as an ingredient in baked goods, eaten, or drunk as an extract. Because of its relative water insolubility, it is unsuitable for intravenous use [21]. Vaporizing cannabis (heating below its flash point), either with a purpose-built vaporizer unit or with a heating wand and a conventional pipe or water pipe, is becoming increasingly popular, especially among medicinal and/or

"health conscious" users. This method of use offers slightly elevated THC availability (allowing the user to "smoke" less) and greatly reduced combustion byproduct toxicity compared to smoking [67].

Cannabinoids are present in the stalks, leaves, flowers, and seeds of the plant, but they are particularly abundant in the resin secreted by the female plant. THC content varies among the available sources and preparations of cannabis. Advances in cultivation (such as hydroponic farming) and plant-breeding techniques have increased the potency of cannabis products over time [97].

During the 1960s and 1970s, an average joint contained about 10 mg of THC. Today, a similar-size joint made of a potent subspecies of *Cannabis sativa* may contain 60–150 mg of THC. This can increase to 300 mg if the joint is laced with hashish oil or resin. The substantial increase in potency in cannabis products today exposes cannabis smokers to many times the THC dose compared to their counterparts in the 1960s and 1970s. This is an important fact, as the effects of THC are dose-related and early research on cannabis was conducted in the 1970s using doses of 5–25 mg THC. Some researchers consider the research published on cannabis use during the 1960s and 1970s to be obsolete [21; 22].

PHARMACOKINETICS OF CANNABINOIDS

Approximately 50% of the THC and other cannabinoids present in a cannabis cigarette enter the mainstream smoke and are inhaled [22]. Smoking style affects the amount absorbed through the lungs, with experienced smokers who inhale deeply and hold the smoke in the lungs for some seconds before exhaling, ingesting virtually all of the cannabinoids present in the mainstream smoke [22].

The onset of action of inhaled cannabis is within seconds, and full effect is achieved within 30 minutes; vaporized cannabis results in higher serum THC levels after 30 to 60 minutes, but this can vary based on self-administration preferences. The bioavailability after oral ingestion is lower than that seen with inhalation; blood concentrations are as low as 25% to 30% of those obtained by smoking the same dose, partly due to hepatic first-pass metabolism [21]. The onset of effect is delayed (up to 4 hours) after oral ingestion, but the duration is prolonged because of continued slow absorption from the gut [21].

As little as 2.5 mg of THC is enough to produce measurable psychological and physical effects in the occasional cannabis user. Upon transferring to the bloodstream, cannabinoids are distributed rapidly systemically, first reaching the fatty tissues and organs with the highest blood flow, such as the brain, lungs, and liver [99]. Within the brain, cannabinoids are differentially distributed, reaching high concentrations in the neocortical areas, especially the frontal cortex; the limbic areas, including the hippocampus and amygdala; sensory areas, such as the visual and auditory cortex; motor areas, including the basal ganglia and cerebellum; and the pons [22]. Whether THC accumulates in the brain with long-term use is unknown, due to limits in THC access and accumulation imposed by the blood-brain barrier.

Cannabinoids are highly fat soluble and accumulate in fatty tissues. From these tissues, the compounds are very slowly released into other parts of the body. In occasional users, the plasma elimination half-life of THC is approximately 56 hours; in chronic users it is shortened to 28 hours. However, due to its sequestration in fat, the tissue half-life is approximately 7 days and complete elimination of one dose may take as long as 30 days [22].

Cannabinoids are mainly metabolized in the liver, where they produce more than 20 metabolites, some of which are psychoactive and many of which have plasma elimination half-lives of the order of 50 hours. The major metabolite is 11-hydroxy-THC, which may be more potent than the parent compound and be responsible for some of the effects of cannabis. Relative to inhalation, first-pass hepatic metabolism with oral ingestion yields a greater proportion of 11-hydroxy-THC [99].

Elimination occurs over several days due to the slow rediffusion of THC from body fat and other tissues. Roughly 20% to 35% of THC is eliminated in urine and 65% to 80% in feces. By five days, 80% to 90% of THC is eliminated, although THC from a single dose can be detected in plasma up to 13 days later in chronic smokers as a result of extensive storage and release from body fat [99].

PHARMACODYNAMICS

Cannabinoids act primarily by binding to the CB1 and CB2 receptors. Both of these receptors are part of the G-protein coupled class, and their activation results in inhibition of adenylate cyclase activity. Identification of agonists and antagonists of these receptors has stimulated interest in medical uses of cannabis [1; 13].

Cannabinoids exert many of their effects by combining with specific receptors in the central nervous system (CNS) and peripheral nervous system. The discovery of cannabinoid receptors led to a search for the endogenous ligand with which the receptors naturally interact. The first substance, discovered in 1992, was eventually isolated and named anandamide after the Sanskrit word for bliss, *ananda*; 2-arachidonoylglycerol was discovered soon after. Anandamides are derivatives of arachidonic acid, a polyunsaturated omega-6 fatty acid, and are related to prostaglandins [22; 68].

Both anandamides and their receptors lie in neuronal lipid membranes and modulate neuronal activity through intracellular G-proteins that control cyclic adenosine monophosphate formation and calcium and potassium ion transport [21]. The endogenous cannabinoid system is a signaling system that includes cannabinoid receptors, endogenous receptor ligands (termed endocannabinoids), and their synthesizing and degrading enzymes [101]. Core functions of the endogenous cannabinoid system have been described as "relax, eat, sleep, forget, and protect," shorthand for the diversity of processes involving the ECS [102]. The ECS regulates neuronal excitability and inflammation in pain circuits and cascades and also helps regulate movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal axis modulation, immunomodulation, mood, wake/sleep cycles, blood pressure, bone density, tumor surveillance, neuroprotection, and reproduction. A number of the cannabinoids' pharmacological effects can be explained on the basis of these interactions, examples being tachycardia and xerostomia, which are caused by the effects of THC on acetylcholine [23].

CB2 receptors are primarily found in immune cells, suggesting that cannabinoids may play a role in the immune response [68]. CB1 receptors are found throughout the body but are concentrated in the brain, with the highest density in the substantia nigra, cerebellum, globus pallidus, and caudate nucleus. Other brain regions with high CB1 receptor density include the cerebellum, hippocampus, cerebral cortex, and nucleus accumbens. The distribution of CB receptors indicates that the endocannabinoid system has effects on a broad range of behaviors [13].

TOXICITY

There are no cases in the literature of death due to toxicity following the maximum oral THC dose in dogs (up to 3,000 mg/kg THC) and monkeys (up to 9,000 mg/kg THC). In animals and humans, it is virtually impossible to induce fatal toxicity, and no human fatalities resulting from cannabis ingestion have been documented to date [73]. The greatest risk for toxicity and potential overdose is among children who may consume cannabis edibles, beverages, or candies inadvertently [98]. In adults, most toxic reactions are mild, but in children, overdose can result in significant respiratory depression [98].

TOLERANCE

Tolerance to most of the THC effects eventually develops in regular users. Cannabis tolerance primarily results from pharmacodynamic mechanisms, including changes in CB1 signaling ability due to receptor desensitization and down-regulation. THC tolerance varies across different brain regions, possibly explaining why tolerance develops to some cannabis effects but not to others [100]. Tolerance to most THC effects develops after a few doses and then disappears rapidly following cessation.

DRUG-DRUG INTERACTIONS

As with many drugs, cannabis can enhance or attenuate the effects of other medications. A combination of dronabinol (a cannabinoid) and prochlorperazine is more effective in reducing chemotherapy-associated nausea and vomiting than prochlorperazine alone [103]. Cannabis can also augment the sedating effects of other psychotropic substances, such as alcohol and benzodiazepines. A number of synergistic effects may be therapeutically desirable, such as the enhancement of:

- Muscle relaxants, bronchodilators, and antiglaucoma medication
- Opiate analgesia
- Phenothiazines' antiemetic effect
- Benzodiazepines' antiepileptic action

The cyclooxygenase inhibitors, indomethacin, acetylsalicylic acid, and other nonsteroidal anti-inflammatory drugs antagonize THC effects, reflecting the involvement of cyclooxygenase activity in several THC effects [23].

THERAPEUTIC USE OF CANNABIS

Use of cannabis for medical purposes was first documented in China thousands of years ago, where it was reportedly used to treat malaria, constipation, rheumatism, and childbirth pain [33]. There are also reports of cannabis mixed with wine being used as an analgesic. Throughout history, the medical use of cannabis has been found in records from Asia, the Middle East, Southern Africa, and South America [33].

Despite being categorized as illegal, cannabis has continued to be an attractive option for self-medication among some patients. In 1978, a compassionate program for medicinal cannabis was established by the U.S. government; this program stopped accepting new candidates in 1991 [1]. Cannabis was reintroduced into medical use in 1996 by popular vote and legislative acts in California. By 2015, 22 states and the District of Columbia had followed suit [104]. (For information on laws pertaining to the medical use of cannabis in your state, visit http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.) In addition, cannabis is used by millions of patients for medicinal purposes in jurisdictions where it remains illegal for medical use [105].

For some clinical conditions, most of the published research involves oral cannabinoids, and there are questions over the extent this efficacy can be extrapolated to cannabis. Some reports indicate that patients benefiting from oral cannabinoids are likely to benefit from smoked cannabis, but the reverse is not always true [106]. For example, inhaled cannabis trials for the management of nausea and vomiting are sparse. Although RTCs of dronabinol or nabilone predominate and have

consistently shown efficacy, patients tend to prefer smoked over oral delivery due to the rapid alleviation of nausea and vomiting, ease of titration, and greater tolerability. Thus, for indications for which cannabis RCTs are few or absent, it seems reasonable to extrapolate non-cannabis cannabinoid efficacy to smoked cannabis.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Dronabinol, a synthetic THC derivative, is approved for the treatment of refractory nausea and vomiting caused by antineoplastic drugs used for the treatment of cancer and for appetite loss in anorexia and cachexia of patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) [23]. Dronabinol and nabilone, another synthetic derivative, are generally considered safe, effective antiemetics and are recommended by the National Comprehensive Cancer Network for this use [74]. A vast body of anecdotal evidence from the past 150 years as well as preclinical and clinical trial results strongly indicate a valuable role for cannabis in controlling nausea and vomiting caused by cytotoxic drug administration or secondary to another primary medical condition [107]. A meta-analysis of cannabinoid efficacy in chemotherapy-induced nausea and vomiting found superior antiemetic efficacy of dronabinol, nabilone, levonantradol (not approved for use in the United States), and smoked cannabis compared with conventional drugs and placebo [108].

CHRONIC PAIN

Cannabis has been safely co-administered with a wide range of other drug agents (as discussed) and acts synergistically with opioids to enhance analgesia and allow opioid dose reduction. Chronic pain treatment often requires multiple drug agents that target different pain mechanisms, and the novel mechanism and superior safety profile of cannabis versus opioids suggests that it can be a valuable addition to therapeutic options for chronic pain [109; 110].

The National Institute for Health and Care Excellence recommends against starting *Cannabis sativa* extract to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so.

(http://www.guideline.gov/content.aspx?id=47701. Last accessed July 24, 2015.)

Level of Evidence: Expert Opinion/Consensus Statement

In one study, 10-mg and 20-mg doses of THC were found to be roughly equivalent to 60 mg and 120 mg codeine doses, respectively, and a strong sedative effect was observed [75]. A 2010 British study found that improved analgesia was realized with a THC/CBD extract oromucosal spray in patients whose pain was not alleviated with strong opioids [76]. Twice as many patients given the THC/CBD extract had a 30% reduction in pain (the measure of success) than those administered placebo or a pure THC extract.

SPASTICITY

Spasticity is a core symptom of multiple sclerosis, is common after stroke and with other neurological conditions, and greatly limits movement, activities of daily living, and participation in life by those afflicted. Oral antispasmodic agents are of limited effectiveness, and beneficial treatment options for spasticity have not significantly expanded since the late 1990s [111]. Consequently, many patients with multiple sclerosis have sought relief through cannabis use. The oromucosal cannabinoid spray nabiximols appears efficacious in multiple sclerosis but is not yet approved for clinical use in the United States [112]. Several clinical trials of cannabis in multiple sclerosis have been performed, and these studies have demonstrated cannabis efficacy in reducing spasticity and pain [113; 114].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Academy of Neurology asserts that clinicians might offer oral cannabis extract to patients with multiple sclerosis to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain).

(http://www.guideline.gov/content.aspx?id=47909. Last accessed July 24, 2015.)

Level of Evidence: A (Established as effective for the given condition in the specified population.)

CANCER- AND HIV-ASSOCIATED ANOREXIA AND WEIGHT LOSS

The effectiveness of cannabis and THC derivatives as appetite stimulants, coupled with their antiemetic, analgesic, anxiolytic, hypnotic, and antipyretic properties, suggests a unique role in alleviating symptoms in selected patients with cancer or AIDS [33]. A double-blind clinical trial of HIV-positive patients found smoked cannabis increased daily caloric intake and body weight, with few adverse effects [115]. Benefits from smoked cannabis reported by 252 patients with HIV/AIDS included relief of anxiety and/or depression (57%), improved appetite (53%), increased pleasure (33%), and pain relief (28%). However, recent use of cannabis was strongly associated with severe nausea [116].

A review of cannabinoid use in cancer patients found a beneficial effect in stimulating appetite in patients who were receiving chemotherapy or experiencing pain [117]. Interestingly, the results of several preclinical and preliminary clinical testing studies have suggested that cannabinoids inhibit tumor and/or malignant cell growth in pancreatic, lung, leukemic, melanoma, oral, and lymphoma cancers and other malignant tumors [118].

TREATMENT-RESISTANT GLAUCOMA

High intraocular pressure is a risk factor for glaucoma, and smoked cannabis has been found to reduce pupil restriction, conjunctival hyperemia, and intraocular pressure by approximately 25% in those with normal range intraocular pressure with visual field changes, healthy adults, and patients with glaucoma [119]. Although other drugs are the preferred first-line agents, some patients and physicians have found cannabis useful when standard therapies fail [120].

ACUTE CANNABIS EFFECTS

Similar to other drugs with an abuse liability, such as heroin, cocaine, amphetamines, and nicotine, the pleasurable effects of cannabis are the result of the release of dopamine in the reward circuitry, comprised of the subcortical ventral tegmentum, nucleus accumbens, striatum, and medial prefrontal cortex [9; 24]. Transmission of dopamine is increased in the nucleus accumbens following acute administration of cannabinoid agonists.

BEHAVIORAL AND PSYCHOLOGICAL EFFECTS

The pharmacological actions of cannabinoids are complex. The resulting effects are a unique combination of those found with the use of depressants and hallucinogens. Because cannabinoid receptors are widely distributed through the body, numerous body systems are affected [2; 22]. The experience of intoxication is highly variable and is influenced by the dose, the environment, and the experience and expectations of the user [24].

Effects on Mood

The euphoriant potential of cannabis is probably the single most important characteristic in sustaining its widespread and often chronic recreational use. This effect varies greatly with dose, route of administration, expectation, environment, and personality of the user. However, dysphoric reactions to cannabis are not uncommon. In some cases, use may result in severe anxiety and panic,

unpleasant somatic sensations, and paranoia. Anxiety-panic reactions are the most common adverse psychological effects of cannabis use. Flashbacks, whereby the original drug experience (usually dysphoria) is re-experienced weeks or months later, are possible and may represent a psychological reaction similar to that of post-traumatic stress disorder [22].

Sedative and Anxiolytic Effects

Following an initial period of excitement after acute ingestion of cannabis, a generalized CNS depressant effect is observed. This may lead to drowsiness and sleep toward the end of a period of intoxication [22].

Effects on Perception

The changes in perception that result from cannabis and THC affect all sensory modalities. Color and sound perception may be heightened, and musical appreciation may be increased. Temporal and spatial perception is distorted, impairing judgment of distance and time. Even after small doses, persons under the influence of cannabis consistently overestimate the passage of time. Persistent visual changes, some lasting for months, have been documented [22].

Effects on Motor Function

As noted, the initial period of excitement and increased motor activity after cannabis ingestion is followed by a state of physical inertia, with ataxia, dysarthria, and general incoordination possibly lasting for several hours. Motor performance, including measurements of body sway, tracking ability, pursuit motor performance, hand-eye coordination, reaction time, and physical strength, is demonstrably impaired [22].

Effects on Cognition and Memory

The effects of cannabis on cognitive processes are characterized initially by subjective feelings of accelerated speed of thought, flight of ideas that may seem unusually profound, and a crowding of perceptions. Higher doses can result in out-of-control thoughts, fragmented thinking, and mental confusion. Cannabis is associated with short-term memory deficits; it is believed that these deficits may be caused by an attention deficit combined with an inability to filter out irrelevant information and the intrusion of extraneous thoughts. Memory lapses may contribute to the distortion in the perception of time and poor psychomotor performance in complex tasks [22].

Psychomotor Performance

Even low doses of THC (5–15 mg) can significantly impair an individual's ability to perform complex or demanding tasks, including those involved in fine hand-eye coordination, complex tracking, divided attention tasks, visual information processing, digit code tests, and alternate addition-subtraction tasks [22]. Psychomotor performance further deteriorates at higher doses, and impairment can persist several hours following a single dose [22].

Aggression and Violence

Cannabis typically decreases aggression and increases sociability. However, some individuals, particularly those under stress and predisposed to violence, become aggressive after taking cannabis. Research has shown that cannabis users with a history of aggression have a 60% greater likelihood of perpetrating partner violence than nonusers [124]. Violent behavior may be more common among those with acute paranoid or manic psychosis induced by cannabis and polydrug use [22].

Psychiatric Symptoms

Cannabis use can lead to a range of short-lived psychiatric symptoms, including depersonalization, derealization, a feeling of loss of control, fear of dying, irrational panic, and paranoid ideas [14]. After taking a large dose of THC, vulnerable users may temporarily experience a form of drug-induced psychosis. This is classified in the DSM-5 as cannabis intoxication with perceptual disturbances or as a substance-induced psychotic disorder and is diagnosed if the hallucinations are not better explained by another medical or mental disorder and if the symptoms appear during or within two hours of substance use or withdrawal [84].

Cannabis-induced psychosis has the potential to require hospital admission. During the initial diagnosis, this psychosis may be misidentified as schizophrenia, as patients may display characteristic schizophrenic symptoms, such as delusions of control, grandiose identity, persecution, thought insertion, auditory hallucinations, altered perception, and blunted affect [24].

PHYSICAL EFFECTS

Cardiovascular Effects

Acute doses of cannabis may induce tachycardia with peripheral vasodilatation, which can result in postural hypotension and a slight decrease in body temperature. Cardiac output may be increased by as much as 30%, accompanied by increased cardiac work and oxygen demand. Because of this, cannabis can aggravate pre-existing heart disease. The absorption of relatively large amounts of carbon monoxide from smoking cannabis also contributes to the long-term cardiovascular risk of chronic cannabis use [22]. Reddening of the conjunctivae, a characteristic sign of cannabis use, is the result of widespread vasodilation [21].

Respiratory Effects

Cannabis smoke contains many of the same constituents as tobacco smoke (minus the nicotine), including bronchial irritants, tumor initiators (mutagens), tumor promoters, and carcinogens. The tar from cannabis smoke also contains higher concentrations of the carcinogens benzanthracenes and benzopyrenes than tobacco smoke tar. Smoking a cannabis cigarette results in inhalation of three times the amount of tar of a tobacco cigarette, and respiratory tract retention is greater than smoking a tobacco cigarette [21; 22]. As a result, cannabis use may result in impairment of lung function, leading to airflow obstruction and hyperinflation [59].

Although many carcinogens and tumor promoters are common to tobacco and cannabis smoke, differences in the active constituents result in different biological outcomes. Molecules in tobacco smoke enhance carcinogenic pathways through several mechanisms. In contrast, molecules in cannabis smoke inhibit carcinogenic pathways through down-regulation of immunologically-generated free radical production (the innate response to inhaled smoke and particulate); THC blockade of enzymatic conversion of smoke constituents into carcinogens; the absence of cannabinoid receptors in respiratory epithelial cells (which maintains DNA damage checkpoint mechanism integrity with prolonged cannabis smoke exposure); and the anti-angiogenic, tumor-retardant, and anti-inflammatory activity of many cannabinoid smoke constituents [125]. Large studies assessing the potential risk of lung cancer with chronic cannabis use have reached different conclusions, with one finding no increased risk and another reporting a twofold increase in the risk of lung cancer among long-term heavy users [126; 127]. Additional research is necessary to parse these findings.

A University of California, San Francisco, study found that vaporizing cannabis eliminates many of the harmful combustion byproducts (e.g., benzene, naphthalene, toluene, other aromatic hydrocarbon toxins) and greatly reduces tar and carbon monoxide from the inhaled charge [67]. Therapeutic plasma THC levels are slightly increased with this administration, and it was determined that vaporizing cannabis is safer than smoking.

Endocrine/Reproductive System Effects

Cannabinoids, including THC, bind to androgen receptors, and cannabis is considered antiandrogenic. However, the drug's effects on fertility are unclear. Chronic cannabis ingestion appears to have negative effects on sperm quality (e.g., a reduction in the volume and number of spermatozoa, changes in morphology and motility) [121]. In women, regular cannabis smoking may be associated with suppression of ovulation. Chronic use

may cause galactorrhea in women and gynecomastia in men. Endocrine changes resulting from cannabis use may be significant in prepubertal users, in whom cannabis use may suppress sexual maturation as well as social and personal development and learning of coping skills. There is no evidence of teratogenicity during pregnancy, but some studies suggest low neonatal birth weight from chronic maternal cannabis smoking, possibly related to fetal hypoxia and placental complications [21; 22].

Developmental Effects

There is some evidence that offspring of mothers who consumed cannabis during pregnancy may be at increased risk for behavioral and conduct problems, impaired executive functioning, and poor school achievement [122]. In addition, adolescents who regularly use cannabis may have impairments of learning and personal development. However, the possible effects of cannabis consumption on educational performance are difficult to demonstrate [14]. As noted, social development and the acquisition of coping skills may also be stunted. In one study, onset of cannabis use before 17 years of age was associated with a significantly increased risk of cannabis dependence, use of other illicit drugs, suicide attempt, depression, and welfare dependence by 30 years of age [123].

LONG-TERM CANNABIS EFFECTS

RESPIRATORY EFFECTS

Chronic cannabis smoking is associated with bronchitis, emphysema, and squamous metaplasia (a pre-cancerous change), which all occur more frequently in those who have only smoked cannabis than in those who have only smoked tobacco. Individuals who are chronic cannabis and tobacco smokers are at an increased risk for respiratory symptoms and histopathological changes than those who only smoke tobacco or cannabis [21; 22].

IMMUNOSUPPRESSANT EFFECTS

There is not sufficient evidence of significant immunological damage in humans from cannabis [22]. However, it is important to note that cannabis may be contaminated with micro-organisms, such as *Aspergillus* and *Salmonella*, as well as fecal matter. Therefore, a potentially serious adverse effect of cannabis is the risk of infection. In addition, chronic cannabis use may lead to impaired pulmonary defense against infection. The risk of infection is of particular concern in patients with HIV/AIDS due to their increased susceptibility to infection from fungal and bacterial contaminants and epithelial damage from the smoke [4].

NEUROPSYCHOLOGICAL IMPAIRMENT

Chronic cannabis use has been reported to adversely affect cognitive functioning, demonstrated by impaired cognitive performance on a wide range of tasks, including memory and executive functioning [13]. Impairment of short-term visual and verbal memory persisting for 6 weeks after cessation of cannabis use has been reported, and there is a potential for persisting memory deficits in academic performance in school-aged children and college students. Adolescents and those with borderline or low intelligence quotient (IQ) may be particularly susceptible to these effects [22; 128]. A small drop in overall IQ among current but not previous heavy users has also been shown [9].

Imaging studies in cannabis users have identified structural brain changes [25]. In studies using magnetic resonance imaging, heavy cannabis use was correlated with larger cerebellum grey matter volume and reduced amygdala and hippocampus grey matter volume as well as changes in higher functional connectivity in the orbitofrontal cortex network and higher structural connectivity in the forceps minor [25; 129].

A prospective study of 1,037 individuals who regularly use cannabis were followed from birth to 38 years of age [128]. The researchers conducted neuropsychological testing at 13 years of age (prior to initiation of cannabis use) at again at 38 years of age and found that persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. In addition, is users who began using cannabis in adolescence, these deficits remained even after cessation of use [128]. This study did not take into account potential confounding variables, such as personality, family situation, or socioeconomic status.

Overall, claims that chronic cannabis use is permanently neurotoxic have produced little scientific validation. Modestly impaired attention and ability to filter out irrelevant information in former cannabis users has been found in some studies, but other studies have not revealed impairment in cognitive function [24; 128].

Although a degree of controversy exists surrounding whether heavy long-term consumption results in cognitive impairment, irreversible impairment seems to be minimal, if it exists at all. Medical use of cannabis for more than 15 years is generally considered to be well-tolerated without significant physical or cognitive impairment [23].

PSYCHIATRIC COMORBIDITY AND CANNABIS USE

Cannabis use disorders are associated with high rates of other psychiatric diagnoses. The most frequent psychiatric comorbidities are depressed mood, major depression, and dysthymia [14]. It is also possible that cannabis use is a risk factor for serious mental illness, such as schizophrenia [14]. Patients with a history of cannabis dependence are at an increased lifetime risk for a variety of other psychiatric disorders, and current cannabis dependence is strongly associated with alcohol misuse, affective and anxiety disorders, and tobacco use in the past year [17]. However, the pathogenesis of most psychoses is not well understood. Based on postmortem and other studies, abnormalities and dysfunction of the endocannabinoid system may play a significant role in psychological disorders (e.g., depression, suicide, schizophrenia), making the use/misuse of exogenous cannabinoids an ongoing area of research for both therapeutic potential and causation [83].

Depression

Although there is little evidence to support a correlation between depression and infrequent cannabis use, a modest association between early-onset or heavy, habitual cannabis use and later depression has been reported [130]. Because there is little evidence of an increased risk of later cannabis use among patients diagnosed with depression, the self-medication hypothesis is not supported. However, research has shown that depression and chronic use of cannabis are associated, and evidence indicates that heavy cannabis use may increase depressive symptoms in some users. It is important to note that this correlation may be the result of common social, family, and contextual factors that increase the risk of both heavy cannabis use and depression. Overall, heavy cannabis use appears to play a minor role in explaining population rates of depression [27].

Psychoses

Healthcare professionals have observed a possible association between habitual cannabis use and psychosis for many years. However, there is considerable disagreement regarding the degree of causation attributable to cannabis use in the development of psychosis among users without an obvious vulnerability to this effect (e.g., genetic factors).

There is biological evidence of a possible causal relationship between cannabis use and psychosis, particularly in relation to non-affective schizophrenia-spectrum disorders [19; 20]. When administered intravenously, delta-9-THC has been found to induce dose-dependent positive and negative psychotic symptoms in individuals with schizophrenia; an interaction between cannabis use and a polymorphism of the catechol-o-methyltransferase gene that codes for dopamine has also been reported [19].

In theory, cannabis use may precipitate a psychosis in several ways [14]:

- Acute induction of a toxic or organic psychosis, with symptoms of confusion and hallucination, that remits on abstinence
- Induction of an acute functional psychosis, similar to an acute schizophreniform state, that lacks the organic features of a toxic psychosis
- Induction of a chronic psychosis that persists after abstinence
- An organic psychosis induced by long-term use that only partially remits after abstinence, leaving a residual deficit state (an amotivational syndrome)

Based on the literature, it is likely that cannabis use induces psychotic disorders in vulnerable individuals, defined as those with a history of unusual experiences that may be in part genetically mediated [19]. The relationship between cannabis use and vulnerability may explain the small (2 to 3 times) increase in risk for psychosis among cannabis users. This interaction has also been used to elucidate the lack of large increases in the incidence rates of psychoses to correspond with the increase in cannabis use rates among young adults and the earlier age of onset of schizophrenia-form disorders in cannabis users [19].

There appears to be at least some evidence linking cannabis use to the development of psychotic disorders, but some argue that the studies have been flawed. Criticisms of studies linking cannabis and psychosis include failure to separate organic and functional psychotic reactions to cannabis; insufficient discrimination between psychoses; and lack of weighing the evidence for and against the category of cannabis psychosis [14]. Although there is evidence to support the belief that cannabis use may contribute to psychosis in certain circumstances, the possible causal mechanisms are complex [14].

A review of evidence from multiple trials demonstrated a likely causal relationship between cannabis use (particularly frequent, chronic use) and psychotic illness, particularly schizophrenia-spectrum disorders [20]. Furthermore, onset of psychotic symptoms in persons with schizophrenia is earlier (by 2.7 years) in those who use cannabis than in nonusers [20]. The first psychotic episode in cannabis users is more likely to present with positive symptoms (e.g., hallucinations, delusions) than negative symptoms (e.g., apathy, social withdrawal) than first episodes in individuals who do not use cannabis.

Researchers have linked new high-potency cannabis strains with increased emergency admissions for psychosis, implicating not only higher levels of THC but also the absence of CBD, which ordinarily tempers the psychotomimetic effects of THC [79; 80]. A British study noted that the typical cannabis product available in the United Kingdom before 2000 was hashish resin, containing essentially equal parts THC and CBD (each up to 4% by weight), and that the typical high-potency herbal cannabis that now dominates the market contains 12% to 18% THC and less than 1.5% CBD. (This is also typical of cannabis available in the United States, particularly strains grown in California [82].) Researchers suspect that the rise in admissions for psychosis is related to this shift. The study concluded that individuals with a longer duration of use and with a preference for high-potency cannabis are at a much greater risk for enduring psychosis than individuals who occasionally smoke hashish [79]. This is supported by research showing that cannabis psychosis is THC dose dependent and that CBD can reverse indicators of THC-induced psychosis in test subjects [80; 81].

There has also been criticism of the belief that chronic heavy cannabis use leads to an amotivational syndrome, described as personality deterioration with loss of energy and drive to work [14]. Some have argued that the supporting evidence for this theory largely originates from uncontrolled studies of long-term cannabis users in various cultures and may be a reflection of ongoing intoxication in frequent users of the drug [14]. More research in this area is required.

Panic Disorder

Cannabis use has also been linked to the development of panic disorder [132]. A study involving 1,000 people 18 to 25 years of age found that 22% reported panic attacks or anxiety symptoms during cannabis intoxication, with women twice as likely as men to report these symptoms [14]. Conversely, in a study of nearly 7,000 adults, the presence of social phobia and panic disorder predicted progression from casual use to cannabis use disorder [131].

An individual's experience of cannabis intoxication may be variable; the same person given the same dose at different times may report different subjective effects. Although many users report a calming, tranquilizing effect, cannabis use may provoke feelings of anxiety or panic in some cases. For patients for whom cannabis use induces panic, a history of previous panic attacks (while sober) may not be present. A study of 66 panic disorder patients found that 24 experienced their first panic attack within 48 hours of cannabis use [54]. It has been suggested that cannabis may provoke anxiety reactions via gamma-aminobutyric acid (GABA) antagonism, which may provoke CNS excitatory neurotransmission and brain hyperexcitability.

Ingestion of high doses of delta-9-THC produces intense anxiety in nearly all users predisposed to anxiety, and the high THC:CBD ratio of cannabis available today may lead to a rise in anxiety/panic disorders among cannabis users in general [82]. In fact, studies indicate that CBD alone has promise in the treatment of social anxiety [133].

Psychosocial Impairment

Antisocial behavior commonly occurs among cannabis users, and this is particularly evident among adolescent users. Adolescents who use cannabis regularly are at risk of experiencing delinquency, school failure, physical and psychological problems, and selling illegal drugs [12].

CANNABIS WITHDRAWAL SYNDROME

A cannabis withdrawal syndrome has been clearly demonstrated and is characterized by a variety of symptoms, including restlessness, nervousness, anxiety, dysphoria, irritability, insomnia, anorexia, muscle tremor, increased reflexes, autonomic effects (e.g., changes in heart rate and blood pressure), sweating, diarrhea, and in some cases aggressive behavior [14; 28; 29; 56]. The most frequent symptoms of cannabis withdrawal are emotional and behavioral in nature and do not typically cause significant physical, medical, or psychiatric disorders [30]. Regular daily use of cannabis can lead to withdrawal symptoms or a full-blown withdrawal syndrome upon cessation of use. With abrupt cessation, withdrawal symptoms emerge within one to two days, reach peak intensity after two to six days, and generally resolve within one to two weeks, though sleep difficulties may persist for more than one month.

Cannabis withdrawal syndrome is included in the DSM-5, and it is new to this edition [84]. Three of the following seven symptom clusters must be identified for a diagnosis according to the DSM-5 definition [84]:

- Irritability, anger, or aggression
- Nervousness or anxiety
- Sleep difficulty (e.g., insomnia, disturbing dreams)
- Decreased appetite or weight loss
- Restlessness

- Depressed mood
- At least one of the following physical symptoms causing significant discomfort
  - Stomach pain
  - Shakiness/tremors
  - Sweating
  - Fever
  - Chills
  - Headache

Using the proposed DSM-5 criteria, researchers asked 384 lifetime, non-treatment-seeking cannabis addicts about their worst abstinence experience and found that 40% would be diagnosed with cannabis withdrawal syndrome [56]. According to the DSM-5, 50% to 95% of adults and adolescents who are enrolled in treatment or who are heavy cannabis users report cannabis withdrawal symptoms [84].

Cannabis withdrawal syndrome typically requires heavy, prolonged use to develop and may significantly impact social, educational, and occupational functioning [84]. In a sample of adolescent cannabis users, the majority reported cannabis withdrawal, with an associated inability to perform school work and increased arguing, that began within 24 hours and worsened during the first several days of the abstinence period, especially in heavy users [32]. The majority of adults seeking treatment for a cannabis use disorder report a history of cannabis withdrawal, with most reporting a co-occurrence of four or more symptoms of substantial severity [30].

Neurochemical causes of cannabinoid withdrawal include reduced dopaminergic activity along the ventral tegmental area-nucleus accumbens pathway, and upregulated expression and release of corticotropin-releasing hormone (CRH) in the central nucleus of the amygdala [13].

COURSE

The onset of abstinence symptoms consistently occurs during the first 1 to 2 days following cessation of cannabis or oral THC administration. Most symptoms return to baseline or to comparison-group levels within 1 to 2 weeks, although irritability, muscle tension, and sleep problems, particularly unusual dreams, may not return to baseline for an extended period. Because most transient symptoms return to baseline and because persons with psychiatric disorders are excluded from studies examining cannabis withdrawal, it is believed that the withdrawal symptoms are not rebound effects indicative of the participants' condition before initiation of cannabis smoking [30; 134].

The administration of cannabis during the first 24 to 96 hours of abstinence results in an abrupt reduction and return to baseline of multiple abstinence symptoms, suggesting that cannabis withdrawal syndrome is specific to THC in humans [30].

CLINICAL SIGNIFICANCE

Cannabis withdrawal has important treatment implications. Multiple symptoms of cannabis withdrawal syndrome are experienced among non-treatment-seeking daily cannabis users as well as inpatients and outpatients with cannabis dependence. In most cases, withdrawal symptoms are clearly observable to persons living with the user, who are able to document the disruption to daily living caused by the symptoms. The majority of persons enrolled in treatment for cannabis dependence acknowledge cannabis withdrawal symptoms, label at least some as moderate-to-severe, and complain that they make cessation of cannabis use more difficult [13; 30]. The symptoms of cannabis withdrawal may overlap with other conditions, including disordered eating, sleep disturbances, and depressive disorders, and therefore heavy cannabis use should be considered in the evaluation of patients with weight loss, sleep problems, and other similar presentations [135].

The significance of cannabis withdrawal and its potentially negative impact on treatment retention and relapse to cannabis use has not escaped the attention of researchers. Several pharmacotherapy trials investigating medications of possible utility in cannabis withdrawal have been undertaken. To date, CBD and nabiximols have both been shown to improve withdrawal symptoms, though additional research is necessary to establish efficacy and safety [136; 137].

TREATMENT OF CANNABIS USE DISORDERS

Until fairly recently, cannabis was not considered a drug with a liability of dependence and addiction. In the limited research, withdrawal did not appear to lead to any obvious physical symptoms, and animals failed to self-administer the drug, a behavior usually associated with drugs of addiction [24]. Few studies had focused on the treatment of cannabis abuse or dependence. However, it is now known that individuals can develop a chronic use pattern associated with dependence symptoms and recurrent psychosocial problems [6; 56]. Two factors have contributed to the historical lack of research: the common beliefs that cannabis abuse rarely occurred as a primary problem and that cannabis use did not produce a true dependence syndrome. Data contrary to these assumptions first appeared in the late 1980s, and treatment development and efficacy studies specific to cannabis dependence first began to appear in the scientific literature during the 1990s [11]. As medicinal use of the drug has accelerated into the mainstream, and bolstered by the discovery of the human endocannabinoid system, a large amount of research into many facets of cannabis and cannabis use has emerged.

CHARACTERISTICS OF PATIENTS SEEKING TREATMENT FOR CANNABIS USE DISORDERS

Although an increasing number of individuals are seeking treatment specifically for a primary problem of cannabis dependence, most do not do so until they are older than 30 years of age. Young adults and adolescents generally seek treatment only when it is mandated by school officials, parents, or the criminal justice system [15].

The constellation of concerns that bring cannabis users to treatment may not be major socioeconomic or psychosocial problems. Rather, patients tend to express more subtle dissatisfaction with multiple areas of functioning and concerns about future health problems, which motivate the desire to quit or reduce use [6]. Individuals seeking treatment for cannabis use tend to exhibit social impairment and psychiatric distress, report multiple adverse consequences associated with cannabis use, and have a history of repeated unsuccessful attempts to stop using. Most patients perceive themselves as unable to quit [10].

Contrary to the popular belief that dependent individuals have to want treatment before it can be effective, most enter treatment in a relatively involuntary state, often to avoid or to undo the consequences of the drug use [34]. A significant opportunity to intervene is often the point at which drug abusers confront the legal consequences of their substance, especially taking into consideration the fact that more drug users are involved with the legal system than with the drug abuse treatment system [15].

PHARMACOTHERAPY

The majority of treatment studies to date involving cannabis use disorders have investigated behavioral and psychosocial therapies. However, given the high rate of relapse and overwhelming numbers of cannabis-dependent individuals, the importance of pharmacotherapy for the treatment of cannabis-dependent individuals, particularly those who have been unresponsive to other treatment modalities, is important [13].

Treatment of Cannabis Withdrawal Symptoms

As cannabis withdrawal symptoms may be a factor contributing to continuing cannabis use, medications alleviating these symptoms could be useful. Unfortunately, there is little research completed that evaluates the effectiveness of potential treatment medications on cannabis withdrawal in humans. According to completed studies, no medication, including selective serotonin reuptake inhibitors, mixed-action antidepressants, atypical antidepressants, anxiolytics, and norepinephrine reuptake inhibitors, has been shown to definitively decrease cannabis use by humans [7; 13; 26; 85].

There is some evidence that bupropion may be effective in lessening the symptoms of cannabis withdrawal [35]. Bupropion facilitates abstinence from cigarette smoking, in part through its ability to decrease negative mood symptoms, and because similar mood symptoms have also been associated with cannabis withdrawal, it was suggested that this medication may have a place in the treatment of cannabis withdrawal. The authors of one study found that bupropion resulted in less craving for the drug, but other studies have reported worsened mood and continued sleep difficulties, possibly caused by bupropion-associated enhanced norepinephrine activity [13; 35; 36].

Other researchers have evaluated the role of nefazodone because of its demonstrated effectiveness in clinical populations with conditions also associated with cannabis withdrawal, including depression, agitation, and anxiety. In a 2009 study, nefazodone decreased irritability and the severity of cannabis dependence, but it is unclear if these effects would ultimately result in improved long-term abstinence [36].

A third study evaluated the effectiveness of divalproex, which was chosen for testing based on evidence of successful treatment of some symptoms associated with cannabis withdrawal, such as irritability and mood lability [13; 37]. Divalproex was not found to positively affect cannabis withdrawal symptoms; in fact, many withdrawal symptoms (e.g., anxiety and irritability) increased compared to placebo. Divalproex also resulted in psychomotor performance disruptions.

Treatment of cannabis withdrawal with gabapentin has shown some promise in a pilot clinical trial [85]. Although the dropout rate was very high (72%), 1,200 mg per day significantly reduced withdrawal symptoms compared to placebo and resulted in decreased cannabis use among those participants that remained [138].Another agent evaluated for its effect on attenuating cannabis withdrawal is dronabinol (oral delta-9-THC) [37]. Use of dronabinol in the treatment of withdrawal symptoms is based on the concept of substituting a longer-acting, pharmacologically equivalent drug for the abused substance to stabilize the patient, with the intent to gradually withdraw the substituted drug. Oral delta-9-THC is successful in markedly reducing withdrawal symptoms, including self reports of drug craving, anxiety, misery, anorexia, and sleep disturbance [140]. Although use of dronabinol is associated with improved withdrawal symptoms and treatment retention, it has not been shown to reduce cannabis self-administration [140].

An issue of potential concern related to treating cannabis-dependent patients with dronabinol is the abuse potential. Abuse liability is influenced by the neurochemical effects as determined by the route of administration, drug concentrations, and the maximum drug concentrations. Thus, administration of dronabinol would be expected to produce much less reinforcement than smoked cannabis. Another advantage is that, unlike smoked cannabis, dronabinol is not associated with adverse pulmonary effects. Considering all of these factors, the benefits of dronabinol in the treatment of cannabis withdrawal appear to outweigh potential risks [13].

One study compared the treatment efficacy of oral dronabinol and the synthetic THC analogue nabilone [86]. The results showed that nabilone has a longer time to peak effect, is more sustained, has fewer negative cognitive effects, and results in greater mood enhancement characteristics compared to dronabinol. Also, the effects are more dose-related, perhaps making it the better option for cannabinoid-replacement withdrawal treatment. Although dronabinol also decreases symptoms of cannabis withdrawal, the drug is ineffective in preventing relapse [86]. Researchers hope nabilone can prove effective for both purposes in clinical trials.

Pharmacotherapy for Relapse Prevention

A small study (11 participants) of daily cannabis users found that nabilone decreased reversed withdrawal-related irritability, sleep disturbances, and anorexia, though psychomotor skills were impaired [60]. Nabilone (8 mg per day) also decreased the rate of relapse, indicating the need for further research [60].

In another study, 25 adult outpatients were randomized to either 6 weeks of placebo or divalproex, then switched to the alternate treatment for an additional 6 weeks. No significant between-groups differences were found in regards to treatment retention, with 38% of divalproex subjects and 33% of control subjects completing the entire study. Persons started on divalproex did not display better outcomes in terms of improvement in cannabis use or psychological symptoms than those started on placebo. All 25 patients had low blood levels of the study medications, suggesting poor compliance. However, retention during the first 8 study weeks was high (>75%), suggesting the medication was discontinued because it was poorly tolerated in this population [31]. Other medications studied for alcohol relapse prevention, including buspirone, baclofen, and mirtazapine, have proven ineffective for cannabis relapse prevention [38; 87].

N-acetylcysteine (NAC), an over-the-counter supplement, has been studied in adolescents with cannabis use disorder [85]. NAC is thought to reinstate normal glutamate activity that is disrupted by chronic cannabis use. The participants who received NAC (1,200 mg twice daily) and contingency management were more than twice as likely to have a negative drug screen compared to those receiving only contingency management [139].

Pharmacotherapy of Cannabis Dependence in Patients with Comorbid Mental Illness

Although clozapine is known to be effective in the treatment of patients with schizophrenia and substance use disorders, its side effect profile limits its clinical utility. A small pilot study comparing clozapine and the second-generation antipsychotic ziprasidone, both agents were found to decrease cannabis use [39]. Ziprasidone was associated with fewer side effects and better compliance with treatment than clozapine. The American Psychiatric Association recommends that patients diagnosed with schizophrenia and cannabis use disorder should be offered pharmacotherapies effective for the treatment of cannabis withdrawal and relapse prevention in addition to psychotherapy [78].

PSYCHOSOCIAL THERAPY

Several psychosocial therapy modalities have been evaluated in the treatment of patients with cannabis use disorders.

Individual Drug Counseling

Cannabis users seeking therapy to quit may participate in standard counseling that is typically offered in community-based substance abuse clinics. Individual drug counseling emphasizes abstinence from cannabis and other drugs through use of self-help groups and a 12-step approach [15].

Contingency Management

Contingency management (CM) approaches to adult substance abuse are effective behavioral interventions to increase drug abstinence and other treatment goals when integrated with other effective psychosocial treatments [40]. Essentially, CM interventions use reinforcement or punishment contingencies to increase or decrease the frequency of predetermined therapeutic and behavioral objectives [12]. Contingency management programs have been found effective to decrease rates of relapse among patients in treatment for cannabis use disorders [40].

Relapse Prevention

Relapse prevention assists patients with decreasing their vulnerability to relapse by addressing topics such as lifestyle balance and managing high-risk situations [11].

Social Support

Social support is based on the necessity of group support for change. Topics discussed in the group setting include getting and giving support, dealing with denial and mood swings, and interacting with peers who continue to use cannabis [11].

Brief Motivational Interviewing

In brief motivational interviewing, a therapist provides feedback from a comprehensive assessment using motivational interviewing techniques. The therapist also instructs subjects on cognitive-behavioral therapy (CBT) techniques that could be used to abstain from cannabis use [11; 41].

Psychosocial Treatment of Adults

One study compared a cognitive-behavioral relapse-prevention treatment; a brief, two-session motivational intervention; and a delayed-treatment control group [41]. The active treatment interventions resulted in greater reductions in cannabis use than delayed treatment. Four months post-intake, participants in the two active groups reported reduced cannabis use compared to the delayed treatment group, reductions in frequency of use per day, lower number of dependence symptoms, and fewer problems related to cannabis use. At 16-month assessment, cannabis use increased in both active treatment groups but was lower than pretreatment levels. Urine drug screens were not obtained, and all drug use data was based on self-report and collateral verification.

In another study, 136 cannabis-dependent adults, 18 to 25 years of age, referred by the criminal justice system, were randomized to one of four treatment conditions. CM consistently produced positive effects in terms of treatment retention and cannabis use, both of which were specifically targeted. There were few significant main effects for motivational enhancement therapy/cognitive-behavioral therapy (MET/CBT) over drug counseling. However, additional analysis suggested that a combination of CM and MET/CBT resulted in better outcomes than MET/CBT without CM and drug counseling plus CM. All three treatments were found to be significantly more effective than drug counseling without CM. Participants assigned to MET/CBT continued to reduce the frequency of their cannabis use through a 6-month follow-up. The study population was noteworthy in that the participants were primarily young African American men with an average of five arrests by 21

years of age, 43% of whom met diagnostic criteria for antisocial personality disorder. Most had not completed high school and were unemployed [15].

In another study, efficacy of two brief interventions for cannabis-dependent adults across three study conditions was compared: two sessions of MET; nine sessions of multicomponent therapy (MET, CBT, and case management); and a delayed treatment control. The study followed 450 adult cannabis smokers with a diagnosis of cannabis dependence at baseline who were evaluated at 4, 9, and 15 months following treatment assignment. The nine-session intervention produced superior outcomes compared with the two-session treatment in terms of reductions in cannabis use and its consequences up to 12 months following treatment termination. The two-session treatment was more effective in use reduction than the control. Overall, the findings suggest that both substance abuse treatment programs and behavioral healthcare providers should consider making cannabis-specific treatment more available and accessible. The authors also conclude that cannabis-focused treatments may be necessary for this population to achieve abstinence or to significantly reduce cannabis use. Complete abstinence is not the only clinically meaningful outcome of treatment, and when given the opportunity, many cannabis abusers respond to treatment primarily by cutting back rather than quitting entirely [6].

A study of 90 cannabis-dependent adults seeking treatment randomly assigned participants to receive CBT, abstinence-based voucher incentives, or a combination of CBT and vouchers for 14 weeks. The authors found that, during treatment, abstinence-based vouchers were effective for facilitating prolonged periods of cannabis abstinence. CBT did not contribute to during-treatment abstinence, but it did enhance the post-treatment maintenance of the initial positive effect of vouchers. These results indicate that abstinence-based vouchers are a valuable treatment option, the use of which leads to greater rates of cannabis abstinence during treatment in comparison with a commonly used with CBT for cannabis dependence [43].

The American Psychiatric Association notes that treatment of cannabis use disorder with CBT and MET may be improved with the concurrent use of CM strategies [78]. Combined treatment results in improved initial and long-term abstinence.

Psychosocial Treatment of Adolescents

Approximately one-third of high school seniors (31.1% to 36.4%) used cannabis at least once in 2013 [5]. Less than 10% of adolescents who report substance use disorder symptoms in the past year have ever received treatment, and when adolescents do enter treatment for cannabis use, only 20% believe their use is problematic [44]. These findings suggest the need for interventions to increase motivation for change and encourage treatment entry for this population.

One study of the efficacy of psychosocial treatments in this patient population included 97 adolescents who had used cannabis at least nine times in the previous month. Participants were randomized to either an immediate two-session motivational enhancement intervention or a 3-month delayed treatment control. The majority (two-thirds) of the sample described themselves as in the precontemplation or contemplation stages of change regarding cannabis use. Cannabis use and negative consequences were assessed at baseline and at 3-month follow-up, and the assessment battery was carefully constructed to not appear biased toward demanding change. Both groups significantly reduced cannabis use at the 3-month follow-up, with an overall reduction in cannabis use by 16% (6 less days) over a 60-day period. Although reductions were modest and no differences between treatments were observed, the study succeeded in recruiting non-treatment-seeking adolescent cannabis smokers who were predominantly in the early stages of readiness for change, overcoming barriers in reaching adolescents who were frequent cannabis users [44].

Kamon et al. reported the results of a 14-week feasibility study of family-based CM with 19 adolescents 15 to 18 years of age [12]. The intervention consisted of a clinic-administered, abstinence-based incentive program; parent-directed CM targeting substance use and conduct problems; a clinic-administered incentive program targeting parental participation; and individual CBT for the adolescent patients. Twice-weekly urine and breath testing was conducted to monitor substance use. The adolescents attended an average of 10.3 of 14 weekly sessions; parents attended an average of 10.6 sessions. By the end of treatment, substance use, externalizing behaviors, and negative parenting behaviors had decreased. Based on results of the urine testing, abstinence increased from 37% at intake to 74% by the end of the study period; 53% of adolescents were abstinent 30 days post-treatment. The efficacy of a family-based CM model to treat adolescent substance use and conduct problems was demonstrated [12].

Psychosocial Treatment of Patients with Comorbid Mental Illness

Cannabis is the most commonly used illicit drug among persons with mental illness and is associated with increased rates of recurrent psychiatric symptomatology and relapse [45]. Unfortunately, the amount and quality of research regarding the psychosocial treatment of these patients is limited. In one study, researchers conducted a randomized, single-blind controlled comparison of routine care with a program of routine care integrated with motivational interviewing, cognitive behavior therapy, and family or caregiver intervention in patients with comorbid schizophrenia and substance use disorder (including cannabis misuse) [45]. They found that the integrated treatment approach resulted in significantly greater improvement in patients' general functioning than routine care alone at the end of treatment and at one year follow-up [45]. Longer and more intensive treatment may be necessary for dually diagnosed patients, particularly those with chronic mental illness [42]. More research with this population is necessary in order to draw definitive conclusions.

12-STEP/SELF-HELP THERAPY

Many persons addicted to cannabis lack the resources for inpatient or outpatient treatment for their substance abuse problem or may be in need of ongoing support following treatment. To meet these needs, self-help groups provide a vital resource for those seeking support for abstinence. Self-help groups are non-professional organizations operated by peers who share the same addictive disorder. Self-help group attendance is free [46].

The most successful self-help groups employ the 12-step program and are modeled after Alcoholics Anonymous (AA). These groups include Narcotics Anonymous (NA) and Marijuana Anonymous (MA). The 12-step model emphasizes acceptance of addiction as a chronic progressive disease that can be arrested through abstinence but not cured. Additional elements of the 12-step model include spiritual growth, personal responsibility, and helping other addicted persons. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution. Groups such as NA and MA are also a resource for emotional support and are perhaps more accurately classified as "mutual help" organizations [46; 47].

Spiritual beliefs and endorsement of the disease concept are not prerequisites for NA or MA attendance, and spiritual beliefs have not been found to cause external attribution for previous drug use or possible future lapse events [48].

Narcotics Anonymous (NA)

Relative to the more established AA, there are few studies published on NA. However, the studies that have been conducted reveal important information about how NA functions to help the new member abstain from drug use.

Improvement in psychological functioning as a result of NA involvement has been observed [49]. Studies have shown that individuals who have been off drugs and involved with NA for longer periods tend to have lower trait anxiety and higher self-esteem scores. Those who are abstinent for more than 3 years exhibit levels of anxiety and self-esteem similar to the general population [49].

Being active as an NA sponsor over a 1-year period has been found to be strongly associated with substantial improvements in sustained abstinence rates, which suggests that providing direction and support to other newer addicts is a way to enhance the likelihood of one's own abstinence [50].

Marijuana Anonymous (MA)

Marijuana Anonymous (MA), a self-help program specific to persons with a desire to stop using cannabis, was formed in California in 1989 by cannabis addicts who felt their addiction to cannabis was not taken seriously in other 12-step meetings. MA is modeled after AA and NA, and members use the same 12-step model. MA meetings can be found in 36 states in the United States and in many countries [51].

In a study of 1,288 male patients, participation in a 12-step program predicted maintenance of cannabis abstinence and the re-initiation of abstinence after a relapse [58]. Participation in 12-step groups during and after treatment has been associated with positive outcomes among substance users, including cannabis-dependent patients [52]. Clinicians should encourage 12-step group participation as an aspect of treatment. A study conducted by Laudet identified two major obstacles to 12-step program participation: motivation and readiness for change and the perceived need for help [52]. Other obstacles to participation include perceived convenience and scheduling issues. This underscores the importance of promoting motivation for change and the need to assess patient beliefs regarding experiences with 12-step programs on a case-by-case basis in order to find a good fit between patient needs and 12-step resources [52].

INTERVENTIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For those who are not proficient in English, it is important that information regarding the use and potential abuse of cannabis and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

PROGNOSIS

Lapse and relapse are common among cannabis-dependent outpatients, with relapse rates similar to those found in studies of alcohol, opiate, and smoking cessation. The relationship between lapse and relapse among 82 patients who achieved at least two weeks of abstinence during outpatient treatment for cannabis dependence was examined by Moore and Budney [53]. The authors found that 71% of those who were abstinent went on to exhibit full relapse, defined as 4 or more days of cannabis use per week.

Studies of treatment efficacy show that cannabis-dependent adults tend to respond well to a variety of interventions. Although continuous abstinence is a less common outcome, all psychosocial therapies tested demonstrate utility in reducing cannabis use when delivered in both individual and group sessions [6]. As noted, CM combined with CBT or motivational enhancement may enhance outcomes [10]. However, low abstinence rates are an indicator of the difficulty in treating cannabis dependence by psychotherapies in outpatient settings. These suboptimal drug use outcomes suggest that continued development and testing of more effective treatments for cannabis dependence should remain a priority [43].

Comorbid mental disorders are also a risk factor for poorer outcomes. In particular, the presence of antisocial personality disorder is associated with increased rates of addictive and externalizing disorders, use of illicit substances in early adolescence, and rates of hyperactivity. These patients have a relatively poor prognosis for treatment outcome [17].

CONCLUSION

Cannabis is a significant drug of recreation and abuse. It is nearly inevitable that healthcare professionals in a variety of settings will have contact with a patient who uses or has used cannabis. Therefore, an understanding of the acute and sustained effects associated with the drug will facilitate better patient care. Knowledge of possible therapeutic uses of the drug is also necessary, as cannabis has become a part of the treatment of some chronic diseases. The information provided in this course should allow clinicians to better address the use of cannabis in their patients as well as to discuss the role and effectiveness of cannabis in ameliorating symptoms associated with chemotherapy/cancer, AIDS, and other conditions.

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Cocaine Use Disorder

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty
Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners
Ronald Runciman, MD
Jane C. Norman, RN, MSN, CNE, PhD
Alice Yick Flanagan, PhD, MSW

Division Planners Disclosure
The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cocaine.

Accreditations & Approvals
NetCE is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

NetCE is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

NetCE, #1092, is approved as a provider for social work continuing education by the Association of Social Work Boards (ASWB) www.aswb.org through the Approved Continuing Education (ACE) Program. NetCE maintains responsibility for the program. ASWB Approval Period: 3/13/2016 to 3/13/2019. Social workers should contact their regulatory board to determine course approval for continuing education credits.

NetCE has been approved by NBCC as an Approved Continuing Education Provider, ACEP No. 6361. Programs that do not qualify for NBCC credit are clearly identified. NetCE is solely responsible for all aspects of the programs.

This course is approved by the Association of Social Work Boards - ASWB NJ CE Course Approval Program Provider #14 Course #304. Social workers will receive the following type and number of credit(s): Clinical Social Work Practice 2, General Social Work Practice 3 for the approval period starting 04/23/2015 and ending 04/23/2017.

NetCE SW CPE is recognized by the New York State Education Department's State Board for Social Work as an approved provider of continuing education for licensed social workers #0033.

This course is considered self-study, as defined by the New York State Board for Social Work. Materials that are included in this course may include interventions and modalities that are beyond the authorized practice of licensed master social work and licensed clinical social work in New York. As a licensed professional, you are responsible for reviewing the scope of practice, including activities that are defined in law as beyond the boundaries of practice for an LMSW and LCSW. A licensee who practices beyond the authorized scope of practice could be charged with unprofessional conduct under the Education Law and Regents Rules.

NetCE is recognized by the New York State Education Department's State Board for Mental Health Practitioners as an approved provider of continuing education for licensed mental health counselors. #MHC-0021.

This course is considered self-study by the New York State Board of Mental Health Counseling.

NetCE is recognized by the New York State Education Department's State Board for Mental Health Practitioners as an approved provider of continuing education for licensed marriage and family therapists. #MFT-0015.

This course is considered self-study by the New York State Board of Marriage and Family Therapy.

A complete Works Cited list begins on page 24.

Mention of commercial products does not indicate endorsement.

This course has been approved by NetCE, as a NAADAC Approved Education Provider, for educational credits, NAADAC Provider #97847. NetCE is responsible for all aspects of their programming.

NetCE is approved as a provider of continuing education by the California Consortium of Addiction Programs and Professionals (CCAPP). Provider Number 5-08-151-0618.

NetCE is approved as a provider of continuing education by the California Association for Alcohol/Drug Educators. Provider Number CP40 889 C 0617.

Designations of Credit

NetCE designates this enduring material for a maximum of 5 AMA *PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

NetCE designates this continuing education activity for 5 ANCC contact hours.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

AACN Synergy CERP Category A.

Social Workers participating in this intermediate to advanced course will receive 5 Clinical continuing education clock hours, in accordance with the Association of Social Work Boards.

NetCE designates this continuing education activity for 2 NBCC clock hours.

NetCE designates this continuing education activity for 5 continuing education hours for addiction professionals.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through December 12, 2017); California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; Florida, Provider #50-2405; Iowa, Provider #295; Kentucky, Provider #7-0054 through 12/31/2017.

Individual State Behavioral Health Approvals

In addition to states that accept ASWB, NetCE is approved as a provider of continuing education by the following state boards: Alabama State Board of Social Work Examiners, Provider #0515; Florida Board of Clinical Social Work, Marriage and Family Therapy and Mental Health, Provider #50-2405; Illinois Division of Professional Regulation for Social Workers, License #159.001094; Illinois Division of Professional Regulation for Licensed Professional and Clinical Counselors, License #197.000185; Illinois Division of Professional Regulation for Marriage and Family Therapists, License #168.000190; Texas State Board of Social Work Examiners, Approval #3011; Texas State Board of Examiners of Professional Counselors, Approval #1121; Texas State Board of Examiners of Marriage and Family Therapists, Approval #425.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide a current, evidence-based overview of cocaine use disorder and its treatment, in order to allow healthcare professionals to more effectively identify, treat, or refer patients who abuse cocaine.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the history and background of cocaine use, including the development of different forms of the drug.
2. Discuss the epidemiology of cocaine use.
3. Describe the pharmacodynamics and pharmacokinetics of cocaine.
4. Review the acute and chronic effects of cocaine use, including effects on fetal development.
5. Select possible treatment modalities for cocaine use disorder, including psychosocial therapy, pharmacotherapy, immunotherapy options, alternative/complementary approaches, and interventions for non-English-proficient patients.
6. Recognize the withdrawal syndrome associated with cessation of cocaine use.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

DEFINITION OF COCAINE ABUSE AND DEPENDENCE

Stimulant drugs are substances that activate the central nervous system (CNS) and peripheral nervous system. There are two main categories of commonly used illicit stimulants: cocaine and amphetamine and its derivatives and analogs, such as methamphetamine. Prescription stimulants (e.g., methylphenidate [Ritalin], mixed salts of amphetamine [Adderall]) used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy, and other disorders, may also be used illicitly. Cocaine and nonprescription amphetamines have the highest potential for abuse and dependence and constitute a serious public health, medical, and criminal justice concern due to the number of individuals addicted to these agents. Repeated use in escalating doses over time can lead to the development of addiction [1; 2].

The syndrome of substance abuse and dependence is highly similar regardless of the particular substance and is best conceptualized as a brain disorder, with a chronically waxing and waning course of relapse and remission. It is associated with neurobiologic changes that result in craving for the substance [3; 4; 5; 6]. The etiology of dependence in any one person is multifactorial, representing the convergence of a multitude of biologic, psychologic, social, and interpersonal factors [1; 5].

Cocaine addiction is best described as a chronic relapsing disease. It is characterized by the compulsive seeking and use of cocaine accompanied by functional and molecular changes to the brain [4; 5]. The single most defining aspect of cocaine use disorder is the salience of the relationship with the drug. The stronger the relationship, the more likely the patient is to continue problematic use despite internal and external consequences. Psychologic dependence, whereby the patient believes the drug is necessary to complete daily activities, alleviate stress, and cope with problems, is a symptom of stimulant dependence. Physiologic adaptation, evidenced by tolerance and withdrawal, is often present but is not sufficient for a diagnosis of cocaine use disorder. Cocaine use disorder is diagnosed behaviorally and is evidenced by at least two of the following within a 12-month period [7; 8]:

- Persistent desire or unsuccessful attempts to cut down or control use
- Great deal of time spent in activities necessary to obtain the drug
- Craving
- Failure to fulfill obligations at work, home, or school as a result of cocaine use
- Continued use despite persistent or recurrent social or interpersonal problems caused by cocaine use
- Important activities abandoned or reduced
- Recurrent cocaine use in physically hazardous situations
- Continued use despite knowledge of a problem likely to have been caused by or exacerbated by cocaine use
- Tolerance
- Withdrawal

Cocaine abuse is a condition of frequent, binge-type use and continued use despite negative consequences, but with less severity and fewer behavioral symptoms than a use disorder [7; 8; 9]. In this course, the term cocaine use disorder will be used interchangeably with cocaine addiction.

HISTORY AND BACKGROUND OF COCAINE USE

FIRST WAVE

Cocaine, a tropane alkaloid, is extracted from the leaves of *Erythroxylumcoca* bush, which contain 0.6% to 1.8% of the alkaloid [3; 5; 10]. Archeologic evidence indicates that use of these leaves for their stimulant and anesthetic properties by South American natives dates back to 2000 B.C.E. [11]. Although Spanish explorers discovered the mild stimulant effects of the leaves and returned to Europe with them in the 16th century, their use did not become widespread for more than 300 years, partially because the leaves lost much of their potency on the journey back to Europe [12].

Cocaine was first isolated and synthesized in 1859 in Germany, and its medicinal effects were first documented in the 1880s [13; 14]. Among the proponents of cocaine during this period was Sigmund Freud, who initially lauded the use of cocaine to treat a variety of conditions (most of which he retracted in 1887), including depression, alcoholism, and morphine addiction, in an 1884 paper entitled *On Cocaine*. The surgeon William Halstead also utilized the drug for its local anesthetic effects [13; 14]. Both men developed documented cocaine addictions. In 1886, the soft drink Coca-Cola, which contained cocaine and caffeine, was introduced. The ability of cocaine to reduce hunger, fatigue, and the need for sleep was highly valued during the industrial revolution in the late 19th century, and its use was encouraged to promote worker productivity [13; 16]. The demand for cocaine skyrocketed during this period; the pharmaceutical company Merck produced 0.75 pounds of cocaine in 1883 and 158,352 pounds in 1884 [9; 12]. Cocaine was widely available during this period in cigarettes, inhalers, candy, elixirs, solutions, and over-the-counter products, as well as in wine and soft drinks [13; 16]. Use of cocaine eventually reached epidemic proportions. In 1910, President Taft declared cocaine to be a public enemy, and strict controls were enacted at the state level [9; 16]. Cocaine was removed from the Coca-Cola formulation in 1903, and the passage of the Harrison Narcotic Act in 1914 severely restricted the manufacture, distribution, and sales of cocaine in the United States. Cocaine use plummeted and remained very low for the next six decades [9; 16].

SECOND WAVE

Cocaine use did not experience a resurgence until the late 1960s, coinciding with the tighter regulatory control and decreased use of amphetamines [12; 17]. The seriousness of cocaine abuse and dependence was discounted in the 1960s and 1970s, and little effort was made to understand the mechanism of cocaine addiction and its treatment, partially because heroin addiction was seen as the most significant drug-related public health concern [18]. The introduction, widespread use, and substantial morbidity and mortality of freebase and crack cocaine in the early 1980s alerted scientists and clinicians of the urgency in understanding the nature of cocaine addiction and in developing effective treatments.

The increase in cocaine use in the 1980s correlated with the introduction of new forms of the drug. When cocaine is treated with hydrochloric acid (HCl), it becomes cocaine HCl, which is highly soluble in water and highly lipophilic. Until the late 1970s, this was the predominant illicit form [9]. Cocaine HCl may be administered intranasally, mixed with water and used intravenously, or combined with heroin and injected, which is referred to as a "speedball" [5; 9]. Freebase cocaine is a highly pure form created by removing the hydrochloride base and is not water soluble. Unlike cocaine in the powdered hydrochloride form, which is destroyed by heat, freebase is smokable. Crack cocaine is made by dissolving cocaine HCl in water, mixing in baking soda, and heating the mixture to create a hard substance that is cut into "rocks" [12]. In the early 1980s, cheap and readily available crack cocaine was introduced, resulting in a rapidly escalating number of regular users and addicts [9].

EPIDEMIOLOGY AND DEMOGRAPHICS OF COCAINE ABUSE AND DEPENDENCE

In 2015, 1.9 million Americans (0.7%) were current users of cocaine (i.e., had used any type of cocaine in the previous month), with 900,000 classified as dependent on or abusing cocaine [19]. Every day, 2,650 people use a cocaine product for the first time, and the mean age at first use is 22 years [19]. Between 2002 and 2013 the number of annual initiates of cocaine declined from 1,032,000 to 601,000, but increased to 968,000 in 2015; of these, the number of crack cocaine initiates declined from 337,000 in 2002 to 37,000 in 2015. In the United States, cocaine is used primarily by young men, who outnumber female users by approximately 2 to 1 [19]. Black and mixed-race Americans have prevalence rates of past month cocaine use double that of whites, although whites account for the greatest number of users; 58% of all past month users are white, 23% are black, and 14% are Hispanic. Overall, environmental and social factors (e.g., approached by someone selling cocaine, parental involvement, religious beliefs, scholastic environment) account for risk of cocaine use considerably more than race or ethnicity [19].

Based on the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episode Data Set (TEDS), primary cocaine treatment admissions decreased between 2003 and 2013 relative to the number of admissions for other substances [20]. In 2003, cocaine treatment admissions for persons 12 years of age or older represented 14% of all treatment admissions, compared with 6.1% in 2013. Data in the 2015 SAMHSA publication represented 49 states, Puerto Rico, and the District of Columbia, and of the 1,683,451 reported treatment admissions for all substances, approximately 102,400 were for primary cocaine use [20]. Approximately 68% of these admissions were for smoked (crack) cocaine.

Cocaine users who ingest cocaine by routes other than smoking were more likely to be white and male than those who smoke cocaine [20]. Cocaine, in general, was the fourth most common illicit drug among treatment admissions in 2013, accounting for 6.1% of TEDS admissions, with smoked cocaine accounting for 4% of total admissions. Of those admitted for smoked cocaine, 57% were black and 31% were white [20].

Certain populations are more vulnerable to cocaine-induced toxicity, primarily due to their inefficient capacity for metabolism and clearance of the drug and its breakdown products. These include the elderly, infants, fetuses, pregnant women, and patients with liver disease [13]. Other factors that influence individual variation in susceptibility to cocaine-induced toxicity include age, sex, body mass, hepatic and renal function, drug-drug interactions, and genetic variability [22]. Black American users are more likely than non-black users to experience rhabdomyolysis, excited delirium, and changes in cardiac rhythm [13].

Gender differences in the effects of cocaine have also been observed. Men who use cocaine experience higher blood concentration levels and greater drug effect than women, and women are more sensitive to the cardiovascular effects than men [12; 23]. Women presenting for treatment of cocaine dependence are more likely than males to be severely dependent, to abuse other drugs, to have a briefer period of abstinence, and to have childhood histories of physical or sexual abuse [18]. Gender differences in comorbidity have also been found, with female cocaine abusers more likely to have major depression and male cocaine abusers more likely to have antisocial personality disorder [18].

COCAINE USE

PHARMACODYNAMICS

Cocaine's specific mechanism of action involves increasing the synaptic transmission of dopamine, serotonin, and norepinephrine by interaction with plasma membrane transporters to block presynaptic reuptake. Action involving the dopamine transporter is the most important in producing the reinforcing effects, which lead to dependence [24]. The increased postsynaptic dopamine activity following its blocked presynaptic reuptake forms the basis of cocaine action [18].

Dopamine receptors are grouped into two families: dopamine D1-like (D1 and D5) and dopamine D2-like (D2, D3, and D4). Both D1-like and D2-like receptors are believed to mediate the acute and chronic effects of cocaine [25; 26]. A study employing multiple regression analysis to identify the biochemical receptor mechanism most associated with the reinforcing properties of cocaine examined dopamine, serotonin, choline, and norepinephrine receptors and their transporters [27]. Researchers found that cocaine binding to the dopamine transporter or cocaine inhibition of dopamine uptake accounted for most of the variability [28].

The basal ganglia, the brain region with the highest density of dopamine receptors, is the site with the highest concentration of cocaine binding [29]. In addition to affinity for mesocorticolimbic dopamine receptors, cocaine also inhibits activity in the locus coeruleus and the pons, providing an anxiolytic effect [12].

PHARMACOKINETICS

Cocaine can be absorbed through any mucous membrane. Different routes of cocaine delivery into the body produce different patterns and levels of blood cocaine concentration. Intranasally administered cocaine is absorbed and distributed into the body gradually, while the onset of effect is rapid when smoked or injected. The effect of cocaine is experienced most rapidly and intensely when smoked, with an onset of effects typically occurring within 8 to 10 seconds; thus, cocaine is most addictive when smoked [24]. Injected cocaine takes twice as long to enter the brain (i.e., 16 to 20 seconds), and snorted cocaine begins to act in three to five minutes [12]. The lungs are the most rapid and efficient cocaine delivery modality because of the large surface area of absorption and rapidity of arterial circulation to the brain [9; 30].

Peak plasma levels of cocaine occur 20 to 40 minutes following intranasal ingestion, with a typical concentration of 100–500 mcg/L. Toxicity is rarely seen at this dose level. Plasma half-life ranges from 31 to 82 minutes, with a mean of 38 minutes [13].

Cocaine has long been used medicinally as a local anesthetic agent and is believed to be the only naturally occurring agent with this specific property [31]. Cocaine interferes with sodium channel activity, leading to diminished or blocked nerve conductivity. By entering the sodium channel and binding to the membrane interior, the drug further inhibits membrane sodium activity in electrically active cells, such as myocardium and nerve cells [30; 31].

The majority of cocaine (i.e., 75% to 90%) is hydrolyzed by plasma and hepatic esterases to ecgonine methyl ester and benzoylecgonine, while a smaller proportion undergoes hepatic demethylation to produce the CNS-active norcocaine [30; 31; 32]. Hepatic metabolism occurs with cytochrome P450-2C9, 2C19, 3A4, and 2D6 [22]. Decreased hepatic perfusion results in prolonged elevation of cocaine levels [30]. Concurrent alcohol use produces the metabolite cocaethylene, which has a longer plasma half-life than cocaine [22; 30]. The rapid metabolism of cocaine in the liver accounts for its short half-life, which also influences the duration of the subjective "high" from a single dose. It is believed that both the intensity of the high and its brief duration contribute to the addictive properties of the drug [24; 30].

EFFECTS OF COCAINE USE		
Type of Use	**Psychologic Symptoms**	**Physiologic Signs**
Acute ingestion	Euphoria Heightened self-confidence, well-being, energy, and alertness Restlessness Reduced need for food Insomnia	Elevated arterial pressure Increased heart rate and respiration Coronary vasoconstriction Increased myocardial oxygen demand Hyperthermia secondary to cutaneous vasoconstriction Increased locomotor activity
Chronic ingestion	Dysphoria Agitation Anxiety and panic Loss of concentration Diminished libido Paranoia Visual or auditory hallucinations Delusions	Pacing Restlessness Hyperactivity Grinding of teeth Mood lability Insomnia
Source: [2; 9; 18]		*Table 1*

USE CHARACTERISTICS OF COCAINE ABUSE

Cocaine users often begin in the evening and use the drug continuously over several hours [33]. Over a longer period of time, cocaine use appears to follow what has been described as an "up-top-down" trajectory [34; 35]. This means that use generally increases to a peak, then decreases. However, this may be more true of certain delivery routes than of others.

EFFECTS OF COCAINE USE

ACUTE EFFECTS

The intensity and quality of CNS effects of cocaine are influenced by the quantity and route of ingestion, as well as past drug use. One hundred milligrams is considered a fairly modest dose, with a high dose being several hundred milligrams [12]. Tolerance to the desired effects of cocaine can result from as little as one week of regular use, although the rapidity of the onset of tolerance varies by the route of administration, dose, and frequency of ingestion [12]. Subjective and behavioral effects from single- and multiple-dose acute ingestion of cocaine include euphoria, increased heart rate, restlessness, anxiety and panic, delusions, heightened alertness, and insomnia (***Table 1***).

CHRONIC EFFECTS

The effects of chronic cocaine use on brain neuronal pathways are influenced by the duration and intensity of cocaine use, length of abstinence, and vulnerability to the effects of cocaine [36]. Long-term use of the drug induces a partial depletion of presynaptic dopamine reserves in the targeted brain regions, which is compensated by an increase in the number of dopamine receptors in the striatal region of the brain [12]. This results in the symptoms of dysphoria, anxiety, restlessness, and paranoia.

Cocaine obtained illicitly is always adulterated, or "cut," resulting in wide variations in concentration and purity. Consequently, users may underestimate the purity of the drug and overdose, which can result in toxicity or even death. Certain adulterants can produce harmful effects, as evidenced by the exaggerated sympathetic stimulation caused by ephedrine, Parkinson-type symptoms caused by manganese salts, and the increased likelihood of seizures with the addition of lidocaine [13].

Cocaine use is responsible for more hospital admissions than any other recreational or illicit drug, and the actual incidence of cocaine-induced toxicity is likely to be under-reported [30; 31].

CNS Effects

The sympathomimetic and vasoconstrictive effects of cocaine can induce migraine-like headaches. Cocaine use is also associated with the development of cerebrovascular pathology, including [30]:

- Ischemic strokes
- Hemorrhagic strokes
- Thromboembolic strokes
- Primary and secondary seizures
- Cocaine-induced excited delirium
- Hyperthermia

Cocaine-induced dopamine accumulation in the basal ganglia may result in movement disorders that can present as Tourette syndrome, dystonic reactions, tardive dyskinesia, and akathisia [12; 31].

Neurocognitive Effects

Chronic and heavy cocaine use can lead to the development of diverse neuropsychologic sequelae [37]. Many studies have been performed utilizing a variety of brain imaging techniques, including brain blood flow studies employing transcranial Doppler; single photon emission computed tomography (SPECT); magnetic resonance angiography (MRA); computed tomography (CT); magnetic resonance imaging (MRI); diffusion tensor imaging (DTI); and positron emission tomography (PET) [37]. Evidence obtained from these brain-imaging studies of patients with cocaine use disorder indicates that cocaine use leads to functional, structural, and molecular changes, including dysfunction in the prefrontal cortex, anterior cingulated gyrus, and basal ganglia. This corresponds with functional impairment in abilities related to executive functioning; error detection and performance monitoring and adjustment; and cognition and movement [37]. However, studies attempting to elucidate the durable structural and functional changes to the brain from cocaine use are not longitudinal, and thus cannot rule out the possibility that structural and functional deficits predispose or contribute to cocaine-induced pathology [36; 38].

Cardiovascular Effects

Drugs that increase brain monoamine concentration also have the potential to elevate peripheral monoamine activity [29]. Cocaine stimulates dopamine and alpha- and beta-adrenergic receptors in the CNS and in the peripheral nervous system, which is the underlying basis of the adverse systemic effects of this drug [12; 30]. The cerebrovascular complications caused by cocaine are the result of its effect on noradrenergic neurotransmission and include vasoconstriction and resultant decrease in blood flow, inflammation of blood vessel walls, and hyperpyrexia [24; 30].

Cocaine produces cardiovascular pathology in susceptible users by altering the myocardium and vasculature in a manner that may eventually manifest as cardiac disease, hypertension, or atherosclerosis [31]. The cocaine molecule has a high affinity for cardiac tissue, and both acute and chronic cocaine use can induce a variety of cardiac complications in persons with a negative history of such conditions, primarily from the powerful sympathomimetic properties of the drug [29; 39]. Specific cocaine-induced cardiac conditions include myocardial infarction, ischemia, arterial thrombosis, ventricular tachycardia, ventricular fibrillation, and sudden death. Other cardiac conditions attributable to cocaine use include dilated cardiomyopathy, hypertension, myocarditis, and coronary artery occlusion [12; 30].

The Institute for Clinical Systems Improvement recommends that beta-blockers should not be administered to patients experiencing chest pain who are suspected of ingesting cocaine, as there is a risk of exacerbating coronary spasm.

(https://www.guideline.gov/summaries/summary/39320. Last accessed March 3, 2017.)

Level of Evidence: High quality (Randomized, controlled trial)

Cigarette smoking acts synergistically with the adrenergic effects of cocaine to further increase vasoconstriction [30; 32]. Other risk factors predisposing users to cocaine-induced cardiovascular disease or events include [30; 31]:

- Myocarditis
- Hypercoagulability
- Early-onset atherosclerosis
- Heavy or chronic alcohol use
- Hyperadrenergic syndrome
- Previous history of excited delirium
- Aneurysm or stroke
- High-risk behaviors for sepsis, such as injecting drug use or unsafe sex practices

Pulmonary Effects

Most of the pulmonary complications from cocaine use involve smoked cocaine in the form of crack or freebase. These effects usually develop shortly after inhalation. The more common symptoms include productive cough, chest pain, shortness of breath, and worsening of pre-existing asthma. Other pulmonary conditions include thermal injury to the airway, asthma severe enough to necessitate mechanical ventilation, interstitial pneumonitis, pneumothorax, pulmonary edema, pulmonary hemorrhage, and degraded pulmonary function [12; 30].

Gastrointestinal Effects

Malnutrition is the most common gastrointestinal (GI) complication from cocaine use. This is influenced by the adverse effect of cocaine on food and beverage consumption, taste, and nutrient absorption. Other GI complications from cocaine use are less common and include gastroduodenal ulceration, acute bowel perforation, liver toxicity, and pancreatic and endocrine disease [12].

Sexually Transmitted Infections

Cocaine abuse is associated with increased transmission of sexually transmitted infections (STIs), primarily as the result of unsafe and/or high-risk sexual practices. The transmission of human immunodeficiency virus (HIV) has been a particular concern and may stem from exchanging sex for money or cocaine and high numbers of homosexual unprotected sexual encounters, particularly anal receptive sex [9; 40; 41].

NEONATAL EFFECTS

Because a number of pregnant women in the United States are believed to use cocaine (estimated at up to 10,000 each year), serious concern has been raised regarding the effects of cocaine on fetal development [19]. There were approximately 1300 admissions with positive pregnancy status to treatment centers for primary cocaine use in 2013 [20].

The adverse effects of cocaine on fetal development stem from its diffusion across the placental barrier, where its vasoconstrictive effect diminishes the flow of blood and oxygen. The resultant hypoxia can retard fetal somatic and CNS development. Damage to the developing fetus can occur in both early and later pregnancy. Although ascertaining the impact of prenatal cocaine exposure is complicated by the influence of other factors, such as maternal nutrition, exposure to STIs/STI treatments, amount and route of ingestion of cocaine, use of alcohol and other drugs, use of tobacco, and the postnatal environment, it is believed that the cocaine-induced effects originate in systems mediated by dopamine function, encompassing the cognitive, motor, emotional, and reward development of the infant [2; 12; 42; 43]. However, some of these effects may be minor in severity and transient in nature, and there is no specific syndrome or condition associated with prenatal cocaine exposure [21; 43]. Other adverse effects from maternal cocaine ingestion include spontaneous abortion, stillbirth, prematurity, and low birth weight [2; 12; 44].

A 2013 systematic review found that the effects of prenatal cocaine exposure may not be as clearly clinically significant as once thought [21]. Although there are obvious early effects (e.g., prematurity, low birth weight) and possible effects on childhood development (e.g., reduced cognition/school performance), test scores and developmental measures were within normal limits in nearly all studies. It is difficult to accurately assess the role of prenatal cocaine exposure on adolescent outcomes due to a host of environmental factors during childhood (e.g., violence exposure, second-hand smoke, malnutrition, toxic exposures). It is safe to say that cocaine exposure causes premature birth or low birth weight, which are known risk factors for hyperactivity disorders.

DIFFERENTIAL DIAGNOSIS

Repeated heavy cocaine use can lead to the development of symptoms that resemble distinct psychiatric and neurologic conditions; therefore, a thorough differential diagnosis is vital. Careful history, observation, and monitoring are useful in performing an accurate differential diagnosis [45]. Some conditions to consider in the differential diagnosis process include mood and psychotic disorders.

The affect and behavior of patients intoxicated with cocaine can mimic a broad spectrum of mood disorders, including the elevated and expansive mood, hypertalkativeness, euphoria, irritability, and sleep and appetite reduction of mania; the volatile cycling of euphoria and dysphoria of bipolar disorder; and the dysphoria, anergia, anhedonia, and suicidal ideation that characterizes acute withdrawal resembling major depression [45]. Cocaine use can also induce the paranoia and delusional thinking that resemble a psychotic disorder [46]. The most frequent delusion types observed in cocaine abusers are the persecutory, jealous, and somatic types [45].

COMORBID ALCOHOL USE DISORDER

Cocaine has a profound liability of abuse and dependency associated with its use [47]. Perhaps the most serious condition associated with repeated use of cocaine is the development of addiction, which may extend to other substances.

Alcohol is a frequently abused substance among patients who use stimulants. Many patients are dependent on both cocaine and alcohol, presenting a challenge for researchers and clinicians in optimizing treatment outcomes [20; 29; 30].

Cocaine abusers consume alcohol for several reasons, including the enhancement and prolongation of euphoria and minimization of the undesired effects. The rewarding effects of both substances are mediated through the mesocorticolimbic dopamine pathway. As noted, the combined effects of cocaine and alcohol can also be explained by the formation of cocaethylene, a metabolic byproduct of ingestion of both substances. Cocaethylene is speculated to be less anxiogenic than cocaine and thus may counteract or mask the dysphoria that can accompany cocaine use. Cocaethylene shares many neurochemical and pharmacologic properties with cocaine and is also an indirect dopamine agonist. Alcohol enhancement of cocaine toxicity is partially explained by the presence of cocaethylene, which increases heart rate and systolic blood pressure. As the result of the substance's cardiotoxic effects, it contributes to the increase in ischemia, infarction, and arrhythmia seen in patients abusing both cocaine and alcohol. Additionally, cocaethylene may elevate the potential of violent ideation, threatening behavior, and violent behavior [48; 49].

Differences in the patterns of combined cocaine and alcohol use have been observed between persons who smoke cocaine compared with those who use intranasally. Users of intranasally administered cocaine typically use alcohol both concurrently and in alternating doses. They also tend to use alcohol excessively. These users usually increase the quantity of both substances when using them together. Crack cocaine users, however, are more likely to ingest alcohol at the end of an episode of use and to drink less alcohol when using cocaine [49]. Co-abusers are also more likely to use alcohol to alleviate the unpleasant after-effects of cocaine use.

TREATMENT OF COCAINE USE DISORDER

Cocaine use disorder shares many characteristics with general substance dependence. However, it also includes specific identifying symptoms. According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), an early sign of cocaine use disorder is difficulty resisting using cocaine whenever it is available [7]. Physiologic dependence is associated with a higher risk for cocaine-related problems. Because frequent dosing is necessary to maintain the desired effects, patients with cocaine use disorder must often deal with the effects of spending large amounts of money on the drug.

Although cocaine has been a drug of abuse for decades, research on the treatment of cocaine use disorder was delayed until the later part of the 20th century. The introduction and widespread use of crack cocaine in the 1980s, severity of the addiction, and comorbid problems finally prompted the scientific community to investigate treatment options [18].

Regardless of therapeutic modality, the goals of treatment for cocaine abuse or dependence are to retain the patient in treatment, disrupt the binge cycle, and prevent relapse [18; 50; 51; 52]. Inpatient treatment is perhaps the most desirable option. It allows the patient to be shielded from the environmental cues that are associated with cocaine use and the resultant euphoria and craving that are triggered by these cues [18].

After the patient has detoxified and acute withdrawal is over, rehabilitation is implemented, typically in three stages. The initial emphasis is on motivating the patient to remain abstinent. This is accomplished by educational lectures, family outreach, and group therapy. Treatment personnel who are themselves recovering can serve as positive role models, and self-disclosure in this context is appropriate and even therapeutic. During this phase, the patient is also introduced to self-help groups such as Alcoholics Anonymous (AA), Cocaine Anonymous (CA), and Narcotics Anonymous (NA) [1; 53].

The second stage of rehabilitation focuses on helping patients rebuild their lives without substances. Patients are given the strategies and tools needed to acquire a sober social network, appropriately cope with stress, and use free time constructively without using cocaine. The third stage of rehabilitation focuses on relapse prevention, which can be addressed in group therapy or individual counseling. Orientation and encouragement of 12-step program involvement occurs during all three stages of treatment. The three-stage treatment modality for stimulant abuse incorporates behavioral, cognitive, and psychologic elements and provides the basis of psychosocial treatment [1]. The use of pharmacotherapy may also be necessary in each stage.

PSYCHOSOCIAL THERAPY

Treatment of substance use and dependence with psychosocial or behavioral therapy is based on the assumption that addictive behavior is developed and maintained by specific mechanisms [52]:

- Expectancies and modeling
- Reinforcing properties of the drug
- Secondary social reinforcement

The goal of these types of treatments is to modify drug-seeking and other behavioral aspects of drug dependency [50]. Psychosocial therapy and pharmacotherapy are not mutually exclusive; in fact, some drug therapies for substance abuse are considered useless without a psychosocial/behavioral component [50; 52].

Psychosocial therapies for stimulant abuse disorders can be divided into two broad categories. The first category consists of therapies that were originally developed for patients with anxiety and depression and modified for use with patients with addictive disorders. This group of therapeutic approaches includes cognitive-behavioral therapy (CBT), the behavioral therapies, and interpersonal therapy. The second group of psychosocial therapies was developed explicitly for substance-abusing patients and includes motivational interviewing and motivation enhancement therapy [50; 54]. All psychotherapies are intended to be delivered in a supportive, empathic manner that minimizes confrontation.

Drug counseling is a widely used therapy approach with cocaine and other substance abusers. It consists of a focus on abstinence, problem solving, and 12-step orientation and involvement. Drug counseling is usually provided by counselors who have a certificate in addiction counseling. A fair number of addiction counselors are themselves recovering from alcohol and/or substance abuse disorders [54].

Contingency Management

There is considerable evidence that cocaine use is sensitive to the application of contingencies. Contingencies occur on a spectrum from contrived to naturalistic. Contingency management (CM) and vouchers are examples of contrived interventions, while 12-step programs are examples of naturalistic interventions [53]. Contrived contingencies may be effective in initially engaging patients in abstinence, but relapse to drug use may occur following removal of the reinforcer. In contrast, naturalistic contingencies are more likely to maintain the initial gains made by the patient and to facilitate the sustained change of behavior over time [55].

The goal of CM interventions is to increase the opportunity cost of stimulant use by arranging an environment where drug use results in the forfeiture of a predetermined item or privilege, referred to as an alternate reinforcer [56]. Treatment with a CM component was first used with cocaine-abusing methadone patients, a highly suitable population for two reasons: cocaine abuse is prevalent among patients with opioid use disorder receiving methadone maintenance, and methadone patients are required to report to the clinic daily to receive their medication under staff supervision. Daily clinic appointments are often considered a significant constraint on employment, travel, and other activities. Patients who are able to abstain from drugs of abuse, as measured by a urine drug screen, may be allowed several days of take-home methadone doses, which can act as a behavioral contingent [57]. Several studies have shown that this contingent condition has led to greater treatment retention and reductions in cocaine use than those found in comparison treatment conditions, although this effect dissipates with longer-term follow-up [55; 58; 59; 60].

Community Reinforcement

Community reinforcement approaches (CRAs) are biopsychosocial interventions designed to engage and change the lifestyle of the drug abuser by addressing the role of environmental cues and alternative reinforcers in influencing behavior. The theoretical basis of the CRA is that substance abuse is maintained by substance-related reinforcers as well as by the absence of competing alternative reinforcers. The primary goal of the CRA is to build and strengthen relationships, recognize appropriate leisure activities, and identify vocational interests of the patient to provide competing reinforcement with cocaine use and the drug-using lifestyle [61]. CRA aims to increase abstinence by increasing or highlighting the opportunity cost of relationships and social support the patient stands to lose through drug use [55]. In addition to integrating cognitive-behavioral and, in some cases, pharmacologic approaches, CRA may also include the use of vouchers, whereby tokens are given to the patient for producing substance-free urine samples, which are then used to purchase goods and services desired by the patient.

A review of four studies utilizing CRA with patients with cocaine use disorder found evidence that CRA employing abstinence-contingent incentives in the form of vouchers was more effective in promoting abstinence than CRA using noncontingent incentives and usual care. Patients assigned to CRA incorporating abstinence-contingent incentives experienced a greater reduction in disease severity as measured by the Addiction Severity Index than comparison groups [61]. Despite early, promising reports of CRA with patients with alcohol use disorder and evidence that patients receiving CRA have demonstrated more favorable drug use outcomes than patients receiving standard outpatient counseling, CRA is seldom used because of the relatively high cost and labor intensity [50; 62].

Motivational Interventions

Motivational interventions for substance abuse stem from the theory that targeting and enhancing motivation to quit drugs will increase positive outcome; positive outcome is increased when motivation comes internally rather than when it is externally imposed. Specifically, motivational-enhancement therapies (MET) are based on the Transtheoretical Stages of Change Theory, which postulates that patients pass through a series of stages of thought, planning, and action in the process of behavior change [63]. MET is intended to enhance motivation and commitment to change, activate patient resources, and facilitate movement along the readiness-to-change spectrum [64]. MET helps patients build internal motivation through the resolution of issues related to ambivalence. The therapeutic approach is characterized by nonconfrontive, nonjudgmental interviewing that helps the patient consider the pros and cons of change. MET also strives to enhance patient self-efficacy [63]. MET seems to be more effective in patients with low initial levels of motivation when used for patients with cocaine use disorder. It tends to result in less relapse to cocaine use and fewer total days of cocaine use [65].

Coping and Social Skill Training

Coping and social skill training (CSST) evolved from social learning theory and is used to improve the inadequate coping skills found in many addicted persons, including deficits in regulation of emotion and in effectively coping with social situations. CSST addresses four primary areas [66]:

- Interpersonal skills
- Cognitive and affective regulation
- Coping skills to manage stressful life events
- Coping skills when substances or substance-related cues are encountered

An added emphasis on drug-related cues is used when CSST is employed with patients with cocaine use disorder [66].

An inventory of high-risk situations for recovering cocaine abusers was developed and validated with a sample of 179 cocaine abusers. The Cocaine High-Risk Situations Questionnaire identified the following situations as the most evocative of urges to use cocaine [67]:

- Negative emotional states, such as depression, fear, or anger
- Peer or other external pressure to use
- Spontaneous urges to use
- Desire to augment positive or elevated mood
- Direct using cues, such as receiving a paycheck or cash

CSST has incorporated these findings into the treatment approach used with cocaine users. Preliminary results indicate some benefit of cocaine-specific CSST in reducing frequency of cocaine use and increasing duration of abstinence from cocaine, although these results have not been replicated in subsequent research [65; 66].

Drug Counseling

A large treatment study performed by the National Institute on Drug Abuse randomized 487 cocaine-dependent outpatients to four treatment conditions [68]. All patients received group drug counseling once a week for six months. In addition, the four groups received individual drug counseling, CBT, supportive-expressive therapy twice a week for three months, or no additional therapy. All drug counseling was 12-step oriented. At six-month follow-up, the entire sample exhibited an overall decline in cocaine use, from an average of 10 times per month at baseline to once per month, with corresponding reductions in psychiatric symptoms. Reductions in cocaine use and in the Addiction Severity Index-Drug Use Composite scores were significantly greater in the group that received individual plus group drug counseling than in either of the psychotherapy groups [54; 68]. Further analysis found that patients assigned to individual drug counseling who were regular participants in 12-step programs achieved the best outcomes of any treatment subgroup [69].

PHARMACOTHERAPY

Because dropout and relapse rates are high among patients in treatment for stimulant abuse, pharmacologic therapy has been used to augment standard psychosocial therapy, with the goal of increasing retention in treatment, reducing relapse rate, and treating coexisting psychiatric disorders that may contribute to poorer prognoses. Pharmacotherapy is based on the classic medical model that addresses any given disorder as the manifestation of neurochemical or biologic imbalance and dysregulation. This imbalance is viewed either as a precursor for addictive behavior or the consequence of repeated exposure to alcohol or drugs [50].

Pharmacotherapy for cocaine use disorder follows the model used in the treatment of alcoholism and heroin addiction, which targets the neurobiologic and behavioral components of addiction [24]. Agonist therapy is a component of several different pharmacotherapy strategies for stimulant abuse and dependence; it partially replaces the effects of the abused drug to stabilize the patient. Antagonist therapy, which blocks the abused drug effect, may be utilized to preclude use, alleviate symptoms of use or withdrawal, or treat comorbid conditions. A combination of these approaches may also be utilized [70].

Although a large number of medications have been used in patients with cocaine use disorder, all are either U.S. Food and Drug Administration (FDA)-approved drugs used off label or investigational drugs [2; 5]. The following overview is comprised mainly of review papers that summarize the efficacy in individual therapeutic classes of drugs.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Department of Veterans Affairs, there is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder.

(https://www.guideline.gov/summaries/summary/49968. Last accessed March 3, 2017.)

Level of Evidence: Reviewed

Antidepressants

The theoretical basis for antidepressant treatment of cocaine addiction is to enhance synaptic monoamine transmission by blocking the presynaptic reuptake of brain catecholamines. The goal of this therapy is the alleviation of cravings for cocaine and reduction of withdrawal symptoms, including dysphoria, depressed mood, and cognitive dysfunction [24; 71]. Three types of antidepressants have been studied: tricyclics, such as desipramine and imipramine; selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and sertraline; and atypical antidepressants, such as bupropion.

A Cochrane review of 31 randomized, double-blind, placebo-controlled studies found only five trials that reported significant differences between the study drug and placebo [71]. Among the reviewed studies, desipramine showed a trend in reducing the frequency of cocaine-positive urine samples; however, the effect was not statistically significant. There were no significant differences between antidepressants and placebo on measures of percentage of abstinent days or total abstinence. There was some evidence that fluoxetine reduced the intensity of craving for cocaine and increased treatment retention, although these findings were inconsistent. Overall, the reviewers' findings did not support the clinical use of antidepressants in the treatment of cocaine use disorder [71].

Psychostimulants

Selegiline is a monoamine oxidase-B (MAO-B) inhibitor used in the treatment of Parkinson disease. However, it has been found to reduce the subjective sensation of "high" and to alter the cerebral metabolism of cocaine. Though promising, more research is needed to confirm the possible efficacy of selegiline and other psychostimulant agents (e.g., bupropion, dexamphetamine, lisdexamfetamine, methylphenidate, modafinil, mazindol, methamphetamine, mixed amphetamine salts) in the treatment of cocaine use disorder [25; 72]. A Cochrane review noted that sustained abstinence was most pronounced with bupropion and dexamphetamine; however, there was high attrition in all included studies, which complicated interpretation of the results [72].

Modafinil is a novel stimulant used to treat narcolepsy and excessive daytime sleepiness, with a pharmacologic mechanism opposite the effects of cocaine-induced neuroadaptation on brain reward systems. This action serves as the basis for its use in cocaine use disorder [86; 87; 88]. Preliminary evidence has suggested that this agent may play an important role in blocking cocaine-induced euphoria, enhancing periods of cocaine abstinence, and reducing total cocaine use, although replication is needed in larger trials for greater study periods [60; 72; 78; 89; 90; 91; 114].

Dopamine Agonists

The difficulties many cocaine addicts encounter in early abstinence, with intense drug craving, fatigue, dysphoria, depression, and difficulties with concentration, are believed to originate from dopamine depletion in key brain systems following chronic enhancement of dopamine transmission. This is the theoretical basis for dopamine agonist treatment [73]. The three most studied dopamine agonists in the treatment of cocaine addiction are amantadine, bromocriptine, and pergolide. A Cochrane review of 24 randomized controlled trials and controlled clinical trials concluded that there were significant forms of bias, including selection bias, performance bias, and detection bias, in all of the studies. The findings did not support the clinical use of dopamine agonists in the treatment of cocaine use disorder [73]. Also, the side effects common with this class of drugs further limit their therapeutic appeal [24]. There is evidence that amantadine may be effective in more severe cases of cocaine withdrawal, but confirmation is needed from additional research [25].

Methylphenidate, a drug used to treat ADHD, shares many of the pharmacologic properties of cocaine, including the inhibition of dopamine, serotonin, and norepinephrine reuptake. On this basis, it has been proposed as an agonist therapy strategy for cocaine use disorder. Evaluation of controlled trials employing methylphenidate have suggested better treatment retention, but no differences have been observed between active drug and placebo groups, indicating a lack of efficacy in the treatment of cocaine use disorder [25; 72]. Methylphenidate has been found to induce craving for cocaine only when administered concomitantly with cocaine cues (e.g., video scenes of subjects self-administering cocaine) [74].

Overall, results from dopamine agonist trials have been disappointing, with neither direct agents, such as bromocriptine and pergolide, or indirect dopaminergic agonists, such as methylphenidate or amantadine, demonstrating consistent efficacy in reduction of withdrawal symptoms [39; 75; 76].

Dopamine Antagonists

Dopamine antagonists, typically D2 antagonists, have been used primarily to block the euphoric or reinforcing drug effect of cocaine. Antipsychotic drugs, such as risperidone, ecopipam, and olanzapine, are usually employed for this use. Studies of these drugs have been typified by high subject attrition, frequent side effects, and poor compliance, resulting in this class being largely discounted as having therapeutic potential [60; 70; 76]. An unfortunate side effect observed during trials of the D1 antagonist ecopipam was that cocaine self-administration increased [113].

Disulfiram

Disulfiram is an oral medication used for decades as aversive therapy for alcohol dependence. It acts by inhibiting aldehyde dehydrogenase, thereby increasing the amount of the toxic alcohol metabolite acetaldehyde. Disulfiram also inhibits the enzyme that converts dopamine to norepinephrine. This increase in dopamine has been hypothesized to make disulfiram a helpful drug for cocaine use disorder. Several studies have been performed with patients with cocaine use disorder, and researchers have found that, relative to placebo, use of disulfiram results in decreased craving for cocaine, increased dysphoria in patients who have ingested cocaine concurrently, decreased quantity and frequency of cocaine use, and reduced number of cocaine-positive urine samples. These results are encouraging. However, additional trials are needed to determine the optimal dose and duration of treatment [25; 77; 78]. A small 2016 trial sought to determine if supplementing CBT with disulfiram would enhance abstinence outcomes but found no benefit with addition of the drug [116].

Gamma-Amino Butyric Acid Agents

Gamma-amino butyric acid (GABA) is the primary inhibitory neurotransmitter in the brain, and evidence suggests that GABA modulates both dopamine brain pathways and the subjective effects of cocaine. There are two primary subtypes of GABA receptors: GABAa and GABAb. GABAa is involved in mediating the effects of antiepileptics, benzodiazepines, barbiturates, and neurosteroids such as progesterone. GABAb is distinct from GABAa in that it mediates the slow inhibitory response to GABA; the antispasm drug baclofen is a GABAb receptor agonist [25].

A rationale for treating cocaine addiction with antiepileptic drugs is the observation of the "kindling" effect of cocaine, whereby repeated administration of subthreshold electrical impulses to specific brain structures increases seizure activity [9]. Randomized, placebo-controlled trials of several GABAergic antiepileptic drugs have produced encouraging results. The antiepileptic and mood stabilizer valproic acid has led to reductions in the frequency and severity of cocaine cravings, self-reported cocaine use, and total number of days of cocaine use in a dose-dependent manner [79]. Topiramate, also an antiepileptic, was found to decrease the total number of cocaine-positive urine screens, although these results require replication [78; 114].

Tiagabine is another antiepileptic drug that increases synaptic GABA levels. Studies with cocaine abusers on methadone maintenance found that patients randomized to tiagabine exhibited less cocaine use than subjects receiving gabapentin or placebo. Baclofen also demonstrated superior ability to reduce cocaine use than placebo, with some evidence of greater efficacy among more severe cocaine addicts [79]. Its use in the treatment of alcohol/cocaine codependence has also been supported [80].

Gabapentin is a GABA analog used as an antiseizure drug and mood stabilizer. Gabapentin has been found to block some of the reinforcing effects of smoked cocaine, although other trials have found no differences between gabapentin and placebo in reducing cocaine use among cocaine-abusing methadone patients [81].

Progesterone possesses GABA agonist, glutamate antagonist, and alpha-adrenergic antagonist properties. Laboratory studies have found that progesterone attenuates some of the reinforcing effects of smoked cocaine among women in the early follicular stage of the menstrual cycle and attenuates some of the subjective and physiologic effects of cocaine. However, it did not alter cocaine self-administration in a mixed-gender sample [25; 79].

Alpha-Adrenergic Antagonists

Cocaine is a powerful stimulator of central and peripheral adrenergic activity. Adrenergic systems mediate several of cocaine's effects, such as increased heart rate, heightened blood pressure, and increased arousal. Adrenergic blockers have been utilized in clinical trials with patients with cocaine use disorder. Labetalol, an alpha- and beta-adrenergic blocker, attenuates some of the physiologic effects of cocaine but has not been shown to alter the subjective drug effect [82]. On the other hand, carvedilol, which has similar pharmacology as labetalol but greater CNS potency, blocked not only some of the cardiovascular effects of acute cocaine ingestion but also some of the subjective effects when given in a lower dose. Use of the beta1- and beta2-adrenergic antagonist propranolol results in greater treatment retention and more frequent drug-free urine samples than placebo among patients with more severe withdrawal symptoms, an effect not observed among subjects with milder withdrawal symptoms [25; 78]. Propranolol administered at a dose of 100 mg/day has been found to be effective in reducing withdrawal symptoms and improving treatment retention among patients with greater cocaine addiction severity [83; 84]. In a separate randomized, placebo-controlled study, a 40-mg dose of propranolol was found to reduce subjective cocaine craving and objective cue reactivity (e.g., heart rate, blood pressure) in response to a video of people using cocaine and in vivo cues (e.g., forms of preferred simulated cocaine/drug paraphernalia) [117]. Overall, adrenergic receptor antagonists seem to be effective in reducing or blocking the physiologic effects of acute cocaine ingestion and may be helpful in symptom reduction in a subset of patients with greater withdrawal severity. However, the American Heart Association has recommended that these agents be avoided for the treatment of cocaine toxicity in the acute setting [85].

IMMUNIZATION AND VACCINE THERAPY

Pharmacotherapy for cocaine use disorder targets brain neuronal pathways, whereas immunotherapy for cocaine use disorder acts peripherally to inhibit the effects of cocaine by blocking or delaying entry of the cocaine molecule into the brain [25]. The impetus for the development and evaluation of biologic therapies for cocaine use disorder stems, in part, from the potential side effects and disappointing results of pharmacotherapy trials targeting reward pathways that mediate the addictive effects of cocaine [24].

The two biologic-based therapies for cocaine use disorder that have been subjected to empirical evaluation are immunization and vaccination. Both are variants of the concept of antagonist therapy to block drug effect [70]. In passive immunization, the catalytic antibodies that bind with and convert circulating cocaine molecules to an inactive molecule through hydrolysis are injected into the patient. The action of the antibody breaks down cocaine into ecgonine methyl ester and benzoic acid, resulting in a lack of desired effects. Active immunization employs vaccination, which triggers the production of antibodies against cocaine through the administration of a cocaine-protein conjugate. Both inactive and active immunization prevent induction of the positive effects of cocaine ingestion. Several drawbacks to vaccine therapy for cocaine use disorder have been identified. These include the lack of protection against drugs that are structurally distinct from cocaine, but that produce the same effect; lack of effect on craving; wide variation in antibody formation across individuals; and patient motivational factors [92].

WITHDRAWAL FROM COCAINE

Physiologic adaptation and psychologic dependence may result from regular, long-term use of cocaine. Withdrawal symptoms are a result of the increased receptor density and receptor supersensitivity to neurotransmitters that characterize the adaptation to chronic cocaine use. Craving may occur either spontaneously or in response to environmental cues. Craving diminishes gradually in most users, but in severe users, it may never become fully extinguished [13; 93].

A triphasic abstinence syndrome from heavy cocaine use has been identified [18]. Phase one is acute withdrawal, or the "crash." Immediately upon cessation of use, a withdrawal syndrome can manifest, consisting initially of a rapidly declining mood and energy level, agitation, and retarded major depression. Depression and dysphoria are observed and reported, as well as agitation, sweating, tachycardia, and unstable blood pressure. Symptoms of paranoia peak and then decline during this period. Patients experience overwhelming cravings to use cocaine at this point, partially to terminate the extreme discomfort of the withdrawal symptoms. However, many patients will attempt to use sedatives, opioids, alcohol, or cannabis to terminate anxiety and agitation and to induce sleep. Phase one can last up to four days [12; 18].

Phase two can last one to ten weeks, during which time patients are likely to experience prolonged anhedonia, impaired motivation, dysphoria, and craving. It is during this period that patients are at highest risk of relapse. Outpatients are especially vulnerable to environmental cue-induced triggers for cocaine use. Persons, places, and things associated with cocaine use stimulate vivid recollection and cocaine-induced euphoria that, when contrasted with the ongoing dysphoria, can make resumption of use irresistible. If relapse occurs during this phase, it can activate the vicious cycle of heavy use, attempts to quit, and relapse [18].

Phase three consists of episodic craving that is gradually diminished if the cocaine user is able to remain abstinent [18]. The severity and duration of the symptoms of cocaine abstinence syndrome may be considerably less in the inpatient setting, where the patient is removed from the ubiquity of triggers encountered in the using environment [18; 93; 94].

The World Health Organization asserts that there is no evidence that medication-assisted withdrawal would benefit pregnant women with cocaine use disorder. (https://www.guideline.gov/summaries/summary/48894. Last accessed March 3, 2017.)

Level of Evidence: Expert Opinion/Consensus Statement

TREATMENT OF CONDITIONS ASSOCIATED WITH COCAINE USE

POLYSUBSTANCE DEPENDENCE

As noted, patients with cocaine use disorder are often found to be addicted to or abuse other substances, such as alcohol, opioids, and benzodiazepines. These patients should be treated with therapies with established efficacy to manage the coexisting substance dependence, such as methadone or buprenorphine for patients with opioid use disorder, or naltrexone, acamprosate, or disulfiram for alcohol dependence [39].

Treatment Issues for Patients with Opioid Use Disorder Who Use Cocaine

Stimulant abuse and dependence is a significant problem among heroin addicts being treated with methadone maintenance therapy and one of the most treatment-resistant behaviors among this population. Numerous studies have evaluated the efficacy of pharmacotherapeutic agents in reducing cocaine use in this patient population [57]. A review of several randomized, double-blind, placebo-controlled studies failed to find superior efficacy on measures of cocaine use and dropout rate among patients receiving any antidepressant for cocaine use disorder [71]. A review of 17 studies involving amantadine, bromocriptine, and pergolide failed to show significant differences in rates of cocaine-positive urine samples [73]. Pergolide has since been withdrawn for human use [115].

The efficacy of voucher-based incentive programs for reducing cocaine use among patients with cocaine use disorder on methadone maintenance is well established and has been extended to the treatment of alcohol, cannabis, nicotine, and opioid dependence [95]. One study demonstrated a 50% abstinence rate at 12 weeks for patients receiving vouchers contingent on abstinence, compared with only 15% abstinence among patients receiving vouchers with no contingency [96]. Another multisite study included patients receiving methadone maintenance for opioid use disorder who exhibited intractable stimulant abuse. These patients were randomized to either usual care or usual care plus voucher-contingent incentive delivered on an intermittent-reinforcement schedule [57]. Results showed that intermittently providing incentives essentially doubled the likelihood of stimulant- and alcohol-free urine samples on any given clinic visit. Patients in the incentive groups were 11 times more likely to achieve 12 or more weeks of continuous abstinence than patients receiving usual care only.

ADHD

As discussed, methylphenidate has not been shown to be effective in reducing cocaine use in patients with cocaine use disorder and comorbid ADHD. However, it does substantially reduce ADHD symptoms [97]. The FDA warns that priapism may occur in men taking methylphenidate products, particularly after a dosage increase or following drug abstinence or an unusually long length of time between doses [15].

MAJOR DEPRESSION

Mood disorders are associated with substance abuse in general, and cocaine abuse and dependence are specifically associated with depression. Lifetime rates of major depression range from 25% to 61% among cocaine-dependent inpatients [98]. Managing both disorders is essential because the presence of one of these disorders decreases the likelihood of remission from the other [98]. With many depressive symptoms resolving in early abstinence, the traditional approach has been to monitor depressive symptoms during the first four weeks of treatment and withhold antidepressant treatment until the end of the four weeks. However, this approach often is not practical, as many cocaine-addicted patients cannot abstain during the initial four weeks. This problem is compounded by the increasing scarceness of resources for inpatient treatment, which underscores the importance of treating both conditions simultaneously [99].

Results from numerous clinical trials support the use of antidepressants in patients with comorbid depression and cocaine abuse. Research has suggested that the more activating antidepressants, such as bupropion and the tricyclics, are more effective than SSRIs, supporting the observation that substance-abusing patients respond preferentially to medications whose direct or side effect profiles resemble the effects of their drug of choice [98]. Unfortunately, tricyclics have worse side effects, tolerability, and safety profiles than SSRIs and should be used with extreme caution in depressed patients [99]. As previously noted, there is no empirical support for antidepressant treatment to reduce cocaine usage in these patients. Although limited, research on behavioral therapy treatment of comorbid depression and cocaine abuse suggests that CBT can promote greater treatment retention and longer periods of abstinence, and patients receiving motivational interviewing remain engaged in aftercare longer and have fewer depression-related hospitalizations following treatment [60; 98].

ALTERNATIVE/ COMPLEMENTARY TREATMENT OF COCAINE USE DISORDER

ACUPUNCTURE

Auricular (ear) acupuncture has become a widely used treatment for cocaine use disorder and is employed by hundreds of treatment centers and clinics in the United States. The procedure, which was developed at Lincoln Hospital in New York City in the 1970s, entails the placement of needles in five ear locations that represent the lung, kidney, liver, sympathetic, and shen men (a universal enhancer) points. This specific methodology has become a standardized treatment for substance abuse and is not specific to cocaine use disorder or abuse [100].

Gates et al. performed a review of seven randomized, controlled trials enrolling 1,433 subjects of auricular acupuncture with cocaine use disorder [100]. Overall, there was little evidence of significant improvement among acupuncture recipients compared to groups receiving either nonaccupoint acupuncture or no acupuncture on measures of severity of dependence, cocaine use self-report, cocaine use assessed by urine toxicology screen, and cocaine craving. As is the case with many studies of addiction, high rates of subject attrition limited the quality of evidence. With any alternative therapy, it is difficult to separate the therapeutic effect of the intervention from the nonspecific effects of interaction with the practitioner and the heightened expectancy of therapeutic benefit. These limitations result in unreliable evidence.

SELF-HELP AND 12-STEP THERAPY

Twelve-step programs for stimulant and other drug abuse and dependence, such as NA and CA, are modeled after AA, an abstinence-based support and self-improvement program that is based on the 12-step model of recovery [105; 106]. AA is widely considered the most successful treatment program for alcoholism and has helped hundreds of thousands of alcoholics achieve sobriety. The 12-step model emphasizes acceptance of addiction as a chronic progressive disease that can be arrested through abstinence but not cured. Additional elements of the AA model include spiritual growth, personal responsibility, and helping other addicted individuals. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution and a resource for emotional support [101; 102].

The understanding of drug addiction as a chronic and relapsing disorder has helped professionals gain a better understanding of the vital role played by 12-step programs. All patients attempting to recover from a substance use disorder will encounter a time when they face urges to use without having access to the resources or assistance of addiction professionals. Twelve-step programs are not considered substitutes for treatment. Instead, they provide ongoing and indefinite support in the achievement and maintenance of abstinence and in personal growth and character development [102; 103].

Part of the effectiveness of AA, NA, and CA is rooted in their ability to provide a competing and alternative reinforcer to drug use. Involvement in a 12-step program can enhance the quality of social support and the social network of the member, which is a potentially highly reinforcing aspect that would be forfeited if drug use was resumed [69]. Other reinforcing elements of 12-step involvement include recognition for increasingly durable periods of abstinence and frequent awareness of the consequences of drug and alcohol use through attendance at meetings [55]. Research has shown that establishing a pattern of 12-step program attendance early in treatment predicts the level of ongoing involvement. Thus, healthcare providers should emphasize and facilitate early engagement in a 12-step program [104].

Although research on efficacy and patient outcome in NA and CA is limited, many prominent addiction researchers have emphasized the important role that ongoing involvement in a 12-step program plays in recovery from substance abuse [103]. An important finding related to 12-step program efficacy was observed by Weiss et al., who found that 12-step attendance was not associated with decreased drug use, but that 12-step involvement (i.e., speaking or performing service work at a meeting, working with a sponsor outside of the meeting, reading 12-step literature, or working on a step) was [69; 104]. In particular, active involvement in a given month predicted a significant reduction in cocaine use the following month. An interesting finding was that patients who involved themselves in 12-step program activities but whose attendance at meetings was inconsistent achieved rates of drug use reduction that were comparable to those who regularly attended and were involved in the 12-step meetings and program.

One study found that the majority of cocaine-dependent outpatients who attended 12-step programs actually attended AA more often than CA. The authors speculated that in addition to AA being more established and available than CA, some patients might have urges for cocaine triggered by the explicit cocaine-related discussion content found in CA [69].

Narcotics Anonymous (NA)

NA was founded in California in 1952 and has grown to include 67,000 weekly meetings in 139 countries. The following demographic information was obtained in a survey returned by almost half of the 22,803 attendees at the 2015 NA World Convention held in Rio de Janeiro, Brazil [106]:

- Gender: 59% male, 41% female
- Ethnicity: 74% white, 11% African American, 6% Hispanic, 4% multiracial, 3% Asian, and 1% Native American/ Alaska Native
- Average abstinence/recovery period: 8.3 years
- Substance(s) used by members:
  - Alcohol: 79%
  - Cannabis: 68%
  - Cocaine: 55%

The NA website provides additional information regarding sponsors and meetings.

INTERVENTIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding the risks associated with the use of cocaine and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

PROGNOSIS

Despite numerous interventions that have demonstrated a degree of efficacy in clinical trials, patients in outpatient treatment for cocaine use disorder exhibit very high rates of dropout and relapse, with an average of approximately 50% of patients enrolled in 90-day outpatient programs terminating prematurely [107]. Among outpatients, abstinence upon treatment entry and in the initial weeks of treatment has been associated with abstinence during post-treatment follow-up, with severity of cocaine abstinence symptoms negatively correlated with outcome [58; 107]. Environmental factors that increase the risk of resumption of cocaine use include contact with drug users or a drinking environment [18]. Patients addicted to crack cocaine are believed to have a higher relapse rate because of the greater intensity of drug craving, which can be triggered by aspects of the using environment [18; 108].

Factors associated with poor prognosis include a dual diagnosis of psychiatric illness, including comorbid major depression [109]. Antidepressants seem to be less effective in managing the depression in these patients and are not generally effective in reducing cocaine use. Such patients have a poorer prognosis than nondepressed cocaine abusers, possibly due to a unique feature that lowers the response rate to antidepressants. The higher rates of character pathology, higher psychiatric distress, and lower psychosocial functioning found in these patients also are believed to affect outcomes [99].

Patients who abuse both cocaine and alcohol constitute a large proportion of those seeking treatment for cocaine abuse and dependence. Addressing dependence to both substances is important, as polysubstance abusers are more likely than monosubstance cocaine abusers to relapse back to cocaine abuse as the result of alcohol consumption [48]. The severity of cocaine use disorder, initial urine drug screen results, and frequency of recent cocaine use also have been shown to significantly impact treatment outcomes in patients with comorbid alcoholism [110].

A study of situational, interpersonal, and intrapersonal factors associated with cocaine relapse was performed in a sample of 132 cocaine-dependent outpatients [111]. At two years following treatment, single variable analysis found that abstinence commitment, self-efficacy, positive mood, family support, employment, attendance at aftercare, and participation in a 12-step program predicted less cocaine use. However, multivariate analysis found that the degree of participation in a 12-step program was the single most robust predictor of reduced cocaine use. The authors of the study concluded that these results further validated the important role that 12-step program involvement plays in abstinence; increasing the emphasis to patients on the importance of 12-step program participation could increase positive outcomes [111].

Short-term outpatient treatment of stimulant abuse and dependence seldom results in abstinence for any sustained period. The traditional view that program failure is a patient problem is being replaced by the view that program failure is reflective of program shortcoming [107; 112].

CONCLUSION

Until the 1980s, cocaine was considered a relatively innocuous recreational drug, and research on the pathophysiology and treatment of cocaine addiction was limited. The introduction and widespread use of crack cocaine, with the associated serious morbidity and profound addiction liability associated with its use, introduced a new emphasis on stemming and treating cocaine use and dependency. The development of pharmacologic interventions and psychosocial therapies for cocaine use disorder has been the focus of much research. It is the goal of this course to provide the knowledge necessary to identify, treat, and provide an appropriate referral to patients with cocaine use or dependence disorders.

RESOURCES

Cocaine Anonymous World Services
PO Box 492000
Los Angeles, CA 90049
310-559-5833
https://www.ca.org

Narcotics Anonymous World Services
PO Box 9999
Van Nuys, CA 91409
818-773-9999
http://www.na.org

National Institute on Drug Abuse
6001 Executive Boulevard
Room 5213, MSC 9561
Bethesda, MD 20892
301-443-1124
https://www.drugabuse.gov

Substance Abuse and Mental Health Services Administration
5600 Fishers Lane
Rockville, MD 20857
877-726-4727
https://www.samhsa.gov

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