Methamphetamine Use Disorder

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Faculty

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Faculty Disclosure

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

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for dental professionals who are involved in the evaluation or treatment of persons who use methamphetamine.

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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 dental 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.

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 [7].

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 [8].

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 psychological factors [9]. 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 [10].

While national trends are showing declines, regional use of methamphetamine continues to vary widely, with the strongest effects felt in the West and Midwest regions of the country, as well as a strong presence in the Southeast. In recent years, methamphetamine use has become more prevalent in areas that historically were not major markets for the drug, particularly the Northeast [11; 12; 13]. Data from the National Institute on Drug Abuse National Drug Early Warning System indicate that treatment admissions for methamphetamine use were less than 1% in sites east of the Mississippi River but ranged from 12% to 29% in sites west of the Mississippi [14]. 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 2020 National Drug Threat Assessment compiled by the U.S. Drug Enforcement Administration (DEA), methamphetamine poses the greatest threat to Guam, with most of the methamphetamine originating from the U.S. mainland, primarily California and Washington [12].

Data from the 2021 National Survey of Drug Use and Health indicate that approximately 2.5 million individuals (0.6% of the population) 12 years of age or older had used the drug in the past year, 1.6 million were current users, and 101,000 were new users [15]. 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 [16]. 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 [16]. 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 811,464 emergency visits in 2021, an increase from 103,000 visits reported in 2011 [11; 17]. Nationwide, methamphetamine/amphetamine admissions to treatment programs accounted for 9% of all admissions in 2015 [18].

Lower prices, higher purity, increased production, and increased flow of methamphetamine across the southwest border has contributed to rising domestic availability. The DEA seized 53,079 kilograms of methamphetamine nationwide in 2019, an increase of 55% from 2018 (34,270 kilograms). Final DEA data from 2020 indicate that domestic methamphetamine lab seizures decreased from 15, 256 in 2015 to 890 in 2019, the lowest reported in 19 years; the majority (84.8%) were small-capacity production laboratories [12]. The seizures of methamphetamine crossing the southwest border of the United States increased 74% from 2018 (39,268 kilograms) to 2019 (68,355 kilograms), as Mexican super-labs produced the preponderance of the drug [12]. The gram price of methamphetamine remains relatively low while the purity and potency remain 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 80% of child abuse cases in the state involved methamphetamine use in one or both parents [19]. 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 [20]. 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 [21]. 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 [21].

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]. The 2021 Youth Risk Behavior Surveillance found that more Hispanic male students (2.2%) had ever used methamphetamine one or more times compared to White (1.5%) or Black (2.0%) male students [22]. Female students (1.8%) are less likely to have used methamphetamine than male students (2.0%), 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 2021 (8.4%), which corresponds with information showing the latest spike of increased use occurring primarily among individuals older than 25 years of age.

Among people 12 years of age or older in 2021, 0.6% (or 1.6 million people) had a methamphetamine use disorder in the past year. The percentage was highest among adults 26 years of age or older (0.7% or 1.5 million people) and lowest among adolescents 12 to 17 years of age (0.1% or 20,000 people) [15]. Age-group differences in the percentage of people with a methamphetamine use disorder in the past year were consistent with the differences described for methamphetamine use in the past year [15].

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 [23]. 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 [24].

Methamphetamine use has increased particularly among people with an existing opioid use disorder [25]. Among treatment-seeking people with opioid use disorder, reports of past-month methamphetamine use nearly doubled, from 18.8% to 34.2%, between 2011 and 2017 [25]. Overall, methamphetamine use is one of the leading causes of drug overdose deaths in the United States, accounting for 10.6% of deaths in 2016 [26]. Of these deaths, 49.8% involved concomitant use of another drug (e.g., heroin, fentanyl, cocaine) [26].

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 [27].

PHARMACOLOGY

Methamphetamine stimulates the release and blocks the presynaptic reuptake of serotonin, dopamine, and norepinephrine [4; 28]. 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 [29].

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 [30].

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 [10]. 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 [10].

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. Approximately 30% to 54% of an oral dose is eliminated in the urine within the first 24 hours, with 10% to 23% as intact drug and the remainder as metabolites [30]. 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 [30]. 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 [10]. 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) [30].

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) [31]. 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) [32].

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 [33]. 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") [33].

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 [33]. 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 [33]. 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 [34; 35].

Four structurally and functionally distinct dopamine neuronal pathways exist in the adult brain [36]:

- 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 [37].

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 [38]. 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

Methamphetamine also can be dissolved in a variety of liquids, including vehicle fluids, fuels, water, and alcoholic beverages, making it more easily smuggled and more difficult to detect. Methamphetamine in solution form is rarely sold on the streets [12]. Methamphetamine in pill form appeared in several states in 2019 and 2020 [12].

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 [39].

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 psychological effects of the drug [40; 41]. 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 generaliz-

ability: 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 [41]. 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 [39]. 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 neuropsychological dimensions three years into abstinence [42; 43].

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 [44].

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; 24; 45; 46; 47; 48; 49]. 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; 10].

Acute methamphetamine ingestion can both exacerbate pre-existing psychopathology and generate comorbidity [50]. 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 [24]. Biologically based causes of methamphetamine-induced mortality include stroke and cerebral hemorrhage, cardiovascular collapse, pulmonary edema, myocardial infarction, hyperpyrexia, and renal failure [4; 49].

SIGNS AND SYMPTOMS OF ACUTE METHAMPHETAMINE USE	
Psychological 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; 24; 45; 46; 47; 48; 49]	*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; 24; 45; 46; 47; 48; 49]. 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 [47].

Dental Effects

"Meth mouth" is widespread among certain populations of methamphetamine users, particularly those incarcerated for methamphetamine-related offenses [47]. "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 [47].

SIGNS AND SYMPTOMS OF CHRONIC METHAMPHETAMINE USE	
Psychological 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 excoriated 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; 24; 45; 46; 47; 48; 49] *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 [51]:

- 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 [39]. Even a sub-neurotoxic reduction of dopamine activity can produce the lingering motivational difficulties often encountered by patients in early to intermediate recovery [39]. 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 [52; 53]. 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 [54]. Substantial impairment in attention/psychomotor speed, verbal learning and memory, and fluency-based measures of executive systems functioning have been reported [55]. Metabolic brain abnormalities in the limbic and paralimbic regions observed in methamphetamine addicts may underlie the affective dysregulation often experienced in early recovery [56].

Cognitive performance in methamphetamine-dependent patients may actually worsen during the first three months of abstinence. Researchers found that abstinent patients with a recent lapse scored worse on neuropsychological testing than patients with ongoing methamphetamine use, indicating that abstinent patients may encounter difficulties in treatment when attention, understanding, and memory are needed [57].

Functional and structural deficits associated with methamphetamine use have been observed 6 to 12 months into continuous abstinence. The authors of one study found significant impairment in reaction time, working memory, and mental concentration [58]. 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 [59]. Ongoing dysfunction in executive control of verbal encoding and retrieval consistent with neurologic damage to the prefrontal cortex has been observed [60]. Significant correlations between aggression severity, extent of serotonin transporter density reduction, and duration of methamphetamine use have been observed [61]. 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 [62; 63; 64; 65].

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 [66]. 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 [67]. 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 neuropsychological disturbances in methamphetamine users with intermediate-length abstinence [66]. 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 [68].

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. Using proton magnetic resonance spectroscopy (MRS), researchers noted neuronal recovery with extended abstinence from methamphetamine and observed partial anterior cingulated cortex normalization that positively correlated with duration of methamphetamine abstinence [69]. The authors of another study, which also used proton MRS, also observed anterior cingulated cortex normalization with sustained methamphetamine abstinence (one to five years) [70]. Others 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 [67]. 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 [71].

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 [72]. 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; 72]. 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 [73]. 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 [58]. However, a study using magnetic resonance spectroscopy and magnetic resonance imaging found no evidence of neuronal damage or loss in selected brain regions [74].

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 [75].

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 [76; 77; 78]. High rates of previous and current suicidal ideation are found in incarcerated methamphetamine abusers, who are also likely in need of psychiatric assistance [79]. The high rates of depres-

sion among methamphetamine-dependent persons may, however, be attributed to baseline depression, situational aspects of the individual's life, or the methamphetamine withdrawal process itself [80].

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 [80]. 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 [80].

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 [80]. 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 [81].

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 [82]. 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 [82]. Violence is also associated with methamphetamine-induced psychoses [28]. 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 [83].

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 [84]. 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 [38]. 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 [38].

WITHDRAWAL FROM METHAMPHETAMINE

The fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) does not distinguish symptoms of methamphetamine withdrawal from that of cocaine or other stimulant drug withdrawal [85]. 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 [76; 86]:

- 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 [87].

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 psychological approaches and is delivered to the patient immediately following acute withdrawal [88].

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 [46]. 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 [89]. 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; 57]. Understanding the effects of methamphetamine use on mood,

neuropsychological 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 [20]. This is illustrated by the culturally sensitive approach tailored for gay and bisexual men, termed gay-tailored cognitive-behavioral therapy (GCBT) [90].

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 [91; 92]. 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 [90; 92]. 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 [88; 93].

Elements of the Matrix Model include [90]:

- Engagement and retention: Emphasizing the patient-therapist relationship
- Structure: Planning and scheduling to help patients eliminate blocks of free time
- Information: Helping patients connect psychological, 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 [88].

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 [46]. 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 [94]. 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 [90].

A 2005 study suggests that CBT can improve the psychological well-being of outpatient methamphetamine users [95]. 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 [95]:

- 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 [96]. 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.

A group of researchers conducted a randomized controlled trial to evaluate the efficacy of brief CBT for regular methamphetamine use among methadone-maintained women [97]. Eligible women received either brief CBT (treatment group) or drug education (control group). Five questionnaires assessed the efficacy of brief CBT at weeks 0, 4, and 12. Urinalysis verified self-reported methamphetamine use at week 0. Urinalyses were also used for participants who reported methamphetamine abstinence at weeks 4 and 12. Of 120 total participants, 16 were lost to follow-up. Compared with the control group, the treatment group showed significant reductions in frequency of methamphetamine use, severity of methamphetamine dependence, and number of days of methamphetamine use at weeks 4 and 12. Significant improvements in readiness to change, psychological well-being, and social functioning were observed in the brief CBT group at weeks 4 and 12.

Nineteen urine specimens (31.66%) in the brief CBT group were negative for methamphetamine use at post-treatment and follow-up; no change was observed in the control group [97].

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 [90].

Researchers 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 [90]. 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.

Application of CBT in lesbian, gay, bisexual, transgender, and intersex (LGBTI) communities has consistently shown positive results. CBT either alone or combined with contingency management reduced methamphetamine use, cravings, or relapse during treatment in this population [98].

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 [90; 99]. 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 [100].

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 [101]. 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 [101].

One study compared the efficacy of CM alone to CM plus strengths-based case management (CM/SBCM) in reducing methamphetamine use [102]. CM/SBCM was associated with attending more sessions for people who reported being in a couple. Participants who earned more rewards in the first part of the study were more likely to have more clean urinalysis in the second part of the study. Also, participants who were in a couple, without sexual abuse history, and less methamphetamine use at baseline tended to have more clean urinalysis in the CM/SBCM intervention [102].

Several factors appear to predict CM treatment outcome, including problem severity, race, HIV status, education, and income. CM therapy was least effective for participants who reported a long history of drug use or more methamphetamine use during baseline; it was most effective in White participants [103; 104; 105; 106].

Conventional Treatment

The efficacy of conventional residential treatment with methamphetamine-dependent patients was the focus of a 2004 study [107]. 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 [107].

The efficacy of two residential treatment programs among 108 methamphetamine users was the focus of another study [108]. Patients from one center (amphetamine-type stimulant group) received conventional group therapy plus an additional 10 hours of group therapy focused on stimulant use. Patients from the other center received conventional group therapy only (treatment as usual). A drop-out rate of 40.7% was observed with no significant difference between the two groups. Patients remained significantly longer in treatment as usual compared to amphetamine-type stimulant treatment. In both treatment programs, craving and psychiatric symptoms significantly decreased while psychosocial resources, processing speed, and cognitive flexibility improved over time. Other cognitive measures yielded mixed results. History of injection drug use was a significant predictor for treatment drop-out [108].

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. The authors of one analysis 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 [109]. 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.

reSET Mobile Application

In 2017, the FDA permitted marketing of reSET, the first mobile medical application to help treat substance use disorders. The reSET device delivers CBT to patients to teach skills that aid in treatment of substance use disorders, to increase abstinence from substance abuse, and to increase retention in outpatient therapy programs [110]. The device has been shown to be effective in reducing methamphetamine use and craving during treatment [98].

Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS)

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive FDA-approved medical procedure for treatment of depression in adults. Transcranial direct current stimulation (tDCS) uses a direct-current field delivered at varying intensities to electrodes placed on the scalp. rTMS acts as a neuro-stimulator; tDCS acts as a neuromodulator. Randomized clinical studies compared rTMS with sham stimulation or with treatment-as-usual among individuals with methamphetamine use disorder. Compared with healthy controls, individuals with methamphetamine use disorder displayed significant reductions in craving, executive functions, withdrawal symptoms, and/or mood status with rTMS [111; 112; 113; 114]. rDCS also has been shown to significantly reduce methamphetamine craving and to increase executive functions compared to controls [115; 116; 117; 118].

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 [119].

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 [120]. Thus, psychosocial therapy remains the backbone of treatment for these patients [121].

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 amphetamine/methamphetamine use disorder.

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed June 9, 2023.)

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, the authors of a controlled trial 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 [99]. These findings suggest that sertraline should not be given to methamphet-

amine 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 [122].

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 [123]. 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 [9]. 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 [124]. 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 [125].

Agonist Replacement Therapy

An approach consistent with the harm reduction model has been proposed and involves prescribing dextroamphetamine to patients addicted to methamphetamine [49]. 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 [126]. 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 [127]. 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 [128]. 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 [129]. 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 [130]. 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 [131]. 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 [132]. A 2020 study was undertaken to determine the efficacy of mirtazapine for the treatment of methamphetamine use disorder and reduction in HIV risk behaviors [133]. Outcomes assessed were positive urine test results for methamphetamine over 12, 24, and 36 weeks (primary outcomes) and sexual risk behaviors (secondary outcomes). Of 241 individuals assessed, 120 were enrolled. Mirtazapine resulted in reductions in positive urine test results at 24 weeks and 36 weeks versus placebo; medication adherence was slightly lower (38.5%) in the mirtazapine group versus the placebo group (39.5%). Changes in sexual risk behaviors were not significantly different at 12 weeks, but individuals assigned to the mirtazapine group had fewer sexual partners and fewer episodes of high-risk sexual behavior [133].

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. Researchers 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 [134]. 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 [135].

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 [136]. 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 [137]. 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. Results of a systematic review of 43 studies and 4,065 participants reporting on 23 individual pharmacotherapies found that neither tricyclic antidepressants nor SSRIs were effective in reducing methamphetamine use [138].

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 [139].

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. Lack of efficacy of dopaminergic medications has been attributed to a decrease in dopamine D2 receptor levels in the striatal subregions in people who chronically abuse methamphetamines [140; 141].

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 [142].

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 [143]. 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 [143]. 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 [144]. These researchers also concluded that naltrexone may be helpful in preventing relapse. The results of a 2019 systematic review of the effects of naltrexone on methamphetamine use indicate that the drug did not significantly affect either abstinence rates or craving levels [145].

Emerging Pharmacotherpies and Other Potential Treatments

A recent Phase III clinical trial found that a combination of oral bupropion and injectable naltrexone was effective in the treatment of moderate-to-severe methamphetamine use disorder [146]. The combination was safe and successfully reduced cravings compared with placebo. Bupropion may alleviate the dysphoria associated with methamphetamine withdrawal by acting on the dopamine and norepinephrine systems, thereby reducing cravings and helping to prevent relapse. Naltrexone may reduce the reward effects and cravings by blocking opioid receptors [147; 148]. Bupropion or naltrexone administered alone showed limited and inconsistent efficacy [118].

Several medications for treatment of methamphetamine use disorder are in different stages of clinical trials, including oxytocin, doxazocin, lobeline, disulfiram, acamprosate, atomoxetine, and entacapone [149].

Immunotherapy is being investigated for treatment of methamphetamine use disorder. Passive immunotherapy involves vaccination with a monoclonal antibody designed to bind to the drug in the bloodstream. Active immunotherapy involves vaccination with an immunogenic methamphetamine-containing conjugate that is able to stimulate specific antibodies that sequester the drug in the brain's periphery, thereby reducing methamphetamine use and relapse [150; 151; 152]. The antibody is in Phase II trials. Despite promising early preclinical results, no active methamphetamine vaccine has reached clinical trials [118].

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 [24; 84; 153]. 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 [84]. 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 [40].

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 [93].

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 5 to 10 times that of the general population [154]. It has been hypothesized that methamphetamine's effects of stimulating energy, confidence, and libido may be particularly effective in counteracting depression or fatigue [155]. This, coupled with the drug's relative inexpensiveness, may make methamphetamine particularly attractive to gay and bisexual men and/or persons with HIV [155]. Methamphetamine use can also increase the frequency and duration of sexual encounters and result in the abandonment of safe sex practices [156]. Consequently, methamphetamine-dependent gay and bisexual men are at heightened risk of STIs, in particular HIV transmission [20]. 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 [93].

The profound connection of methamphetamine use with HIV infection in gay and bisexual men in urban settings has been documented by researchers who found that 61% of a sample of 162 methamphetamine-dependent, treatment-seeking outpatients in Los Angeles were HIV-positive [157]. In another study, 77.6% of a sample of 143 outpatients in San

Francisco were HIV-positive [158]. 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 [157]. 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 [159].

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 [160; 161]. 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 [162]. 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 [163].

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://rhntc.org/sites/default/files/resources/mtc_male_prevrhc_2014.pdf. Last accessed June 9, 2023.)

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; 164]. 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 [20].

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 [165]. Case management and behavioral contracting have also been identified as useful approaches to engage and maintain rural residents in therapy [164]. 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 [164]. Other possible approaches in the treatment of rural methamphetamine abuse include treatment of jail and prison inmates and the use of drug courts [164].

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 [166]. 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 [93; 167].

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 [77]. Management strategies for aggressive and violent patients include [168]:

- 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 [169].

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 has helped hundreds of thousands of alcoholics achieve sobriety [170]. 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 [170].

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 [171]. 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 [172].

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. One study 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 [173]. 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 [173]. 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 [46]. Poor prognosis and relapse are associated with [124; 174; 175; 176]:

- 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 [57; 177].

Neurobiologic factors associated with prognosis have been identified [174]. 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 [67].

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.

Works Cited

1. Hunt D, Kuck S, Truitt L. *Methamphetamine Use: Lessons Learned*. Cambridge, MA: ABT Associates Inc.; 2006.
2. Degenhardt L, Topp L. "Crystal meth" use among polydrug users in Sydney's dance party subculture: characteristics, use patterns and associated harms. *Int J Drug Policy*. 2003;14(1):17-24.
3. Nordahl TE, Salo R, Leamon M. Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. *J Neuropsychiatry Clin Neurosci*. 2003;15(3):317-325.
4. Meredith CW, Jaffe C, Ang-Lee K, Saxon AJ. Implications of chronic methamphetamine use: a literature review. *Harv Rev Psychiatry*. 2005;13(3):141-154.
5. Anglin MD, Burke C, Perrochet B, Stamper E, Dawud-Noursi S. History of the methamphetamine problem. *J Psychoactive Drugs*. 2000;32(2):137-141.
6. United Nations Office on Drugs and Crime. Regional Trends: East and Southeast Asia: Summary, Emerging Trends and Concerns. Available at http://www.unodc.org/documents/southeastasiaandpacific//2012/12/ats-2012/section/2012_Regional_ATS_Report_SEA.pdf. Last accessed June 6, 2023.
7. Edström B. The forgotten success story: Japan and the methamphetamine problem. *Japan Forum*. 2015;27(4):519-543.
8. Reuter P, Caulkins JP. Does precursor regulation make a difference? *Addiction*. 2003;98(9):1177-1179.
9. Kongsakon R, Papadopoulos KI, Saguansiritham R. Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. *Int Clinl Psychopharmacol*. 2005;20(5):253-256.
10. Cho AK, Melega WP. Patterns of methamphetamine abuse and their consequences. *J Addict Dis*. 2002;21(1):21-34.
11. National Institute on Drug Abuse. Methamphetamine Research Report. What is the Scope of Methamphetamine Abuse in the United States? Available at https://nida.nih.gov/publications/research-reports/methamphetamine/what-scope-methamphetamine-misuse-in-united-states. Last accessed June 6, 2023.
12. U.S. Drug Enforcement Administration. 2020 National Drug Threat Assessment Summary. Available at https://www.dea.gov/sites/default/files/2021-02/DIR-008-21%202020%20National%20Drug%20Threat%20Assessment_WEB.pdf. Last accessed June 6, 2023.
13. Dombrowski K, Crawford D, Khan B, Tyler K. Current rural drug use in the U.S. Midwest. *J Drug Abuse*. 2016;2(3):pii-22.
14. Artigiani EEH, McCandlish D, Wish ED. *Methamphetamine: A Regional Drug Crisis*. College Park, MD: National Drug Early Warning System; 2018.
15. Substance Abuse and Mental Health Services Administration. 2021 National Survey of Drug Use and Health Releases: Detailed Tables. Available at https://www.samhsa.gov/data/release/2021-national-survey-drug-use-and-health-nsduh-releases#detailed-tables. Last accessed June 6, 2023.
16. The Regents of the University of Michigan. Monitoring the Future Survey: 2016 Data from In-School Surveys of 8th-, 10th-, and 12th-Grade Students. Available at http://www.monitoringthefuture.org/data/16data.html#2016data-drugs. Last accessed June 6, 2023.
17. Drug Abuse Warning Network (DAWN). Findings from Drug-Related Emergency Department Visits, 2021. Available at https://store.samhsa.gov/sites/default/files/pep22-07-03-002.pdf. Last accessed June 6, 2023.
18. Substance Abuse and Mental Health Services Administration. Treatment Episode Data Set (TEDS): 2005-2015, National Admissions to Substance Abuse Treatment Services. Available at https://www.samhsa.gov/data/report/treatment-episode-data-set-teds-2005-2015-national. Last accessed June 6, 2023.
19. HIPRC808. Drug Facts: Methamphetamine. Available at https://www.hiprc808.org/meth. Last accessed June 6, 2023.
20. Freese TE, Obert J, Dickow A, Cohen J, Lord RH. Methamphetamine abuse: issues for special populations. *J Psychoactive Drugs*. 2000;32(2):177-182.
21. Hawai`i Free Press. News Release: 2011 Hawaii Meth Use and Attitudes Survey Shows Significant Shifts in Attitudes Among Teens and Young Adults. Available at http://www.hawaiifreepress.com/ArticlesMain/tabid/56/ID/4586/Hawaii-Meth-Survey-Shows-Significant-Shifts-in-Attitudes.aspx. Last accessed June 6, 2023.
22. Centers for Disease Control and Prevention. YRBSS Results. Youth Risk Behavior Survey 2021 Results. Available at https://www.cdc.gov/healthyyouth/data/yrbs/results.htm. last accessed June 6, 2023.
23. Wu LT, Schlenger WE. Psychostimulant dependence in a community sample. *Subst Use Misuse*. 2003;38(2):221-248.
24. Cretzmeyer M, Sarrazin MV, Huber DL, Block RI, Hall JA. Treatment of methamphetamine abuse: research findings and clinical directions. *J Subst Abuse Treat*. 2003;24(3):267-277.
25. Ellis MS, Kasper ZA, Cicero TJ. Twin epidemics: the surging rise of methamphetamine use in chronic opioid users. *Drug Alcohol Depend*. 2018;193:14-20.
26. Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M. Regional differences in the drugs most frequently involved in drug overdose deaths: United States, 2017. *Natl Vital Stat Rep*. 2019;68(12):1-16.
27. von Mayrhauser C, Brecht ML, Anglin MD. Use ecology and drug use motivations of methamphetamine users admitted to substance abuse treatment facilities in Los Angeles: an emerging profile. *J Addict Dis*. 2002;21(1):45-60.

28. Boles SM, Miotto K. Substance abuse and violence: a review of the literature. *Aggress Violent Behav*. 2003;8(2):155-174.
29. Rawson R, Huber A, Brethen P, et al. Methamphetamine and cocaine users: differences in characteristics and treatment retention. *J Psychoactive Drugs*. 2000;32(2):233-238.
30. National Highway Traffic Safety Administration. Drugs and Human Performance Fact Sheets: Methamphetamine (and Amphetamine). Available at https://www.nhtsa.gov/sites/nhtsa.gov/files/809725-drugshumanperformfs.pdf. Last accessed June 6, 2023.
31. National Institute on Drug Abuse. The Neurobiology of Drug Addiction [Archived Content]. Available at https://www.drugabuse.gov/publications/teaching-addiction-science/neurobiology-drug-addiction. Last accessed June 6, 2023.
32. Cornish JW, O'Brien CP. Crack cocaine abuse: an epidemic with many public health consequences. *Annu Rev Public Health*. 1996;17:259-273.
33. Riddle EL, Fleckenstein AE, Hanson GR. Role of monoamine transporters in mediating psychostimulant effects. *AAPS J*. 2005;7(4):E847-E851.
34. Barr AM, Panenka WJ, MacEwan GW, et al. The need for speed: an update on methamphetamine addiction. *J Psychiatry Neurosci*. 2006;31(5):301-313.
35. Panenka WJ, Procyshyn RM, Lecomte T, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. *Drug Alcohol Depend*. 2013;129(3):167-179.
36. Harvey JA. Cocaine effects on the developing brain: current status. *Neurosci Biobehav Rev*. 2004;27(8):751-764.
37. Sofuoglu M, Kosten TR. Novel approaches to the treatment of cocaine addiction. *CNS Drugs*. 2005;19(1):13-25.
38. Cartier J, Farabee D, Prendergast ML. Methamphetamine use, self-reported violent crime, and recidivism among offenders in California who abuse substances. *J Interpers Violence*. 2006;21(4):435-445.
39. Davidson C, Gow AJ, Lee TH, Ellinwood EH. Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. *Brain Res Brain Res Rev*. 2001;36(1):1-22.
40. Brecht ML, O'Brien A, von Mayrhauser C, Anglin MD. Methamphetamine use behaviors and gender differences. *Addict Behav*. 2004;29(1):89-106.
41. Cadet JL, Krasnova IN. Chapter 5: molecular bases of methamphetamine-induced neurodegeneration. *Int Rev Neurobiol*. 2009;88:101-119.
42. Salo R, Nordahl TE, Galloway GP, Moore CD, Waters C, Leamon MH. Drug abstinence and cognitive control in methamphetamine-dependent individuals. *J Subst Abuse Treat*. 2009;37(3):292-297.
43. van Holst RJ, Schlit T. Drug-related decrease in neuropsychological functions of abstinent drug users. *Curr Drug Abuse Rev*. 2011;4(1):42-56.
44. Copeland AL, Sorensen JL. Differences between methamphetamine users and cocaine users in treatment. *Drug Alcohol Depend*. 2001;62(1):91-95.
45. National Institute on Drug Abuse. DrugFacts: What is Methamphetamine? Available at https://www.drugabuse.gov/publications/drugfacts/methamphetamine. Last accessed June 6, 2023.
46. Rawson RA, Huber A, Brethen P, et al. Status of methamphetamine users 2–5 years after outpatient treatment. *J Addict Dis*. 2002;21(1):107-119.
47. Curtis EK. Meth mouth: a review of methamphetamine abuse and its oral manifestations. *Gen Dent*. 2006;54(2):125-129.
48. National Institute on Drug Abuse. Methamphetamine: Overview. Available at https://www.drugabuse.gov/publications/research-reports/methamphetamine/overview. Last accessed June 6, 2023.
49. Shearer J, Sherman J, Wodak A, van Beek I. Substitution therapy for amphetamine users. *Drug Alcohol Rev*. 2002;21(2):179-185.
50. Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, et al. Psychopathology in methamphetamine-dependent adults 3 years after treatment. *Drug Alcohol Rev*. 2010;29(1):12-20.
51. American Dental Association. Meth Mouth: How Methamphetamine Use Affects Dental Health. Available at https://www.mouthhealthy.org/en/az-topics/m/meth-mouth. Last accessed June 6, 2023.
52. London ED, Berman SM, Voytek B, et al. Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. *Biol Psychiatry*. 2005;58(10):770-778.
53. Tobias MC, O'Neill J, Hudkins M, Bartzokis G, Dean AC, London ED. White-matter abnormalities in brain during early abstinence from methamphetamine abuse. *Psychopharmacology (Berl)*. 2010;209(1):13-24.
54. Bae SC, Lyoo IK, Sung YH, et al. Increased white matter hyperintensities in male methamphetamine abusers. *Drug Alcohol Depend*. 2006;81(1):83-88.
55. Kalechstein AD, Newton TF, Green M. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *J Neuropsychiatry Clin Neurosci*. 2003;15(2):215-220.
56. London ED, Simon SL, Berman SM, et al. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Arch Gen Psychiatry*. 2004;61(1):73-84.

57. Simon SL, Dacey J, Glynn S, Rawson R, Ling W. The effect of relapse on cognition in abstinent methamphetamine abusers. *J Subst Abuse Treat*. 2004;27(1):59-66.
58. Chang L, Smith LM, LoPresti C, et al. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Res*. 2004;132(2):95-106.
59. Salo R, Ursu S, Buonocore MH, Leamon MH, Carter C. Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2009;65(8):706-709.
60. Woods SP, Rippeth JD, Conover E, et al. Deficient strategic control of verbal encoding and retrieval in individuals with methamphetamine dependence. *Neuropsychology*. 2005;19(1):35-43.
61. Sekine Y, Ouchi Y, Takei N, et al. Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. *Arch Gen Psychiatry*. 2006;63(1):90-100.
62. Popova NK. From genes to aggressive behavior: the role of serotonergic system. *Bioessays*. 2006;28(5):495-503.
63. Badawy AA. Alcohol and violence and the possible role of serotonin. *Crim Behav Ment Health*. 2003;13(1):31-44.
64. Krakowski M. Violence and serotonin: influence of impulse control, affect regulation, and social functioning. *J Neuropsychiatry Clin Neurosci*. 2003;15(3):294-305.
65. de Almeida RM, Ferrari PF, Parmigiani S, Miczek KA. Escalated aggressive behavior: dopamine, serotonin and GABA. *Eur J Pharmacol*. 2005;526(1-3):51-64.
66. Iudicello JE, Woods SP, Vigil O, et al. Longer term improvement in neurocognitive functioning and affective distress among methamphetamine users who achieve stable abstinence. *J Clin Exp Neuropsychol*. 2010;32(7):704-718.
67. Volkow ND, Chang L, Wang GJ, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry*. 2001;158(3):377-382.
68. Kitamura O, Takeichi T, Wang EL, Tokunaga I, Ishigami A, Kubo S. Microglial and astrocytic changes in the striatum of methamphetamine abusers. *Leg Med (Tokyo)*. 2010;12(2):57-62.
69. Nordahl TE, Salo R, Natsuaki Y, et al. Methamphetamine users in sustained abstinence: a proton magnetic resonance spectroscopy study. *Arch Gen Psychiatry*. 2005;62(4):444-452.
70. Salo R, Buonocore MH, Leamon M, et al. Extended findings of brain metabolite normalization in MA-dependent subjects across sustained abstinence: a proton MRS study. *Drug Alcohol Depend*. 2011;113(2-3):133-138.
71. Wang GJ, Volkow ND, Chang L, et al. Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. *Am J Psychiatry*. 2004;161(2):242-248.
72. Smith L, Yonekura ML, Wallace T, Berman N, Kuo J, Berkowitz C. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. *J Dev Behav Pediatr*. 2003;24(1):17-23.
73. Colby JB, Smith L, O'Connor MJ, Bookheimer SY, Van Horn JD, Sowell ER. White matter microstructural alterations in children with prenatal methamphetamine/polydrug exposure. *Psychiatry Res*. 2012;204(2-3):140-148.
74. Alicata D, Chang L, Cloak C, Abe K, Ernst T. Higher diffusion in striatum and lower fractional anisotropy in white matter of methamphetamine users. *Psychiatry Res*. 2009;174(1):1-8.
75. Salo R, Flower K, Kielstein A, Leamon MH, Nordahl TE, Galloway GP. Psychiatric comorbidity in methamphetamine dependence. *Psychiatry Res*. 2011;186(2-3):356-361.
76. Dyer KR, Cruickshank CC. Depression and other psychological health problems among methamphetamine dependent patients in treatment: implications for assessment and treatment outcomes. *Aust Psychol*. 2005;40(2):96-108.
77. Zweben JE, Cohen JB, Christian D, et al. Psychiatric symptoms in methamphetamine users. *Am J Addict*. 2004;13(2):181-190.
78. Semple SJ, Grant I, Patterson TL. Negative self-perceptions and sexual risk behavior among heterosexual methamphetamine users. *Subst Use Misuse*. 2005;40(12):1797-1810.
79. Akiyama K, Saito A, Shimoda K. Chronic methamphetamine psychosis after long-term abstinence in Japanese incarcerated patients. *Am J Addict*. 2011;20(3):240-249.
80. Chen CK, Lin SK, Sham PC, et al. Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychol Med*. 2003;33(8):1407-1414.
81. Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. *Br J Psychiatry*. 2004;185:196-204.
82. Hser YI, Evans E, Huang YC. Treatment outcomes among women and men methamphetamine abusers in California. *J Subst Abuse Treat*. 2005;28(1):77-85.
83. McKetin R, Lubman DI, Najman JM, Dawe S, Butterworth P, Baker AL. Does methamphetamine use increase violent behaviour? Evidence from a prospective longitudinal study. *Addiction*. 2014;109(5):798-806.
84. Cohen JB, Dickow A, Horner K, et al. Abuse and violence history of men and women in treatment for methamphetamine dependence. *Am J Addict*. 2003;12(5):377-385.
85. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

86. Mancino MJ, Gentry BW, Feldman Z, Mendelson J, Oliveto A. Characterizing methamphetamine withdrawal in recently abstinent methamphetamine users: a pilot field study. *Am J Drug Alcohol Abuse*. 2011;37(2):131-136.
87. Newton TF, Kalechstein AD, Duran S, Vansluis N, Ling W. Methamphetamine abstinence syndrome: preliminary findings. *Am J Addict*. 2004;13(3):248-255.
88. National Institute on Drug Abuse. Principles of Drug Addiction Treatment: A Research-Based Guide (3rd Edition). Available at https://archives.nida.nih.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition. Last accessed June 6, 2023.
89. Gould TJ. Addiction and cognition. *Addict Sci Clin Pract*. 2010;5(2):4-14.
90. Shoptaw S, Reback CJ, Peck JA, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*. 2005;78(2):125-134.
91. Smout MF, Longo M, Harrison S, Minniti R, Wickes W, White JM. Psychosocial treatment for methamphetamine use disorders: a preliminary randomized controlled trial of cognitive behavior therapy and acceptance and commitment therapy. *Subst Abuse*. 2010;31(2):98-107.
92. Voccia FJ, Montoya ID. Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. *Curr Opin Psychiatry*. 2009;22(3):263-268.
93. Rawson RA, Gonzales R, Brethen P. Treatment of methamphetamine use disorder: an update. *J Subst Abuse Treat*. 2002;23(2):145-150.
94. Rawson RA, Marinelli-Casey P, Anglin MD, et al. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction*. 2004;99(6):708-717.
95. Feeney GFX, Connor JP, Young R, Tucker J, McPherson A. Improvement in measures of psychological distress amongst amphetamine misusers treated with brief cognitive-behavioral therapy (CBT). *Addict Behav*. 2006;31(10):1833-1843.
96. Yen CF, Wu HY, Yen JY, Ko CH. Effects of brief cognitive-behavioral interventions on confidence to resist the urges to use heroin and methamphetamine in relapse-related situations. *J Nerv Ment Dis*. 2004;192(11):788-791.
97. Alammehrjerdi Z, Briggs NE, Biglarian A, Mokri A, Dolan K. A randomized controlled trial of brief cognitive behavioral therapy for regular methamphetamine use in methadone treatment. *J Psychoactive Drugs*. 2019;51(3):280-289.
98. AshaRani PV, Hombali A, Seow E, et al. Nonpharmacological interventions for methamphetamine use disorder: a systematic review. *Drug Alcohol Depend*. 2020;212:108060.
99. Shoptaw S, Huber A, Peck J, et al. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2006;85(1):12-18.
100. Roll JM, Huber A, Sodano R, Chudzynsky JE, Moynier E, Shoptaw S. A comparison of five reinforcement schedules for use in contingency management-based treatment of methamphetamine abuse. *Psychol Rec*. 2006;56(1):67-81.
101. Petry NM, Peirce JM, Stitzer ML, et al. Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs: a national drug abuse treatment clinical trials network study. *Arch Gen Psychiatry*. 2005;62(10):1148-1156.
102. Corsi KF, Shoptaw S, Alishahi M, Booth RE. Interventions to reduce drug use among methamphetamine users at risk for HIV. *Curr HIV/AIDS Rep*. 2019;16(1):29-36.
103. Brown HD, DeFulio A. Contingency management for the treatment of methamphetamine use disorder: a systematic review. *Drug Alcohol Depend*. 2020;216:108307.
104. Reback CJ, Peck JA, Fletcher JB, Nuno M, Dierst-Davies R. Lifetime substance use and HIV sexual risk behavior predict treatment response to contingency management among homeless, substance-dependent MSM. *J Psychoactive Drugs*. 2012;44(2):166-172.
105. Corsi KF, Shoptaw S, Alishahi M, Booth RE. Interventions to reduce drug use among methamphetamine users at risk for HIV. *Curr HIV/AIDS Rep*. 2019;16(1):29-36.
106. Reback CJ, Peck JA, Dierst-Davies R, Nuno N, Kamien JB, Amass L. Contingency management among homeless, out-of-treatment men who have sex with men. *J Subst Abuse Treat*. 2010;39(3):255-263.
107. Gunter TD, Black DW, Zwick J, Arndt S. Drug and alcohol treatment services effective for methamphetamine abuse. *Ann Clin Psychiatry*. 2004;16(4):195-200.
108. Kamp F, Proebstl L, Hager L, et al. Effectiveness of methamphetamine abuse treatment: predictors of treatment completion and comparison of two residential treatment programs. *Drug Alcohol Depend*. 2019;201:8-15.
109. Brecht ML, Anglin MD, Dylan M. Coerced treatment for methamphetamine abuse: differential patient characteristics and outcomes. *Am J Drug Alcohol Abuse*. 2005;31(2):337-356.
110. U.S. Food and Drug Administration. FDA News Release. FDA Permits Marketing of Mobile Medical Application for Substance Use Disorder. Available at https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-mobile-medical-application-substance-use-disorder. Last accessed June 6, 2023.
111. Su H, Zhong N, Gan H, et al. High frequency repetitive transcranial magnetic stimulation of the left dorso lateral prefrontal cortex for methamphetamine use disorders: a randomised clinical trial. *Drug Alcohol Depend*. 2017;175:84-91.
112. Liang Y, Wang L, Yuan TF. Targeting withdrawal symptoms in men addicted to methamphetamine with transcranial magnetic stimulation: a randomized clinical trial. *JAMA Psychiatry*. 2018;75(11):1199-1201.

113. Liu T, Li Y, Shen Y, Liu X, Yuan TF. Gender does not matter: add-on repetitive transcranial magnetic stimulation treatment for female methamphetamine dependents. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;92:70-75.

114. Yuan J, Liu W, Liang Q, Cao X, Lucas MV, Yuan TF. Effect of low-frequency repetitive transcranial magnetic stimulation on impulse inhibition in abstinent patients with methamphetamine addiction: a randomized clinical trial. *JAMA Netw Open*. 2020;3(3):e200910.

115. Shahbabaie A, Ebrahimpoor M, Hariri A, et al. Transcranial DC stimulation modifies functional connectivity of large-scale brain networks in abstinent methamphetamine users. *Brain Behav*. 2018;8(3):e00922.

116. Alizadehgoradel J, Nejati V, Sadeghi Movahed F, et al. Repeated stimulation of the dorsolateral-prefrontal cortex improves executive dysfunctions and craving in drug addiction: A randomized, double-blind, parallel-group study. *Brain Stimul*. 2020;13(3):582-593.

117. Xu X, Ding X, Chen L, et al. The transcranial direct current stimulation over prefrontal cortex combined with the cognitive training reduced the cue-induced craving in female individuals with methamphetamine use disorder: A randomized controlled trial. *J Psychiatr Res*. 2021;134:102-110.

118. Moszczynska A. Current and emerging treatments for methamphetamine use disorder. *Curr Neuropharmacol*. 2021;19(12):2077-2091.

119. Ciccarone D. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. *Prim Care*. 2011;38(1):41-58, v-vi.

120. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological treatment of methamphetamine/amphetamine dependence: a systematic review. *CNS Drugs*. 2020;34(4):337-365.

121. Rose ME, Grant JE. Pharmacotherapy for methamphetamine dependence: a review of the pathophysiology of methamphetamine addiction and the theoretical basis and efficacy of pharmacotherapeutic interventions. *Ann Clin Psychiatry*. 2008;20(3):145-155.

122. Zorick T, Sugar CA, Hellemann G, Shoptaw S, London ED. Poor response to sertraline in methamphetamine dependence is associated with sustained craving for methamphetamine. *Drug Alcohol Depend*. 2011;118(2-3):500-503.

123. Piasecki MP, Steinagel GM, Thienhaus OJ, Kohlenberg BS. An exploratory study: the use of paroxetine for methamphetamine craving. *J Psychoactive Drugs*. 2002;34(3):301-304.

124. Newton TF, Roache JD, De La Garza R 2nd, et al. Bupropion reduces methamphetamine-induced subjective effects and cue-induced craving. *Neuropsychopharmacology*. 2006;31(7):1537-1544.

125. Pérez-Mañá C, Castells X, Torrens M, Capellà D, Farre M. Efficacy of psychostimulants drugs for amphetamine abuse or dependence. *Cochrane Database Syst Rev*. 2013;9:CD009695.

126. Laqueille X, Dervaux A, El Omari F, Kanit M, Baylé FJ. Methylphenidate effective in treating amphetamine abusers with no other psychiatric disorder. *Eur Psychiatry*. 2005;20(5-6):456-457.

127. Galloway GP, Buscemi R, Coyle JR, et al. A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. *Clin Pharmacol Ther*. 2011;89(2):276-282.

128. Longo M, Wickes W, Smout M, Harrison S, Cahill S, White JM. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. *Addiction*. 2010;105(1):146-154.

129. De La Garza R 2nd, Zorick T, London ED, Newton TF. Evaluation of modafinil effects on cardiovascular, subjective, and reinforcing effects of methamphetamine in methamphetamine-dependent volunteers. *Drug Alcohol Depend*. 2010;106(2-3):173-180.

130. Shearer J, Darke S, Rodgers C, et al. A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. *Addiction*. 2009;104(2):224-233.

131. Heinzerling KG, Swanson AN, Kim S, et al. Randomized, double-blind, placebo-controlled trial of modafinil for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2010;109(1-3):20-29.

132. McGregor C, Srisurapanont M, Mitchell A, Wickes W, White JM. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: a comparison of mirtazapine and modafinil with treatment as usual. *J Subst Abuse Treat*. 2008;35(3):334-342.

133. Coffin PO, Santos GM, Hern J, et al. Effects of mirtazapine for methamphetamine use disorder among cisgender men and transgender women who have sex with men: a placebo-controlled randomized clinical trial. *JAMA Psychiatry*. 2020;77(3):246-255.

134. Heinzerling KG, Shoptaw S, Peck JA, et al. Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2006;85(3):177-184.

135. Urschel HC 3rd, Hanselka LL, Baron M. A controlled trial of flumazenil and gabapentin for initial treatment of methylamphetamine dependence. *J Psychopharmacol*. 2011;25(2):254-262.

136. Brodie JD, Figueroa E, Laska EM, Dewey SL. Safety and efficacy of gamma-vinyl GABA (GVG) for the treatment of methamphetamine and/or cocaine addiction. *Synapse*. 2005;55(5):122-125.

137. Galloway GP, Newmeyer J, Knapp T, Stalcup SA, Smith D. Imipramine for the treatment of cocaine and methamphetamine dependence. *J Addict Dis*. 1994;13(4):201-216.

138. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological treatment of methamphetamine/amphetamine dependence: a systematic review. *CNS Drugs*. 2020;34(4):337-365.

139. Wachtel SR, Ortengren A, de Wit H. The effects of acute haloperidol or risperidone on subjective responses to methamphetamine in healthy volunteers. *Drug Alcohol Depend*. 2002;68(1):23-33.

140. London ED. Impulsivity, stimulant abuse, and dopamine receptor signaling. *Adv Pharmacol*. 2016;76:67-84.

141. Boileau I, Payer D, Houle S, et al. Higher binding of the dopamine D3 receptor-preferring ligand [11C]-(+)-propyl-hexahydro-naphtho-oxazin in methamphetamine polydrug users: A positron emission tomography study. *J Neurosci*. 2012;32(4):1353-1359.

142. Johnson BA, Ait-Daoud N, Elkashef AM, et al.; Methamphetamine Study Group. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. *Int J Neuropsychopharmacol*. 2008;11(1):1-14.

143. Jayaram-Lindström N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2008;165(11):1442-1448.

144. Anggadiredja K, Sakimura K, Hiranita T, Yamamoto T. Naltrexone attenuates cue- but not drug-induced methamphetamine seeking: a possible mechanism for the dissociation of primary and secondary reward. *Brain Res*. 2004;1021(2):272-276.

145. Lam L, Anand S, Li X, Tse ML, Zhao JX, Chan EW. Efficacy and safety of naltrexone for amfetamine and methamphetamine use disorder: a systematic review of randomized controlled trials. *Clin Toxicol (Phila)*. 2019;57(4):25-233.

146. Trivedi MH, Walker R, Ling W, et al. Bupropion and naltrexone in methamphetamine use disorder. *N Engl J Med*. 2021;384(2):140-153.

147. Weber SC, Beck-Schimmer B, Kajdi ME, Muller D, Tobler PN, Quednow BB. Dopamine D2/3- and μ-opioid receptor antagonists reduce cue-induced responding and reward impulsivity in humans. *Transl Psychiatry*. 2016;6(7):e850.

148. Jayaram-Lindstrom N, Guöerstam J, Häggkvist J, et al. Naltrexone modulates dopamine release following chronic, but not acute amhetamine administration: a translational study. *Transl Psychiatry*. 2017;7(4):e1104.

149. U.S. National Library of Medicine. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/. last accessed June 6, 2023.

150. Hossain MK, Hassanzadeganroudsari M, Nurgali K, Apostolopoulos V, Vaccine development against methamphetamine drug addiction. *Expert Rev Vaccines*. 2020;19(12):1105-1114.

151. Stevens MW, Henry RL, Owens SM, Schutz R, Gentry WB. First human study of a chimeric anti-methamphetamine monoclonal antibody in healthy volunteers. *MAbs*. 2014;6(6):1649-1656.

152. Stevens MW, Tawney RL, West CM, et al. Preclinical characterization of an anti-methamphetamine monoclonal antibody for human use. *MAbs*. 2014;6(2):547-555.

153. Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. *Psychiatr Clin North Am*. 2010;33(2):339-355.

154. International AIDS Society USA. Methamphetamine Use in Urban Gay and Bisexual Populations. Available at https://www.iasusa.org/wp-content/uploads/2006/06/14-2-84.pdf. Last accessed June 6, 2023.

155. Shoptaw S. Methamphetamine use in urban gay and bisexual populations. *Top HIV Med*. 2006;14(2):84-87.

156. Mausbach BT, Semple SJ, Strathdee SA, Patterson TL. Predictors of safer sex intentions and protected sex among heterosexual hiv-negative methamphetamine users: an expanded model of the theory of planned behavior. *AIDS Care*. 2009;21(1):17-24.

157. Peck JA, Shoptaw S, Rotheram-Fuller E, Reback CJ, Bierman B. HIV-associated medical, behavioral, and psychiatric characteristics of treatment-seeking, methamphetamine-dependent men who have sex with men. *J Addict Dis*. 2005;24(3):115-132.

158. Shoptaw S, Klausner JD, Reback CJ, et al. A public health response to the methamphetamine epidemic: the implementation of contingency management to treat methamphetamine dependence. *BMC Public Health*. 2006;6:214.

159. Farabee D, Prendergast M, Cartier J. Methamphetamine use and HIV risk among substance-abusing offenders in California. *J Psychoactive Drugs*. 2002;34(3):295-300.

160. Parsons JT, Kowalczyk WJ, Botsko M, Tomassilli J, Golub SA. Aggregate versus day level association between methamphetamine use and HIV medication non-adherence among gay and bisexual men. *AIDS Behav*. 2013;17(4):1478-1487.

161. Moore DJ, Blackstone K, Woods SP, et al. Methamphetamine use and neuropsychiatric factors are associated with antiretroviral non-adherence. *AIDS Care*. 2012;24(12):1504-1513.

162. Ellis RJ, Childers ME, Cherner M, Lazzaretto D, Letendre S, Grant I. Increased human immunodeficiency virus loads in active methamphetamine users are explained by reduced effectiveness of antiretroviral therapy. *J Infect Dis*. 2003;188(12):1820-1826.

163. Cherner M, Letendre S, Heaton RK, et al. Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*. 2005;64(8):1343-1347.

164. Kraman P. *Trends Alert: Drug Abuse in America–Rural Meth*. Lexington, KY: The Council of State Governments; 2004.

165. Clark JJ, Leukefeld C, Godlaski T. Case management and behavioral contracting components of rural substance abuse treatment. *J Subst Abuse Treat*. 1999;17(4):293-304.

166. Zorick T, Nestor L, Miotto K, et al. Withdrawal symptoms in abstinent methamphetamine-dependent subjects. *Addiction*. 2010;105(10):1809-1818.

167. MacDonald K, Wilson MP, Minassian A, et al. A retrospective analysis of intramuscular haloperidol and intramuscular olanzapine in the treatment of agitation in drug- and alcohol-using patients. *Gen Hosp Psychiatry*. 2010;32(4):443-445.

168. Petit JR. Management of the acutely violent patient. *Psychiatr Clin North Am*. 2005;28(3):701-711.

169. Zeller SL, Rhoades RW. Systematic reviews of assessment measures and pharmacologic treatments for agitation. *Clin Ther*. 2010;32(3):403-425.

170. Humphreys K, Wing S, McCarty D, et al. Self-help organizations for alcohol and drug problems: toward evidence-based practice and policy. *J Subst Abuse Treat*. 2004;26(3):151-158.

171. Kadden RM, Litt MD. The role of self-efficacy in the treatment of substance use disorders. *Addict Behav*. 2011;36(12):1120-1126.

172. Kelly JF, Urbanoski KA, Hoeppner BB, Slaymaker V. Facilitating comprehensive assessment of 12-step experiences: a multidimensional measure of mutual-help activity. *Alcohol Treat Q*. 2011;29(3):181-203.

173. Lyons T, Chandra G, Goldstein J. Stimulant use and HIV risk behavior: the influence of peer support group participation. *AIDS Educ Prev*. 2006;18(5):461-473.

174. Paulus MP, Tapert SF, Schuckit MA. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Arch Gen Psychiatry*. 2005;62(7):761-768.

175. Yen CF, Chang YP. Relapse antecedents for methamphetamine use and related factors in Taiwanese adolescents. *Psychiatry Clin Neurosci*. 2005;59(1):77-82.

176. Tuliao AP, Liwag ME. Predictors of relapse in Filipino male methamphetamine users: a mixed methods approach. *J Ethn Subst Abuse*. 2011;10(2):162-179.

177. Maglione M, Chao B, Anglin MD. Correlates of outpatient drug treatment drop-out among methamphetamine users. *J Psychoactive Drugs*. 2000;32(2):221-228.

Evidence-Based Practice Recommendations Citations

Management of Substance Use Disorders Work Group. *VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders*. Washington, DC: Department of Veterans Affairs, Department of Defense; 2021. Available at https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed June 9, 2023.

Marcell AV, Male Training Center for Family Planning and Reproductive Health. *Preventive Male Sexual and Reproductive Health Care: Recommendations for Clinical Practice*. Philadelphia, PA: Male Training Center for Family Planning and Reproductive Health; 2014. Available at https://rhntc.org/sites/default/files/resources/mtc_male_prevrhc_2014.pdf. Last accessed June 9, 2023.