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Neurologic Manifestations of Chronic Methamphetamine Abuse

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COMMENTARY ON METHAMPHETAMINE ABUSE FOR PSYCHIATRIC PRACTICE

Every decade seems to have its own unique drug problem. The 1970s had hallucinogens, the 1980s had crack cocaine, the 1990s had designer drugs, the 2000s had methamphetamine (Meth), and in the 2010s we are dealing with the scourge of prescription drug abuse. While each of these drug epidemics has distinctive problems and history, the one with perhaps the greatest impact on the practice of Psychiatry is Meth. By increasing the extracellular concentrations of dopamine while slowly damaging the dopaminergic neurotransmission, Meth is a powerfully addictive drug whose chronic use preferentially causes psychiatric complications. Chronic Meth users have deficits in memory and executive functioning as well as higher rates of anxiety, depression, and most notably psychosis. It is because of addiction and chronic psychosis from Meth abuse that the Meth user is most likely to come to the attention of the practicing Psychiatrist/Psychologist.

Understanding the chronic neurologic manifestations of Meth abuse will better arm practitioners with the diagnostic and therapeutic tools needed to make the Meth epidemic one of historical interest only.

Keywords

Methamphetamine abuse; Psychosis; Parkinson's; Chorea; Punding; Formication

The current epidemic of methamphetamine abuse in the United States is not surprising. Methamphetamine can be produced from a wide variety of starting materials and methods. This fact is in contrast to cocaine, which is only commercially grown in South America, must be extracted from the plant, converted to its free-base form, shipped overseas (escaping detection by the Drug Enforcement Administration [DEA]), and then distributed, typically through gangs, to clients on the street.¹ Based on the attractiveness of methamphetamine to both users and its manufacturers, it is only surprising that the current outbreak of methamphetamine abuse in the United States took so long to reach epidemic proportions.

In 1893, methamphetamine was synthesized from ephedrine (derived from the plant *Ephedra sinica*) by Nagai Nagayoshi.^{2,3} Eventually, a synthetic version would find its way to the consumer market as an over-the-counter (OTC) nasal decongestant and a bronchodilator.^{4–6} Far from an OTC drug today, the Food and Drug Administration (FDA) has characterized methamphetamine as a schedule II drug, which can only be prescribed for attention-deficit/hyperactivity disorder, extreme obesity, or to treat narcolepsy.

With the world on the brink of war, and its toxic effects not yet well described, the clinical effects of methamphetamine were thought to be ideal for the soldier in combat: increased alertness and aggression, plus decreased hunger and need to sleep. In World War II, the United States, Germany, and Japan all readily employed it with their troops^{5,7}; it has been estimated that the United States alone distributed 200 million tablets to troops.⁴ After the war, Japan experienced widespread abuse as army surpluses flooded the market. Although methamphetamine usage in Japan declined in the 1960s, it resurged in the 1970s and continues to be a problem today.^{7,8} In 1954, at the height of its first epidemic, there were an estimated 2 million methamphetamine users in Japan. Although still highest in Asia, methamphetamine abuse has become a worldwide epidemic. A 2008 United Nations Office on Drugs and Crime Reports estimated 25 million abusers of amphetamines worldwide, exceeding the number of users for both cocaine (14 million) and heroin (11 million).⁹

After World War II, many US soldiers and civilians continued to use methamphetamine, which at that time was available by prescription in an injectable form. When Abbott and Burroughs-Wellcome withdrew their injectable formulations in the early 1960s, an opportunity arose for the illegal manufacturing and distribution of methamphetamine.⁴ West Coast motorcycle gangs, such as the infamous Hells Angels, quickly seized on this opportunity, and by the 1970s gangs were largely responsible for the manufacturing, distribution, and use of methamphetamine in the United States. It was from the transportation of methamphetamine in the crankshafts of motorcycles that it got its street name of crank.¹⁰ At that time, methamphetamine was produced primarily from the precursors phenyl-2-propanone and methylamine (the P-2-P method).^{5,8} The combination of a crack down by the Department of Justice on West Coast gangs and the Controlled Substances Act of 1970, which made the ingredients of the P-2-P method controlled substances, resulted in a shift in the manufacturing and distribution of methamphetamine to small makeshift laboratories.

In the 1980s, a crystalline form of methamphetamine that could be smoked, called ice, began to be imported from Asia to Hawaii.¹⁰ This highly addictive form of methamphetamine quickly found its way to the US West Coast and slowly began working its way east¹¹; by 1990, methamphetamine had replaced cocaine as the stimulant of choice among drug users in many areas of California.¹² What would ultimately propel methamphetamine abuse to the forefront of the DEA war on drugs, and to the front pages of mainstream magazines and newspapers, was the rural meth lab. Unlike the cultivation of the coca leaf or opium poppy, the manufacture of methamphetamine is not limited by geographic location. By using OTC ephedrine and pseudoephedrine as the main precursors, making methamphetamine became simpler and more efficient. Methamphetamine laboratories manufacturing relatively pure crystal methamphetamine began to pop up across the Midwest; with the small investment of approximately \$200, a methamphetamine cook could easily earn between \$2000 and \$5000.¹³ Despite the relative simplicity of its synthesis (by traditional chemistry standards), cooking methamphetamine requires heating volatile hydrocarbons. When done by those without chemistry backgrounds and, as it often is, in poorly ventilated areas, fires and explosions can ensue. In fact, many methamphetamine laboratories have been discovered only after they have caught fire or exploded.^{14,15} In an attempt to decrease the growing methamphetamine crisis, Congress passed the 2005 Combat Methamphetamine Epidemic Act, which limited access to pseudoephedrine. This limitation shut down vast numbers of small and medium-sized laboratories, resulting in a decline in the number of admissions for methamphetamine abuse in 2006—the first time in 10 years.¹⁰

With increasing numbers of large-scale manufacturers in Mexico, and other parts of the world, methamphetamine continues to be a significant problem in the United States. Because it has its most devastating effects on the central nervous system (CNS), it is

important for neurologists to recognize signs of abuse and the many neuro-logic problems caused by methamphetamine. This article should help the practicing neurologist recognize and treat these patients, improving their chance to function drug free in society.

PHARMACOLOGY AND TOXICOLOGY

Both the acute and chronic neurologic effects of methamphetamine are the result of its pharmacology and toxicology. The acute effects of methamphetamine are those of the flight-or-fight response: increased heart rate and blood pressure, vasoconstriction, bronchodilation, and hyperglycemia.¹⁶ In addition, methamphetamine causes CNS stimulation, which may result in euphoria, increased energy and alertness, intense curiosity and emotions, decreased anxiety, and enhanced self-esteem.¹⁶

Whether snorted, smoked, or injected, methamphetamine rapidly crosses the blood brain barrier where it can exert powerful effects on several neurochemical systems. Because of its lipophilic nature, methamphetamine has increased CNS penetration and is more potent than its parent compound, amphetamine.¹⁷ Once in the CNS, it binds to dopamine, norepinephrine, and, to a lesser extent, serotonin transporters located on neuronal cell membranes; at higher concentrations, methamphetamine may also cross the cell membranes independent of transporter binding. Once bound, transporters pump methamphetamine into the neuron where it is taken up by vesicular monoamine transporters. The high pKa (pKa =10.1) of methamphetamine¹⁸ disrupts the proton gradient, which normally keeps monoamines within the vesicle. This causes monoamines to leave the vesicle and accumulate in the cytoplasm where they are reverse transported out of the cell through the same transporters that pumped methamphetamine into the cell.^{19,20}

In addition to increasing their release, methamphetamine also decreases mono-amine reuptake and enzyme degradation.²¹ The net result is that methamphetamine causes a rapid and sustained increase in the extracellular concentrations of mono-amines. One of the reasons methamphetamine has exceeded cocaine in worldwide usage is that it has a longer half-life (12 hours compared with 90 minutes) and, therefore, a much longer duration of action,²² allowing the drug addict to have a longer and more sustained high. Although many receptors have been implicated in mediating the complex physiologic responses to amphetamines, the underlying clinical effects associated with methamphetamine use involve excessive stimulation of the sympathetic nervous system. It is the rapid and sustained activation of this system that is responsible for methamphetamine's recognizable adrenergic toxidrome: tachycardia, hypertension, mydriasis, diaphoresis, and psychomotor agitation. In addition, it is the prolonged release of central monoamines and activation of the sympathetic nervous system that is responsible for most of the acute neurologic complications associated with methamphetamine use (eg, strokes, seizures, agitation, and hyperthermia).^{20,23,24} The sustained and repeated release of central monoamines is also largely to blame for the chronic neurologic effects of methamphetamine abuse.²⁰

With repeated use in both humans and experimental animal models, methamphetamine depletes the brain's stores of dopamine and damages dopamine and serotonin nerve terminals. This may be a contributing factor to methamphetamine's high abuse potential; without the drug, users may have an impaired ability to experience pleasure (anhedonia), slipping into a deep depression. Based on current evidence, the complex mechanisms by which methamphetamine damages neurons involves increases in intracellular and extracellular concentrations of dopamine, which sets off a cascade of events, including oxidative stress, neuroinflammation, and excitatory neurotoxicity.²⁵

It has also been shown that hyperthermia, a known complication of methamphetamine use, exacerbates this neurotoxicity.²⁵ Although this article focuses predominantly on

methamphetamine, the similarities in the pharmacology, toxicology, and clinical effects between methamphetamine, amphetamine, and other stimulants (eg, cocaine and 3,4-methylenedioxymethamphetamine [ecstasy]) makes the following discussions on neurologic complications largely translatable to other CNS stimulants.

NEUROPSYCHIATRIC COMPLICATIONS

Dopamine and serotonin neurons project widely throughout the CNS and are known to influence a variety of behaviors and functions. It should not be surprising that chronic methamphetamine abuse, which can damage dopamine and serotonin nerve terminals, is associated with deficits in neuropsychological testing. It has been estimated that 40% of methamphetamine users have abnormalities on neuropsychiatric tests.²⁶ In a well-done meta-analysis of studies examining the effects of chronic methamphetamine abuse on neuropsychiatric function, the most frequently reported deficits involve episodic memory, executive function, and motor function.²⁷ Of these, the greatest impairments are in episodic memory; this form of memory is thought to be the most susceptible to neuronal dysfunction.²⁸ As episodic memory allows one to consciously re-experience past events,²⁸ methamphetamine users who, by virtue of damaged episodic memory, forget past mistakes associated with their drug usage may be doomed to repeat them.

Another effect of chronic methamphetamine abuse is damage to executive function. With impaired executive function, methamphetamine abusers are likely to be distractible, impulsive, act inappropriately despite social cues to the contrary, and lack goals. In studies, patients addicted to methamphetamine prefer smaller, immediate rewards over larger, delayed rewards.²⁹ To overcome that wish for immediate rewards, addicts must activate the higher cognitive control systems, which, by virtue of their damaged executive system, is not an easy task for methamphetamine-dependent individuals.²⁹ Another consequence of impaired executive function, demonstrated in patients with damaged frontal lobes, is perseveration: the inability to change behavior even when the current behavior becomes destructive.³⁰ It is easy to imagine how damage to episodic memory and executive function might result in continued methamphetamine abuse despite the physical and emotional toil it reaps on users and their families. By chemically converting users into a modern Phineas Gage, methamphetamine exerts a powerful influence on behavior and decision making. Although not specifically tested, it is also possible that persons with damaged episodic memory and executive function, before using drugs, may be more susceptible to drug abuse and addiction and may have a greater risk for relapse.

Although studies show motor deficits in chronic methamphetamine abusers, these deficits do not typically involve gross movements, as with Parkinson's disease, but rather affect fine-motor dexterity (eg, placing pegs in a pegboard). These deficits would seem to be in line with studies showing that damage to dopamine terminals is more prevalent in the caudate (more involved in cognitive motor activities) than the putamen (more involved in pure motor activities) regions of the basal ganglia.^{31,32}

Along with neuropsychiatric deficits, methamphetamine abusers suffer from mental illnesses, with anxiety,^{33–35} depression,^{27,35–37} and psychosis^{22,27,37,38} being the most commonly reported. Of these, the neurologist is perhaps most likely to be confronted with patients suffering from psychosis.

After World War II, Japan suffered not only from a methamphetamine epidemic but also from an epidemic of drug-induced psychosis.^{39–42} It has been estimated that at its height (between 1945–1955), there were as many as 200,000 persons in Japan with drug-induced psychosis.⁴² Although much of the research on methamphetamine-induced psychosis has

been conducted in Japan, similar reports have been reported in the United States and other countries.^{43,44}

The symptoms of methamphetamine-induced psychosis are similar to those seen with schizophrenia; the most frequently reported symptoms are delusions of persecution and auditory hallucinations.^{39-42,44-46} Although not as commonly reported, negative symptoms (eg, poverty of speech and psychomotor retardation) have also been seen with methamphetamine-induced psychosis.⁴⁴ In addition to a similar symptomatology, both schizophrenia and amphetamine-evoked psychosis can be effectively treated with dopamine antagonists.⁴⁷ The similarities between these disorders have led many researchers to use amphetamines to model schizophrenia in laboratory animals.^{42,48}

The development of psychosis is more readily seen in people using higher methamphetamine concentrations for prolonged periods of time.^{39,45,46,49,50} The reported doses required, duration of abuse, and onset of symptoms are highly variable, as is the duration of psychotic symptoms (from 1 week to an indefinite duration).^{16,51} Even if symptoms abate with abstinence, they can reemerge with repeat usage or under stressful situations.⁴⁰ One of the debates associated with psychosis and methamphetamine is whether it is the result of methamphetamine-induced neurotoxicity (ie, altered dopaminergic neurotransmission) or whether the 2 disorders coexist so that persons with mental illness are more likely to abuse methamphetamine (so-called dual diagnosis). The latter seems to be supported by data showing that persons with predispositions to mental illness, such as strong family histories, are significantly more likely to develop methamphetamine-associated psychosis.^{49,50} Furthermore, schizophrenics given low doses of methamphetamine will have exacerbations of their symptoms.⁵² Therefore, it has been suggested that in susceptible individuals methamphetamine abuse may be a trigger that unmasks schizophrenia/psychosis.⁵³ Others have suggested that persons with schizophrenia/psychosis seek out illicit drugs as a form of self-treatment,⁵⁴ or, as recent data suggests, that neuronal deficits underlying the development of schizophrenia make individuals more prone to develop drug addiction.⁵⁵ Either way, it is clear that methamphetamine abuse can result in the development of acute and, in some cases, chronic psychosis and that practicing neurologists should be aware of this association. With the significant increase in the number of persons abusing methamphetamine, it remains to be seen if there will be a concomitant rise in patients requiring treatment for psychosis.

FORMICATION

One interesting aspect of chronic methamphetamine psychosis is the delusion of parasitosis or formication (the thought that one is infested with and being bitten by bugs).^{43,46,56-59} Commonly known as *meth mites*, this is a frequent complaint in heavy daily users of methamphetamine. In studies of patients admitted to drug treatment facilities for methamphetamine abuse, approximately 40% of the patients report having had formication^{43,46}; if the patients had ever suffered from psychosis, then the percentage of persons experiencing formication rose to 70%.⁴⁶ It is interesting that similar symptoms have been reported in animals chronically administered d-amphetamine.^{57,58,60} These delusions may cause patients to repetitively pick at their skin resulting in scarring of their face and extremities.^{59,61} Constant picking combined with neglect of hygiene also increase the risk for developing skin infections, including abscesses and cellulitis from methicillin-resistant *Staphylococcus aureus*.⁶² Along with abstinence from drug usage, dopamine antagonists have been shown to help patients with drug-induced formication.⁵⁷ Although formication is not unique to methamphetamine (it has also been reported with cocaine⁶³ and schizophrenia⁵⁷), the finding of multiple pockmarks on a patient's face and extremities, or

recurrent skin abscesses in these areas, should increase a clinician's suspicion of chronic methamphetamine abuse.

STEREOTYPY OR PUNDING

One of the unique manifestations of methamphetamine abuse is the development of punding. The word *punding* is Swedish for "blockhead."^{64,65} It was first coined by Rylander, who learned of the slang term from chronic amphetamine and phenmetra-zine (another stimulant abused in Sweden in the 1960s) users as they described the abnormal persistent behaviors displayed by themselves and other addicts.⁶⁴ Punding has since become a term for non-goal-directed repetitive activity. Patient-reported examples include assembling and disassembling clocks and watches or incessantly sorting through purses. What makes these behaviors troublesome is the duration of time users would dedicate to such tasks without any apparent gain. There seems to be a predilection for punding to entail activities that users had previously been involved with. For example, a carpenter abusing amphetamines may repetitively build wooden objects; artists may doodle, paint, or draw excessively; a businessman may make and add to spreadsheets for hours.⁶⁶ There is also a gender-related component: men typically tinkering with electronics and women more commonly involved in grooming behaviors, such as hair brushing and nail polishing.^{64,65,67-69} It is interesting that stereotyped repetitive movements, such as head bobbing, licking, gnawing, and sniffing, are also seen in a variety of animals given amphetamines.⁷⁰

Although first reported in amphetamine abusers, punding has also been reported in cocaine users⁷¹ and, more recently, in patients with Parkinson's disease receiving dopamine replacement therapy.^{66,67} Similar to chronic stimulant abusers, patients with Parkinson's disease have dysfunctional dopaminergic neurotransmission and can develop psychosis.⁶⁷ This finding suggests a similar pathophysiologic mechanism. Although few controlled studies have been done on punding with substance abuse, there is some data available on its incidence. In a study of 50 patients addicted to cocaine, Fasano reported that 38% had some form of punding.⁶⁶ These patients spent, on average, 3 hours a day engaged in their repetitive activities.⁶⁶ One patient reported spending up to 14 hours a day playing computer games and collecting things.⁶⁷ It is interesting that the majority of interviewed patients in this study reported that their behavior began shortly after their first drug usage. In addition, the duration and amount of drug use did not seem to predict which users would develop punding and which would not.⁶⁷ This finding suggests that, like the development of stimulant-induced psychosis, there may be a predisposition for the development of punding that is merely brought out by the drug. As previously discussed, the same abnormal brain circuitry that increases one's risk for becoming addicted may also be involved in the development of such stereotyped behaviors. In his first report on the topic, Rylander described punding in 26% (40 of 150) of the amphetamine addicts he interviewed.⁶⁴ These patients shared identical symptomatology as the cocaine addicts and patients with Parkinson's disease who engaged in punding. The majority of the drug addicts did not describe associated anxiety or distress over their activities, but thought of them with amusement. Some even found them pleasurable. When abstaining from drug usage, punding typically abates. Although the neurologic mechanisms behind punding are not yet well delineated, it appears to involve dopamine. Repeated dosing of amphetamines in animals results in behavioral sensitization. This sensitization is manifested as increased locomotion and stereotypic behavior with each subsequent dose of amphetamine. This sensitization appears to involve both glutamate and dopamine, and, more recently, dopamine-mediated decreases in acetylcholine have been implicated.^{67,72,73} As concentrations of extracellular dopamine increase with each subsequent dose of amphetamine, one could envision over time this excess dopamine causing neurotoxicity or change the normal balance between dopamine 1 (D1) and dopamine 2 (D2) receptor activity⁵²; In a review on the topic, Fasano makes a strong

argument for the involvement of both D1 and D2 receptors in the development of punning, and suggests that, if needed, treatments might include atypical antipsychotics.⁶⁶

CHRONIC METHAMPHETAMINE ABUSE AND THE DEVELOPMENT OF PARKINSON'S DISEASE

People with Parkinson's disease^{66,67} also exhibit unusual impulse-control disorders and punning. Similar to methamphetamine abusers, patients with Parkinson's disease, whether they are newly diagnosed⁷⁴ or have had dopamine-replacement therapies,⁷⁵ have gender-specific compulsivity problems. Men more frequently suffer from pathologic gambling and compulsive sexual behavior, whereas women tend toward compulsive buying and binge eating. The collective animal and human data clearly show that high-dose methamphetamine abuse causes alterations in striatal dopaminergic neurotransmission. Numerous pathology and imaging studies have shown reductions in striatal dopamine, tyrosine hydroxylase, and dopamine transporters.^{6,32,76–80} Because these findings are also found in persons with Parkinson's disease, it is logical to expect that chronic methamphetamine addicts would develop signs of Parkinson's disease.

The current and prevailing theory is that abusing methamphetamine does not increase one's risk of developing Parkinson's disease or Parkinsonism.^{31,32,76} Several hypotheses have been put forth to explain the discrepancy between the research and clinical data.^{31,32,76} The simplest hypothesis is that they are different disorders. Parkinson's disease involves loss of dopaminergic neurons in the substantia nigra, whereas methamphetamine abuse causes alterations in dopaminergic nerve terminals, but not in the cell bodies themselves.³² In studies of methamphetamine abusers, the reductions in dopamine have a different distribution than in patients with Parkinson's disease. Methamphetamine users have greater dopamine reductions in the caudate compared with the putamen, with patients with Parkinson's disease showing the opposite.³² Another hypothesis is that once users become drug abstinent, the damaged dopaminergic nerve terminals begin to recover; decreases in dopamine transporters of methamphetamine abusers were found to significantly recover with prolonged (>12 months) abstinence.⁷⁹

Another hypothesis is that methamphetamine abusers do not actually damage their dopaminergic nerve terminals, and that the findings of reduce dopamine levels represent a compensatory response to repeated elevations in monoamines. The strongest argument for this has been that the vesicular transporter-2 (VMAT2), which is known to be reduced in Parkinson's disease and to be resistant to drug-compensatory regulation, is not significantly reduced in abstinent methamphetamine abusers.^{6,81} In fact, a more recent positron emission tomography (PET) study of nonabstinent methamphetamine abusers found increases in VMAT2.⁸² This finding was thought to be caused by reductions in vesicular dopamine, depleted from recent release, resulting in less dopamine being available to compete for binding to VMAT2.⁸²

Another intriguing hypothesis involves nicotine and nicotine receptors. Acetylcholine nicotinic mechanisms can influence the behavioral and neurochemical effects of psychomotor stimulant drugs and vice versa.⁸³ An overwhelming number of methamphetamine users smoke cigarettes compared with the general population (87%–92% vs 22%).⁸⁴ Because cigarette smoking negatively correlates with development of Parkinson's disease,⁸⁵ methamphetamine abusers may be protected or self-treated.³¹

Some researchers think that methamphetamine abuse does increase the risk for developing Parkinson's disease.^{76,86,87} One retrospective study, looking at hospital admissions over a 10-year period, found an increased incidence of Parkinson's disease among patients who had

a prior history of being admitted with a methamphetamine-related problem.⁸⁷ Because it may take many years before reductions in dopamine reach the levels mediating clinical symptoms, it is possible that the patients enrolled in many of the prospective clinical studies are not old enough to show symptoms; the majority of studies involve young adults. What instead may occur is that as methamphetamine use increases in young adults, we may see a shift in the age of onset of Parkinson's disease. There have been 2 studies involving the same group of patients that support this idea. In a phone survey of patients with Parkinson's disease receiving care at 1 of 3 clinics, patients with Parkinson's disease were significantly more likely (odds ratio = 8, confidence interval 1.6–41.4) to have used amphetamines than their unaffected spouses,⁸⁸ and in the majority of these patients, their exposures to amphetamines occurred years (~27) before symptoms onset.⁸⁸ Compared with patients with Parkinson's disease without a history of exposure, those patients with a history of amphetamine use were significantly younger at the age of symptom onset, but not at the age of diagnosis.⁸⁶ This study is small, however, and subject, by its design, to recall bias. Further work is needed to confirm whether there is, in fact, an association between amphetamine use and the development of Parkinson's disease.

CHOREOATHETOID MOVEMENTS AND DYSKINESIAS

A potential complication of methamphetamine-induced damage to the dopaminergic nervous system is the development of dyskinesias and choreoathetoid movements.⁸⁹ There have been numerous reports of choreoathetoid movements (involuntary purposeless and uncontrollable movements with features of both chorea and athetosis) in patients using or abusing amphetamines.^{46,68,69,90–94} In one report, patients with underlying chorea (Sydenham, Huntington, and Lupus) were given an intravenous dose of amphetamine to assess its effect on their baseline movements. In each of these patients, amphetamine dramatically worsened their underlying chorea.⁹⁵ The increases in limb movements provoked by amphetamines could be prevented if patients were pretreated with the D2 antagonist haloperidol.⁹⁵ Because a group of control patients without chorea that were given amphetamine did not develop movement disorders, the investigators suggested that the development of chorea from amphetamines may require a underlying damage to the striatum.⁹⁵ This supposition would seem to be supported from several lines of evidence. For one, numerous studies have shown that methamphetamine abusers have evidence of dopaminergic neurotoxicity in the striatum.^{6,25,96} Additionally, chronic methamphetamine abusers, even without frank chorea, often have demonstrable movement disorders.⁹⁷ Furthermore, in some patients, movement disorders can last for years even after they have stopped using amphetamines.^{64,68} Lastly, patients who have stopped abusing amphetamine, and subsequently recovered from their choreoathetoid movement disorder, will often redevelop symptoms the first time they use amphetamines again, suggesting that patients may become permanently susceptible.⁶⁸

The description of choreoathetoid movements typically involves the limbs, neck, and face and often has a rhythmic dancelike quality. Similar to other dyskinesias, symptoms disappear while patients sleep.⁶⁸ Although in some patients dopamine antagonists and benzodiazepines have been found to relieve symptoms,^{69,91,95} in others they have had no benefit.⁶⁸ Not limited to amphetamines, choreoathetoid movements have also been reported with other stimulants, including cocaine (known as crack dancing).^{64,97–99} Although the paucity of literature on this topic suggests that the development of these symptoms is rare, the fact that there are street names for this in English and Spanish suggests that it may occur more commonly than reported.⁹⁸ It is a sad and real possibility that, among other reasons, many of the homeless persons seen dancing and writhing around on the street corners of many major cities may be manifesting signs of stimulant-induced choreoathetoid movements.

DENTAL CARIES

Although not traditionally considered a neurologic complication, the development of dental caries and teeth erosion in chronic methamphetamine abusers may be the result of elevations in brain monoamines. Referred to as *meth mouth*, advanced dental caries, tooth loss, and tooth fractures seen among methamphetamine users is the result of decreased saliva production (xerostomia) combined with teeth grinding (bruxism) and jaw clenching.^{100–108} Additional contributors to methamphetamine-related tooth decay include poor oral hygiene combined with the consumption of sugar-containing carbonated soft drinks, which is a common habit among methamphetamine users, with Mountain Dew being their drink of choice.^{100–102,106,109} Dental caries seen with meth mouth occur in a similar pattern to other disorders involving xerostomia (eg, Sjögren and radiation), involving the buccal smooth surface of the posterior teeth and the interproximal areas of the anterior teeth.^{100,102} Decay can progress to complete destruction of dental enamel, with many young methamphetamine addicts requiring dentures.¹¹⁰ The mechanism of methamphetamine-induced xerostomia appears to be mediated by central alpha-2 receptors, which, when bound by norepinephrine, decreases salivary flow.^{103,109,111} Along with increasing dopamine, methamphetamine causes sustained increases in extracellular concentrations of norepinephrine.¹¹² Although the cause of bruxism is not well known, it is thought to be of central origin and, likewise, to involve central mono-amines.^{107,108,113} Unlike nocturnal bruxism, methamphetamine users will often have bruxism day and night.^{107,108} Although the practicing neurologist is unlikely to be consulted to see patients because of dental caries, recognizing the dental and dermatologic manifestations of chronic methamphetamine abuse may help to identify at-risk patients.

SUMMARY

Chronic methamphetamine abuse has devastating effects on the CNS. The degree to which addicts will tolerate the dysfunction in the way they think, feel, move, and even look, is a powerful testimony to the addictive properties of this drug. Although the mechanisms behind these disorders are complex, at their heart they involve the recurring increase in the concentrations of central monoamines with subsequent dysfunction in dopaminergic neurotransmission. The mainstay of treatment for the problems associated with chronic methamphetamine abuse is abstinence. However, by recognizing the manifestations of chronic abuse, clinicians will be better able to help their patients get treatment for their addiction and to deal with the neurologic complications related to chronic abuse.

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KEY POINTS

- Methamphetamine abuse can cause a chronic psychosis similar to schizophrenia.
- A common manifestation of Meth psychosis is delusional parasitosis.
- Repetitive non-goal directed behaviors (punding) can result from chronic Meth abuse.
- As with other stimulants, Meth abuse can cause choreoathetoid movements.
- Dopamine receptor antagonists are the most effective treatments for Meth's chronic psychiatric manifestations.