Methamphetamine Abuse and Dependence

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Faculty Disclosure

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

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Division Planner Disclosure

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

Audience

This intermediate course is designed for psychologists 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 psychologists to more effectively identify, treat, or refer methamphetamine-abusing patients.

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 neurobiological function in abstinent users.
6. Describe comorbid conditions associated with methamphetamine abuse and dependence.
7. Identify signs and symptoms of methamphetamine withdrawal syndrome.
8. Outline possible treatment modalities for methamphetamine dependence and comorbid conditions, detailing implications for special populations, the importance of 12-step programs, and interventions for non-English proficient patients.
9. Review the prognosis for those dependent on methamphetamine.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

INTRODUCTION

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

HISTORY AND BACKGROUND OF AMPHETAMINES AND METHAMPHETAMINE

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

Amphetamine and methamphetamine were originally synthesized in Japan in 1893 for use as substitutes for the plant-derived ephedrine, which has been used for centuries in Asia to treat respiratory conditions [1; 4]. Widespread use began in World War II (WWII), when American, German, and Japanese soldiers utilized the drugs to increase endurance and performance and to counter fatigue [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 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. This seems to be improving, however, as data from 2007 to 2011 show that methamphetamine-related crime decreased 6% [6].

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

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

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

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

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

EPIDEMIOLOGY AND DEMOGRAPHICS OF USE

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

While national trends are showing declines, regional use of methamphetamine continues to vary widely, with the strongest effects felt in the West and parts of the Midwest and rural areas being the most severely impacted [10]. During the first half of 2012, treatment admissions for methamphetamine use were highest in Hawaii and San Diego, second highest in San Francisco, and third highest in Denver and Phoenix [11]. The higher use of methamphetamine in Western states is also reflected by the number of persons under its influence who come into contact with law enforcement. According to a 2013 national drug threat assessment compiled by the Drug Enforcement Administration (DEA), a large percentage of male arrestees tested positive for methamphetamine in Western cities (e.g., 42.9% in Sacramento, California; 22.9% in Portland, Oregon). The percentages declined in cities further east (e.g., 5.9% in Denver, Colorado; 0.4% in Washington, DC; 0.1% in New York City) [12].

The number of current users of methamphetamine increased between 1996 and 2006 to a peak of 731,000, but decreased to 353,000 in 2010 [12]. A 2012 survey found that approximately 1.2 million individuals 12 years of age or older had used the drug in the past year and that 440,000 reported using it in the past month [11]. According to data from the 2012 Monitoring the Future (MTF) survey, which examines adolescent drug use and attitudes, approximately 1% of 8th, 10th, and 12th graders had used methamphetamine in the past year. This indicates that 10th and 12th graders are using methamphetamine less than they did 5 years ago, whereas use by 8th graders has not dropped significantly during this period. Overall, use of methamphetamine by adolescents has declined significantly since 1999, when the drug was first added to the MTF survey [11].

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 approximately 103,000 emergency visits in 2011, a decrease from 132,576 visits reported in 2004 [11]. Nationwide, admissions to treatment programs for any methamphetamine abuse decreased from 8.1% in 2005 to 5.6% in 2011 [11].

The economic downturn beginning in late 2007 fostered a new increase in methamphetamine usage and production, as users of more expensive drugs switched to methamphetamine and more individuals began manufacturing and dealing the drug as a source of income [13]. Lower prices, higher purity, increased production, and increased flow of methamphetamine across the southwest border has contributed to rising domestic availability. Nevertheless, methamphetamine demand and use has stabilized and the number of new and current users has remained statistically similar from 2008 to 2011 [12]. Final DEA data from 2013 indicates that methamphetamine lab seizures rose from 1,519 in 2008 to 3,898 in 2012 [12]. Between 2008 and 2012, the seizures of methamphetamine crossing the southwest border of the United States increased nearly five-fold (from 2,282.6 kg to 10,636.5 kg) [12].

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

Although traditionally used by college students and white, working-class males 18 to 34 years of age on the West Coast, the demographics are now much broader. Native American and Hispanic persons constitute a growing population of methamphetamine users; however, relatively few African Americans are regular users of methamphetamine [1]. The declines in admissions to treatment programs among whites between 1997 and 2007 (81% to 65%) were offset by sharply increased numbers of Hispanics being admitted (9% to 21%) [17]. Additionally, the 2013 Youth Risk Behavior Surveillance found that more Hispanic students (4.5%) had ever used methamphetamine one or more times compared to white (3%) or black (1.3%) students [18]. Female students (3%) are slightly less likely to have used methamphetamine than male students (3.4%), 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 2009 (4.1%) to 2013 (3.2%), which corresponds with information showing the latest spike of increased use occurring primarily among individuals older than 25 years of age.

RISK FACTORS FOR METHAMPHETAMINE USE DISORDER

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

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

PHARMACOLOGY

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

Purity of methamphetamine is typically very high, at 60% to 90%. It is predominantly d-methamphetamine, which has greater CNS potency than the l-isomer. Common doses of abuse are 100 to 1000 mg/day, and chronic users on a binge may take up to 5000 mg/day [24].

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

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

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

NEUROBIOLOGY OF STIMULANT ADDICTION

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

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

The different mode of action of these two classes of drugs on monoamine transporters influence dopaminergic signaling and result in important differences in physiological and functional impact [27]. Generally speaking, the uptake blockers bind and inhibit dopamine transport through the dopamine transporter (DAT); inhibited DAT activity results in elevated extracellular dopamine levels, which in turn stimulates dopamine receptors, causing vesicles to move to the cytosol [27]. In contrast, the releasers elevate extracellular dopamine levels through the disruption of vesicular pH gradients, redistributing vesicular dopamine into the cytoplasm and releasing dopamine through reverse transport and/or channel-like DAT activity [28; 29].

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

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

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

USE CHARACTERISTICS OF METHAMPHETAMINE ABUSE

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

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

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

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

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

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

EFFECTS OF METHAMPHETAMINE USE

ACUTE EFFECTS

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

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

CHRONIC EFFECTS

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

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
Physiological signs	Increased heart rate Elevated body temperature Insomnia Increased blood pressure Increased respiration rate Profuse sweating Tremors Neurological symptoms, such as headaches Vision loss
Behavioral signs	Excessive talkativeness Excitation Agitation Aggressive behavior Uncontrollable jaw clenching Restlessness Performance of repetitive, meaningless tasks
Source: [3; 10; 20; 39; 40; 41; 42]	*Table 1*

and explosions during production, and chemical burns from contact with precursors or byproducts of production [40].

Dental Effects

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

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

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

SIGNS AND SYMPTOMS OF CHRONIC METHAMPHETAMINE USE	
Psychological symptoms	Persistent anxiety Paranoia Insomnia Auditory hallucinations Delusions Psychotic or violent behavior Homicidal or suicidal thinking
Physiological 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) Dermatological conditions, such as excorciated skin lesions Constipation from dehydration and lack of dietary fiber Dyspnea and coughing up blood from smoking
Behavioral signs	Unprovoked violent behavior Poor coping abilities Disorganized lifestyle Unemployment Relationship estrangement
Source: [3; 10; 20; 39; 40; 41; 42]	*Table 2*

Cognitive and Neurobiological Effects

Prolonged use of methamphetamine is associated with changes to the brain and CNS through several general mechanisms, including depletion of presynaptic monoamine reserves, down-regulation of neurotransmitter transporters and receptors, and neurotoxicity through reactive metabolic byproducts of dopamine and serotonin. Neurotoxicity can occur from as little as several days of methamphetamine exposure and may persist for months and even years [33]. Even a sub-neurotoxic reduction of dopamine activity can produce the lingering motivational difficulties often encountered by patients in early to intermediate recovery [33]. Another mechanism of methamphetamine-induced neurotoxicity is the substantial and prolonged release of the excitatory neurotransmitter glutamate triggered by acute ingestion [3].

Cognitive and Neurobiological Dysfunction in Abstinent Methamphetamine Users

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

Cognitive performance in methamphetamine-dependent patients may actually worsen during the first 3 months of abstinence. Simon et al. 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 [50].

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

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

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

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

Neonatal Effects

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

COMORBID CONDITIONS ASSOCIATED WITH METHAMPHETAMINE USE

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

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

PSYCHOSES

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

Psychotic symptoms are associated with both methamphetamine use and methamphetamine withdrawal. Most users of methamphetamine develop psychoses, typically auditory hallucinations, persecutory delusions, and delusions of reference, within one week of continuous use [72].

Continued use results in further loss of insight, increased psychoses, and possible violent behavior. Although psychotic symptoms resolve within 96 hours following cessation for many users, a sizeable percentage of patients remain psychotic for months or even years after they stop using the drug [72].

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the National Institute for Health and Clinical Excellence, healthcare professionals in all settings should routinely ask adults and young people with known or suspected psychosis about their use of alcohol and/or prescribed and nonprescribed (including illicit) drugs.

(http://www.guidelines.gov/content.aspx?id=34832. Last accessed June 3, 2014.)

Level of Evidence: Expert Opinion/Consensus Statement

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

AGGRESSIVE AND VIOLENT BEHAVIOR

The acute effects of methamphetamine can include irritability, agitation, hypervigilance, and possibly violent outbursts, and chronic use of methamphetamine has a greater association with violent behavior than any other psychoactive drug [74]. Biological factors play a role in methamphetamine-induced violent behavior, with alteration in serotonin, dopamine, and norepinephrine levels being implicated. A study of more than 1000 methamphetamine outpatients found that 11.7% experienced difficulty in controlling violent behavior in the past month, with no significant gender differences [74]. Violence is also associated with methamphetamine-induced psychoses [22]. A community sample of 205 methamphetamine users in Los Angeles County found that 26.8% (30% male, 23% female) committed acts of violence under the influence of methamphetamine, including acts of domestic, drug-related, or gang-related violence or random acts of violence, such as road rage or stranger assault. Although methamphetamine use creates the clear potential for violent behavior, the authors of the study emphasize that violent behavior is not an inevitable outcome of even heavy, long-term methamphetamine use [75].

Users of methamphetamine are also at high risk for being recipients of violence. A study of 1016 methamphetamine outpatients found that 85.4% of women and 69.6% of men reported physical abuse [76]. Women were significantly more likely to have been physically assaulted by a partner, while men were significantly more likely to have been assaulted by a friend or stranger. Violence associated with methamphetamine is also related to the protection of illegal production sites, distribution and trafficking operations, and territories in the black market drug business [32]. Among paroled inmates, methamphetamine use is associated with violent crime and recidivism, even after controlling for demographic variables, indicating the need for greater treatment engagement and parole supervision among parolees with a history of methamphetamine dependence [32].

WITHDRAWAL FROM METHAMPHETAMINE

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

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

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

TREATMENT OF METHAMPHETAMINE USE DISORDER

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

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

Enhancing motivation for abstinence, improving strategies for avoiding use, and facilitating relapse prevention require the patient's attendance, comprehension, and effective memory recall [81]. However, as discussed, chronic methamphetamine abuse results in cognitive impairment in the form of deficits in attention, impulse control, and task performance. Methamphetamine users who are cognitively impaired will not be able to benefit from such treatment programming [3; 50]. Understanding the effects of methamphetamine use on mood, 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 [15]. This is illustrated by the culturally sensitive approach tailored for gay and bisexual men, termed gay-tailored cognitive-behavioral therapy (GCBT) [82].

PSYCHOSOCIAL THERAPY

The Matrix Model

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

Elements of the Matrix Model include [82]:

- Engagement and retention: Emphasizing the patient-therapist relationship
- Structure: Planning and scheduling to help patients eliminate blocks of free time
- Information: Helping patients connect 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 [80].

A convenience sample of 114 patients out of an original population of 500 patients receiving the Matrix Model was analyzed for follow-up 2 to 5 years after treatment initiation [39]. A combination of self-report and urine screen revealed that in the 30 days preceding the follow-up interview, 82.5% reported no methamphetamine use, 11.4% reported some use, and 6.1% reported daily use. This is compared with 13.2% no use, 38.6% some use, and 47.4% daily use in the 30 days prior to treatment intake. Other drug use also decreased from intake to follow-up, and full-time employment increased from 26% at baseline to 62% at follow-up. Interestingly, the frequency of depression, headache, and hallucinations were statistically unchanged from baseline to follow-up. Although these results indicate decreased methamphetamine and other substance use and increased psychosocial function associated with Matrix Model-based treatment, 77% of the sample was lost to follow-up, and there was evidence that the subjects in the sample utilized treatment services significantly more than the pooled population of patients, hampering the generalizability of this data.

In a multisite study across 8 different communities, 978 methamphetamine-dependent outpatients were randomized to either the Matrix Model or conventional outpatient treatment [86]. Conventional treatment was considered the best available option in the eight communities in which the study took place. Significant variation existed in the conventional outpatient conditions. Although subjects receiving the Matrix Model exhibited significantly better treatment retention, program completion, treatment engagement, more methamphetamine-free urine samples, and longer periods of abstinence during treatment than conventional treatment recipients, these differences did not persist into the post-treatment follow-up period. No differences were noted in methamphetamine-free urine at 6-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 8 different types of comparison treatment conditions increased within-group variance and obscured differences among the groups.

Cognitive-Behavioral Therapy (CBT)

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

A 2005 study suggests that CBT can improve the psychological well-being of outpatient methamphetamine users [87]. Specifically, a 4-week, one hour per week CBT intervention was delivered to 507 outpatients (87.2% amphetamine-dependent), consisting of well-defined cognitive, behavioral, and motivational interviewing methods focused on five core areas [87]:

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

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

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

Gay-Tailored Cognitive-Behavioral Therapy (GCBT)

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

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

Contingency Management (CM)

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

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

Conventional Treatment

The efficacy of conventional residential treatment with methamphetamine-dependent patients was studied by Gunter, Black, Zwick, and Arndt [92]. A sample of 199 methamphetamine abusers was admitted to an inpatient residential treatment setting for a mean stay of 86 days. Treatment consisted of group therapy, individual case management, and psychiatric assessment and referral in a semi-structured environment. The therapy was performed by trained chemical dependency counselors with knowledge of methamphetamine addiction. At 60 days following admission, significant reductions were observed on measures of anxiety (e.g., compulsions, obsessions, social phobia, generalized anxiety) and major depression. Approximately 25% of the sample was available for 6-month follow-up, with significant reductions in methamphetamine use noted through self-report. Conclusions of efficacy are severely limited by subject attrition and subjective, nonverifiable outcome measures [92].

Coercive Interventions

Although many patients with methamphetamine addiction are coerced into treatment through criminal justice or child protection services pressure, little research has been completed about the outcome of such patients. Brecht, Anglin, and Dylan evaluated the treatment outcomes of 350 outpatient methamphetamine abusers randomly selected from a large database of outpatient and residential treatment patients in Los Angeles County [93]. Approximately 50% of the sample reported legal coercion as the motivation to enter treatment. Coerced clients remained in treatment longer but did not significantly differ from noncoerced clients in abstinence rates at 6-month follow-up (59% coerced versus 49% noncoerced). Although there were no significant differences between the groups in percentage of days of methamphetamine use or percentage of patients reporting complete abstinence at 24-month follow-up, the number of months in treatment was associated with a more positive outcome, suggesting a benefit of longer treatment programs for methamphetamine-dependent patients.

PHARMACOTHERAPY AND BIOLOGICAL THERAPY

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

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

Serotonergic Agents

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

Another trial using the SSRI paroxetine to treat methamphetamine dependence was reported by researchers who randomized 20 methamphetamine-dependent patients to either paroxetine 20 mg/day or placebo for 8 weeks [97]. The substantial attrition rate (85%) prohibited any conclusions regarding efficacy to be drawn. However, the authors stated that the weight gain, sexual side effects, and sedation often induced by paroxetine and other SSRIs are opposite of the desired effects of methamphetamine, possibly heightening problems with patient acceptance and compliance with this class of medications.

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

Norepinephrine and Dopamine Reuptake Blockers

As noted, chronic methamphetamine use can result in neuroadaptation in presynaptic dopamine neurons, manifesting as dysphoria, drug craving, and cognitive impairment in early abstinence. This indicates the possible utility of the dopamine and norepinephrine reuptake blocker bupropion. In a randomized, single-blind, placebo-controlled trial, 26 non-treatment-seeking subjects meeting the criteria for methamphetamine abuse or dependence received either a placebo two times per day or 150 mg extended-release bupropion two times per day for 6 days in addition to IV methamphetamine or placebo [98]. Subjects were housed in a clinical research unit during the study. Compared with placebo, bupropion treatment was associated with reduced ratings of "drug effect," "high," and "desire to use," as well as reduced cue-elicited cravings. The sample was small, however, and the results require replication. A Cochrane Review that included 11 studies (791 participants) evaluated the safety and efficacy of psychostimulants (including bupropion) for amphetamine abuse or dependence. Results of the review found no significant differences between the drugs and placebo in their ability to reduce amphetamine use or craving or to increase sustained abstinence [99].

Agonist Replacement Therapy

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

Preliminary data from an investigation utilizing methylphenidate to treat withdrawal symptoms in non-ADHD, long-term prescription amphetamine abusers appears promising [100]. Specifically, severe and protracted depression following amphetamine cessation was resolved with ongoing methylphenidate treatment at long-term (2- to 4-year) follow-up assessment.

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

Modafinil

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

GABA Receptor Agonists

Gamma-aminobutyric acid (GABA) neurons decrease dopamine transmission in the nucleus accumbens and ventral tegmental mesolimbic regions, possibly decreasing the reinforcing effects of methamphetamine and providing the basis for trials of GABA agonists with methamphetamine-abusing patients. Heinzerling et al. reported the results of two GABA agonists, baclofen (20 mg three times per day) and gabapentin (800 mg three times per day), in a double-blind, randomized, placebo-controlled trial of 16 weeks duration [107]. A total of 88 methamphetamine-dependent outpatients were randomized to either baclofen, gabapentin, or placebo, and all subjects attended clinic three times a week for assessment, counseling, and urine drug testing. There were no statistically significant differences in completion of the 16-week trial, reduction in depressive symptoms, craving of methamphetamine, or reduction in methamphetamine-positive urine samples between the groups. However, when patients with high protocol adherence were compared, baclofen recipients exhibited greater numbers of methamphetamine-negative urine samples relative to gabapentin and placebo subjects, suggesting a small but positive effect of baclofen in reducing methamphetamine use. Greater attendance of psychosocial therapy groups was also associated with decreased methamphetamine use across all three groups, underscoring the importance of psychosocial therapy augmentation of pharmacotherapy for methamphetamine addiction.

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

The safety and efficacy of another GABA agonist, gamma vinyl-GABA (GVG), was evaluated in a 9-week, open-label, pilot study involving 10 methamphetamine-dependent, 17 methamphetamine- and cocaine-dependent, and 3 cocaine-dependent subjects [109]. Because GVG has not received FDA clearance in the United States due to concerns over concentric visual field defects associated with its use, the study was carried out in Mexico. A total of 18 subjects completed the trial. Of those 18, 16 subjects tested negative for methamphetamine and cocaine during the last 6 weeks, with a median of 42 days drug free for this group during the 63-day study period. Visual field defects were not observed during the study period. Although unblended and lacking a control group, these results are promising, especially in light of the absence of effective pharmacotherapy for methamphetamine addiction. However, more rigorous testing must be completed before any conclusions regarding efficacy and safety can be drawn.

Tricyclic Antidepressants

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

Dopamine Antagonists

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

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

Opioid Antagonists

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

The opiate receptor antagonist naltrexone, commonly used to treat alcohol and opiate dependence, has been demonstrated to reduce cravings and relapse in methamphetamine addicts in a small scale Swedish study [113]. The participants in the treatment group reported significantly reduced craving levels and amphetamine use and had a greater number of amphetamine-negative urine samples (65.2%) compared to the placebo group (47.7%). The length of time until a relapse was longer in the treatment group (6 weeks) compared to the control (3 weeks). An earlier animal study found that naltrexone reduced drug-seeking behavior following administration of conditioned environmental cues in rats that had exhibited extinction behavior in response to a sudden switch from an amphetamine solution to saline solution; however, when primed with methamphetamine, naltrexone had no effect on cue induced drug-seeking [114]. These researchers also concluded that naltrexone may be helpful in preventing relapse.

TREATMENT OF METHAMPHETAMINE USE IN SPECIAL POPULATIONS

Women

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Society of Obstetricians and Gynaecologists of Canada, healthcare providers should employ a flexible approach to the care of women who have substance use problems and they should encourage the use of all available community resources.

(http://www.guideline.gov/content.aspx?id=33136. Last accessed June 3, 2014.)

Level of Evidence: II-2B (There is fair evidence from well-designed cohort or case-control studies to recommend the clinical preventive action.)

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

Gay, Bisexual, and HIV-Positive Patients

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

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Centers for Disease Control and Prevention recommends more frequent sexually transmitted infection screening (at 3- to 6-month intervals) for men who have sex with men who have sex in conjunction with methamphetamine use.

(http://www.guidelines.gov/content.aspx?id=22578. Last accessed June 3, 2014.)

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 [126]. Methamphetamine users in rural areas, especially areas designated as frontier regions (defined as 6 persons or less per square mile) are likely to experience great difficulty in accessing medical, psychiatric, or substance abuse services. Even self-help groups are likely to be nonexistent in these areas, and when they are available, the degree of anonymity in a 12-step group in a small town may be compromised. The nearest available small city often serves as the population center for the region. Social services in these cities may be overwhelmed by numbers of transient persons from the surrounding rural areas needing services in addition to the inhabitants of the city [15].

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

TREATMENT OF AGITATION ASSOCIATED WITH METHAMPHETAMINE ABUSE

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

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

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

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

ALTERNATIVE/COMPLEMENTARY TREATMENT OF METHAMPHETAMINE DEPENDENCE

Self-Help and 12-Step Therapy

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

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

Crystal Meth Anonymous (CMA)

Although a fairly new organization, CMA meetings can be found in over 114 metropolitan areas throughout the United States, Canada, New Zealand, and Australia. Only a few studies involving members of CMA have been published; not surprising considering it is a relatively new organization. Lyons et al. primarily focused on the role of CMA on sexual behavior in a subpopulation of methamphetamine- and cocaine-abusing gay and bisexual men attempting to abstain from sex through 12-step program involvement [135]. The qualitative study noted that many methamphetamine users have difficulty with sex in recovery because sex is so intimately associated with methamphetamine use. Although the reductions in stimulant use were not explicitly measured, data gathered from this study indicate that CMA involvement led to dramatic reductions in the number of sexual partners (reduced from 7 per month to 1 per month) and the frequency of unprotected anal intercourse (declined from 70% to 24%). The authors concluded that although the reductions in HIV risk behavior may not be entirely due to the teachings of CMA, the program appears to be a valuable forum to help methamphetamine- and cocaine-addicted persons work through issues, such as sex, that are intimately associated with their stimulant abuse [135]. For additional information, please visit the CMA website at http://www.crystalmeth.org.

INTERVENTIONS FOR NON-ENGLISH PROFICIENT PATIENTS

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

PROGNOSIS

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

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

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

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

CONCLUSION

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

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