

Emerging research on methamphetamine

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Purpose of review

To describe and review the literature published on methamphetamine in 2003–2004, with a particular focus on patterns of use, its effects on the user and society, and progress being made towards effective treatment strategies.

Recent findings

The methamphetamine epidemic continues to grow, dominating drug use trends in many parts of the world, and signifying an increasing need for effective treatment. In addition to the already-documented physical effects of the drug, preliminary evidence suggests methamphetamine dependence may cause long-term neuronal damage. Recently abstinent users have been found to do poorly on neurocognitive tests of attention and motor skills, both factors that can adversely affect treatment outcomes. Methamphetamine use is also implicated in aggression and violence and there are increasing presentations to emergency rooms. It also affects the developing fetus, as well as children and adults who are exposed to toxic chemicals at laboratory sites. Outpatient programs, such as the Matrix Model, show improved in-treatment performance. Case management was found to be an effective intervention. Agonist-type pharmacotherapy in combination with quality behavioral therapy should produce benefit and a reduction in risks caused by stimulant abuse.

Summary

The increasing evidence that methamphetamine has adverse effects on the human brain indicates the pressing need for effective prevention and treatment approaches. There is a need to take these findings, particularly those that involve cognitive deficits, into consideration in current treatment programs and when developing new treatments.

Keywords

amphetamine, amphetamine-type substances, Ice, methamphetamine, methamphetamine treatment, speed

Abbreviations

ATS amphetamine-type stimulant
MRI magnetic resonance imaging

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Introduction

The use of methamphetamine and other amphetamine-type stimulants (ATSs) has become an epidemic in many parts of the world. This article examines the research published during 2003–2004 and covers not only the effects on users, but also the impact on other members of society. As the different terms used in the articles reviewed in this paper show, one of the problems in monitoring use is that distinctions between the different types of amphetamine and methamphetamine are not always made and the terms are often used interchangeably.

Prevalence and patterns of use

Amphetamine-type substances come in different forms and with different names. 'Speed' ('meth', 'crank') is a powdered methamphetamine of relatively low purity and sold in grams or ounces. It can be snorted or injected. 'Pills' can be pharmaceutical grade stimulants such as dexamphetamine, or they can be methamphetamine powder that has been pressed into tablets and sold as amphetamines or Ecstasy. Pills can be taken orally, crushed for inhalation, or dissolved in water for injection. There is also a damp, sticky powder of higher purity that is known as 'Base' in Australia [1]. 'Ice', also known as 'Crystal', is methamphetamine that has been 'washed' in a solvent to remove impurities; it has longer-lasting physical effects and purity levels above 80% [2]. Ice can be smoked in a glass pipe, 'chased' on aluminum foil, mixed with marijuana and smoked through a bong, or injected.

The main source countries for methamphetamine are Myanmar, China, and the Philippines [3]. Methamphetamine is also produced in Mexico and California in 'Super Labs' which can make 10 or more pounds per 24 h using diverted ephedrine or pseudoephedrine, and it is also made in small laboratories ('box labs') by independent 'cooks' who use cold and influenza medications.

The United Nations Office on Drugs and Crime [3] estimates that 30 million people use ATSs compared

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with 15 million who use opiates and 13 million who use cocaine. Sixty percent of ATS users (mostly methamphetamine users) live in Asia. The annual prevalence of use among those aged 15–64 was found to be highest in Thailand (5.6% in 2001), Australia (4.0% in 2001), New Zealand (3.4% in 2001), the Philippines (2.8% in 2000), Honduras (2.5% in 1997), the UK (1.6% in 2003), the US (1.4% in 2002), Taiwan (1.2% in 2001), the Czech Republic (1.1% in 2002), South Africa and Germany (0.6% in 2002), and Japan (0.3% in 2001) [4].

Caulkins [5**] has assessed the US methamphetamine epidemics to be more complex than other drug epidemics such as cocaine or Ecstasy because of the extreme spatial variation in patterns of use. Use has stabilized at endemic levels in the West while it is still a growing epidemic in the Midwest and is just beginning in the East. Caulkins has made the following predictions: methamphetamine use will grow very quickly for a number of years in specific cities; use may reach high levels; a substantial proportion of the nation's population lives in regions where methamphetamine is not yet widely available; and the drug is spreading into regions that previously had little methamphetamine use.

The increase in the supply and consumption of ATSs in Southeast Asia has implications for neighboring countries such as Australia because of the geographic proximity and the potential 'spillover' of the market into Australia [6*]. The 2003 Party Drug survey found that Ice users (compared with users of Speed or Base) were significantly more likely to report that they had 'binged' on stimulants in the past 6 months (i.e. used the drug continuously for more than 48 h without sleep) and to report that drug use caused social, work, and financial problems [7]. A study of a sample of 'crystal meth' users in Sydney found that users reported benefits that included alertness, energy, aphrodisiac effects, sociability, euphoria, and loss of inhibitions. Although most had not had extensive experience with Ice, they reported high rates of physical and psychological side effects, including 'comedown', paranoia, inability to sleep, addiction, and aggression [8*].

Risk of HIV

Many methamphetamine users are at high risk of sexually transmitted and blood-borne diseases. A study of 139 HIV-negative heterosexuals who had become dependent on methamphetamine found that they used the drug to get high, to get more energy, and to party. They reused syringes, shared needles, drank alcohol daily, used other drugs, had unprotected sex, had multiple sex partners, and engaged in marathon sex [9*]. Use of methamphetamine, and particularly Ice, has increased at gay circuit and dance parties. Ice appears to be especially sexually arousing and disinhibitory and is strongly associated with sexual behaviors that put men at risk from HIV infection

[10*]. Sex and the use of methamphetamine are not only integrally connected, but participants report sex on methamphetamine as 'compulsive' and 'obsessive', with loss of control over their sexual expression [11*]. A study of 194 HIV-positive men who had sex with men found that methamphetamine injectors not only had more years of use and were heavier users, but they scored significantly higher on measures of impulsivity and experiences of rejection and lower on measures of emotional support [12*]. Medical complications for methamphetamine abuse in HIV-infected patients include hypertension, hyperthermia, rhabdomyolysis, and stroke, and some researchers suggest that dopaminergic systems are vulnerable to the combined neurotoxicity of HIV infection and methamphetamine [13*].

Use in the workplace

There is evidence that some individuals may use methamphetamine in the work arena. A report dated 22 July 2004 from Quest Diagnostics [14], which provides workplace drug testing, found that among general US workforce employees, the incidence of positive drug tests attributed to amphetamines rose from 0.34% in 2002 to 0.49% in 2003 – a 44% increase, which is the largest single-year increase in amphetamine use documented by the Drug Testing Index over the past 5 years.

Impact of methamphetamine on others

In a trauma center serving Hawaii, patients who were positive for amphetamine or methamphetamine were more likely to have intentional self-inflicted injury or intentional assaults. They were older, had significantly longer hospital stays, significantly higher hospital charges, and were more likely to be admitted to hospital. Methamphetamine use results in trauma center resource utilization out of proportion to injury severity [15].

Methamphetamine also places a burden on emergency departments in terms of the treatment of patients who suffer burns in methamphetamine laboratory explosions. These burns patients were found to require two to three times the standard Parkland formula resuscitation, and burns larger than 40% of the total body area resulted in 100% mortality [16]. Patients admitted to a burns unit also present new challenges for the treating team because such patients can become violent and frequently need assistance with detoxification. Routine drug screens are mandatory in identifying methamphetamine users to alert burns unit personnel to particular management problems and to target individuals who may be receptive to drug rehabilitation [17]. In addition, secondary contamination injuries to emergency department personnel result when exposed victims (including those injured as methamphetamine is being manufactured) enter the department without being properly decontaminated [18].

Methamphetamine use during pregnancy may affect the developing fetus. Methamphetamine exposure throughout gestation has been associated with decreased growth in infants exposed only for the first two trimesters. They were found to be significantly smaller for gestational age compared with the unexposed group; 4% required pharmacologic intervention for withdrawal from methamphetamine. Methamphetamine-exposed infants whose mothers smoked tobacco had significantly decreased growth relative to infants exposed to methamphetamine alone [19[•]]. Animal studies have found a range of physical, motor, neurotransmitter, and behavioral effects in methamphetamine-exposed rats and their offspring, including increased maternal and offspring mortality, retinal defects, cleft palate and rib malformations, decreased rate of physical growth, and delayed motor development.

Neurotoxic effects include neurochemical alterations in areas of the brain associated with learning, leading to cognitive impairment, behavioral deficits, increased motor activity, and enhanced conditioned avoidance responses. Human studies are limited, but the findings suggest that children may be at risk developmentally due to both the direct effects of prenatal drug exposure and the caregiving environment associated with that drug use. Maternal drug use is associated with risk factors such as poverty, chaotic and dangerous lifestyles, symptoms of psychopathology, history of childhood sexual abuse, and involvement in difficult or abusive relationships with male partners [20[•]].

Children are frequently found in laboratory surroundings and are exposed to toxic chemicals and fumes through absorption, inhalation, or ingestion, as well as being in homes with poor sanitation, hygiene, and nutrition. There can also be a high incidence of developmental delays. The California drug-endangered children's units were created to address the needs of these children through collaborative efforts among child protective workers, district attorneys, physicians, and police officers [21[•]].

Effects of methamphetamine on users

Methamphetamine use in the short term causes increases in heart rate, blood pressure, temperature and rate of breathing, constriction of blood vessels, and cardiac arrhythmia. Over longer periods of time, methamphetamine use is associated with health problems such as stroke, cardiac valve sclerosis, decreases in lung function, pulmonary hypertension, poorer cognitive functioning, and poorer mental health. Current health problems among methamphetamine users were predicted by greater age and by more prolonged methamphetamine use, especially among younger people. Reduction of methamphetamine use among younger people is important in promoting their later health. Drug treatment

services could be improved by a greater understanding of how early experiences influence health later [22^{••}].

Methamphetamine induces dose-dependent brain hyperthermia that precedes and is greater than overall body hyperthermia, suggesting methamphetamine-induced neuronal activation is a contributing source of that hyperthermia. Methamphetamine administered during social interaction was found to produce stronger and longer-lasting increases in brain and body temperature than those induced by the drug alone, heating the brain in some animals near its biological limit, which increases the risk for adverse effects [23[•]].

In Thailand, a high frequency of recent amphetamine use has been found among hospital patients with malaria. Oral use of amphetamines may lead to misdiagnosis, since coma and fever are features of amphetamine poisoning as well as malaria. The excessive sleepiness after withdrawal from amphetamines can prompt concerns that the patient is developing cerebral malaria or hypoglycemia. Amphetamines interact with drugs such as catecholamines, which are used in antimalarial treatment [24].

Patients taking amphetamines are also at increased risk of gingival enlargement [25], as well as chewing and grinding movements (bruxism) [26].

Methamphetamine abuse adversely impacts social support and social networks, as well as behavioral functioning [27]. It produces a variety of effects including irritability, physical aggression, hyperawareness, hypervigilance, and psychomotor agitation. Chronic intoxication can produce a psychotic paranoid state with frightening delusions that may result in aggressive acts. With increased dosage and duration of administration, amphetamines can produce delirium, which is manifested by disorientation, confusion, fear, and anxiety. During high-dose use, individuals can experience stimulant-induced psychosis characterized by delusions, paranoid thinking, and compulsive behavior. There is also substantial evidence that the effects caused by amphetamines are associated with violence [28[•]].

The Methamphetamine Treatment Project in California found participants had high levels of psychiatric symptoms, particularly depression and attempted suicide, as well as anxiety and psychotic symptoms. They reported high levels of problems controlling anger and violent behavior, with a correspondingly high frequency of assault and weapons charges. The findings support the value of integrated treatment for co-occurring conditions, especially the importance of training counseling staff to handle psychotic symptoms when needed [29[•]]. This project also found that 80% of women and 26% of men

reported abuse or violence from their partner. Men were more likely to report experiencing violence from friends and others. Past and current interpersonal violence is a characteristic of the lifestyles of the majority entering treatment for methamphetamine dependence [30•].

Methamphetamine use has been related to myocardial infarction, pulmonary edema, and aortic dissection. Acute coronary syndrome is common in patients hospitalized for chest pain after methamphetamine use and the frequency of other potentially life-threatening cardiac complications is appreciable. While a normal electrocardiogram lowers the likelihood of acute coronary syndrome, an abnormal finding is not helpful in distinguishing patients with or without the condition. These events occur in patients with and without underlying coronary disease and may involve multiple pathophysiologic mechanisms [31•]. Wijetunga *et al.* [32•] described cardiomyopathy due to methamphetamine exposure, finding that the pathogenesis is probably similar to that of cocaine and catecholamine-induced cardiomyopathy.

Persecutory delusion was the most common lifetime psychotic symptom, followed by auditory hallucinations, strange or unusual beliefs, and thought reading among methamphetamine psychotic inpatients in a multi-country study involving Australia, Japan, the Philippines, and Thailand. Auditory hallucinations were the most common current symptom, followed by strange or unusual beliefs and visual hallucinations. Apart from a factor of anxiety and depression, the results yielded a two-factor model of psychotic symptoms. The negative syndrome comprised impaired speech, psychomotor retardation, and flattened/incongruous affects. The positive syndrome consisted of delusions, hallucinations, and incoherent speech. Both positive/disorganized and negative syndromes should be taken into account in assessing methamphetamine psychotic symptoms [33•].

A study of 405 methamphetamine users in Taipei found pre-morbid schizoid/schizotypal personality predisposed methamphetamine users to develop psychoses. The greater the vulnerability, the longer the psychosis would persist. Those with psychosis were younger at first use, used larger amounts, had significantly higher mean Premorbid Schizoid and Schizotypal Trait scores, and higher rates of depressive disorder, alcohol dependence, and antisocial personality disorders [34•].

A prospective study of the methamphetamine withdrawal syndrome found moderate levels of depression during the first several days of abstinence, with minimal levels thereafter. The most prominent symptoms were anhedonia, irritability, and poor concentration. The withdrawal syndrome associated with methamphetamine

dependence varied considerably in intensity and duration, but generally was mild and resolved quickly for most individuals. Retrospective studies had reported a more prolonged time course [35•]. Methamphetamine-dependent individuals who were abstinent for 5–14 days performed significantly worse than controls on neurocognitive measures sensitive to attention/psychomotor speed, on measures of verbal learning and memory, and on executive system measures sensitive to fluency. These individuals were more likely than nondrug users to be classified as impaired in the areas of attention/psychomotor speed, learning and memory, and executive systems functioning. The differences were not attributable to demographic profile, estimated premorbid IQ, and level of self-reported depression. The severity of neurocognitive impairment is likely associated with worse functional outcomes, including poorer vocational functioning and an elevated risk of relapse to dependence [36••]. Recently, abstinent methamphetamine-dependent patients demonstrated quantitative EEG abnormalities that are consistent with a generalized encephalopathy. These changes in brain electrical activity are frequently associated with a range of cognitive and psychiatric abnormalities [37•].

When the cognitive performance of those who remained abstinent, relapsed, or continued to use during treatment was compared, the performance of the relapse group was worse than the abstinent group for episodic memory and significantly worse than that of the group that continued to use during treatment. This suggests that treatment providers can expect the cognitive problems of methamphetamine users entering treatment to worsen, at least during the first 3 months of abstinence, and that these users might benefit from the inclusion of strategies to compensate for cognitive problems. The specific impairment associated with episodic, but not working, memory found for the relapse group suggests that a mechanism may exist that underlies both recall and recognition and that this mechanism may be particularly vulnerable to the effects of relapse to methamphetamine use [38•].

Among 50 twin pairs in which only one member had heavy stimulant abuse (cocaine/amphetamines), abusers performed significantly worse than nonabusers on functions of attention and motor skills. Abusers, however, performed significantly better on one test of attention that measured visual vigilance. Within the abuser group, higher levels of stimulant use were largely uncorrelated with neuropsychological test scores, although a few significant correlations indicated better functioning with more stimulant use. The study demonstrated that deficits in attention and in motor skills persisted after 1 year of abstinence from stimulant use and raised hypotheses regarding relative strengths on a vigilance task among abusers [39•].

Preliminary evidence from the literature on neuropsychological effects of methamphetamine use on neurotransmitters and cognition suggests that methamphetamine dependence may cause long-term neuronal damage in humans, with concomitant deleterious effects on cognitive processes such as memory and attention [40**]. Abusers of methamphetamine have higher self-ratings of depression and anxiety than controls and they differ significantly in relative regional glucose metabolism: lower in the anterior cingulate and insula and higher in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum, and cerebellum. The relationships between relative glucose metabolism in limbic and paralimbic regions and self-reports of depression and anxiety in methamphetamine abusers suggest that these regions are involved in affective dysregulation and may be an important target for therapeutic intervention during early abstinence and withdrawal when mood disturbances may complicate treatment [41**].

Methamphetamine abusers who remain abstinent for 9 months or longer show modest improvement in performance on some tests of motor skill and memory and they appear to recover from some of the drug's damaging effects on metabolism in the thalamus. However, drug-related deficits appear to persist longer in the striatum. Persistent decreases in striatal metabolism in methamphetamine abusers could reflect long-lasting changes in dopamine cell activity and decreases in the nucleus accumbens could account for the persistence of amotivation and anhedonia in detoxified methamphetamine abusers. The recovery of thalamic metabolism could reflect adaptation responses to compensate for the dopamine deficits, and the associated improvement in neuropsychological performance further indicates its functional significance [42*].

Methamphetamine damages monoaminergic systems in the mammalian brain. Recent reports have provided conclusive evidence that methamphetamine can cause neuropathological changes in the rodent brain via apoptotic mechanisms akin to those reported in various models of neuronal death. In addition, the deleterious effects of the drug consist of cell death in the cortex, striatum, and hippocampus [43**]. Using magnetic resonance imaging (MRI) and new computational brain mapping techniques, Thompson *et al.* [44**] demonstrated systematic brain structural deficits with chronic methamphetamine abuse in humans and related these deficits to cognitive impairment. MRI-based maps suggest that chronic methamphetamine abuse causes a selective pattern of cerebral deterioration that contributes to impaired memory performance. Methamphetamine may also selectively damage the medial temporal lobe and, consistent with metabolic studies, the cingulate-limbic cortex, inducing neuroadaptation, neuropil reduction, or cell death.

Prominent white matter hypertrophy may result from altered myelination and adaptive glial changes, including gliosis secondary to neuronal damage. These brain changes may help account for the symptoms of methamphetamine abuse, providing therapeutic targets for drug-induced brain injury.

While substantial inroads have been made toward understanding the neurobiology of amphetamine-induced toxicity, the mechanisms by which amphetamines lead to selective dopamine and 5-HT damage are not yet known, nor are the mechanisms, time course, and features of recovery. A focused effort toward defining the functional consequences of amphetamine toxicity in animals and humans is in order and is likely to yield important information regarding the basic neurobiology of monoaminergic neurons, their involvement in neurodegenerative diseases and their role in normal and abnormal behavior [45*].

Treatment

Treatment for methamphetamine abuse is a recent phenomenon and, for the most part, is based on previous treatment approaches for cocaine abuse [27]. But there are some aspects of methamphetamine-related disorders that are specific to the consequences of using the drug. The development of treatments is particularly critical for a number of user groups including those who experience persistent psychosis, pregnant women and women with children, gay and bisexual men, and users involved in the criminal justice system [46**], as well as for rural populations and Hispanics.

A randomized controlled trial of methamphetamine-dependent gay and bisexual males found that drug treatment produced significant reductions in methamphetamine use and sexual risk behaviors. Drug treatment merits consideration as a primary HIV prevention strategy for this population [47*] as it resulted in reduced sexual risk behaviors and reduced stimulant use after treatment [11*].

Volkow *et al.* [48**] proposed a model to explain the loss of control and compulsive drug intake that characterize addiction. In drug addiction, the value of the drug and drug-related stimuli is enhanced at the expense of other reinforcers. This is a consequence of conditioned learning and of the resetting of reward thresholds as an adaptation to the high levels of stimulation induced by drugs of abuse. During exposure to the drug or drug-related cues, the memory of the expected reward results in overactivation of the reward and motivation circuits while decreasing the activity in the cognitive control circuit. This contributes to an inability to inhibit the drive to seek and consume the drug and results in compulsive drug intake. Treatment strategies can

include (a) interventions to decrease the rewarding value of drugs, such as pharmacological treatments that interfere with the drug's reinforcing effects, as well as treatments that make the effects unpleasant; (b) interventions to increase the value of the nondrug reinforcers, such as pharmacological and behavioral treatments that increase sensitivity to natural reinforcers and establish alternative reinforcing behaviors; (c) interventions to weaken learned drug responses, such as behavioral treatments to extinguish the learned positive associations with the drug and drug cues but also treatments that promote differential reinforcement of other behaviors; and (d) interventions to strengthen frontal control, such as cognitive therapy. This model highlights the need for therapeutic approaches that include pharmacological as well as behavioral interventions in the treatment of drug addiction.

Psychosocial and behavioral approaches are currently the primary treatments for methamphetamine-dependent individuals, although research continues on replacement pharmacotherapies. The Center for Substance Abuse Treatment's Tip #33: Treatment of stimulant abuse [49] remains a basic guide for clinicians. The Matrix Model, a manualized 16-week outpatient treatment approach for treating stimulant disorders, combines techniques and materials from the cognitive behavioral therapy literature to include accurate information on the effects of stimulants, family education, Twelve-Step program participation, and positive reinforcement for behavior change and treatment compliance. It has been assessed in several large groups and outcomes have demonstrated that, in general, the treatment response of methamphetamine-dependent individuals was positive. Compared with clients who participated in outpatient 'treatment as usual', Matrix clients were 38% more likely to stay in treatment, 27% more likely to complete treatment, and 31% more likely to have negative methamphetamine urine test results. However, the Matrix approach did not produce superior outcome at discharge or follow-up, although, with its multiple components in an intensive structured protocol, it significantly improved in-treatment performance which is an advancement in the field and is consistent with the increasing body of literature supporting such an approach [50••]. Findings of the Methamphetamine Treatment Project continue to support the value of integrated treatment for co-occurring conditions, and especially the importance of training counseling staff to handle psychotic symptoms when needed [29•].

The Iowa Case Management Project was designed to supplement treatment interventions by providing outreach activities such as visiting clients in their homes, assisting with transportation to and from services, and providing emergency funds on a limited basis. Results

from the project indicate that comprehensive case management is an effective intervention for improving employment status and lowering the incidence of depression [27].

While specific behavioral interventions are useful in the treatment of substance use disorders, medications also have an important role in treatment. Promising results are emerging for an agonist-type or 'replacement' strategy paralleling that for nicotine and opioid dependence. In a detailed review, Grabowski and colleagues [51••] have examined the current status of preclinical research agonist and antagonist pharmacotherapy strategies, and in particular the use of stimulant medications in cocaine dependence and amphetamine replacement strategies for amphetamine dependence. These authors concluded that the risks in a replacement/agonist-like strategy for stimulant dependence are manageable. Joint application of quality behavioral therapy and a potent stimulant, with appropriate monitoring procedures, should produce benefit and a reduction in risk compared with continuation of the usual patterns of stimulant abuse and dependence. Collaborative efforts of preclinical and clinical researchers will be important in the development of specific medications and conceptualization of optimal strategies, regimens, and preparation forms.

Conclusion

Progress, albeit rather slow, is being made toward developing effective treatment for methamphetamine dependence. Much work remains to be done, including the development of treatments for psychotic symptoms, the withdrawal syndrome, cognitive performance, neuronal damage, and structural brain alterations.

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- of special interest
- of outstanding interest

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- 37** Newton T, Cook I, Kalechstein A, *et al.* Quantitative EEG abnormalities in recently abstinent methamphetamine dependent individuals. *Clin Neurophysiol* 2003; 114:410–415.

This sample of 11 methamphetamine-dependent patients and 11 nondrug-using volunteers was studied using quantitative EEGs to characterize abnormalities in brain function.

- 38** Simon S, Dacey J, Glynn S, *et al.* The effect of relapse on cognition in abstinent methamphetamine abusers. *J Subst Abuse Treat* 2004; 27: 59–66.

Data from 75 participants in a longitudinal study of methamphetamine abuse were used to differentiate between the cognitive performance of those who remained abstinent, relapsed, or continued to use during treatment.

- 39** Toomey R, Lyons M, Eisen S, *et al.* A twin study of the neuropsychological consequences of stimulant abuse. *Arch Gen Psychiatry* 2003; 60:303–310.

This co-twin research design controlled for familial vulnerability to identify neuropsychological deficits that were consequences of stimulant use.

- 40** Nordahl T, Salo R, Leamon M. Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. *J Neuropsychiatry Clin Neurosci* 2003; 15:317–325.

This excellent review provides an outline and synthesis of studies that assess the neurotoxic mechanisms of methamphetamine, as well as those that evaluate the cognitive sequelae of methamphetamine abuse.

- 41** London E, Simon S, Berman S, *et al.* Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Arch Gen Psychiatry* 2004; (61):73–84.

This is an important study of regional brain function and its possible relationships with negative affect in newly abstinent methamphetamine abusers. Seventeen abstaining abusers were compared with 18 controls during performance of a vigilance task using measures of mood and cerebral glucose metabolism fluorodeoxyglucose positron emission tomography.

- 42** Wang G, Volkow N, Chang L, *et al.* Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. *Am J Psychiatry* 2004; 161:242–248.

This is a study of brain glucose metabolism as measured with positron emission tomography and fluorodeoxyglucose in five methamphetamine abusers evaluated after abstinence intervals of less than 6 months and 12–17 months.

- 43** Cadet J, Jayanthi S, Deng X. Speed kills: cellular and molecular bases of methamphetamine-induced nerve terminal degeneration and neuronal apoptosis. *FASEB J* 2003; 17:1776–1788.

This is an excellent review of 208 articles providing an interim account for the role of oxygen-based radicals and the participation of transcription factors and the involvement of cell death genes in methamphetamine-induced neurodegeneration.

- 44** Thompson P, Hayashi K, Simon S, *et al.* Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neurosci* 2004; 24:6028–6036. This is a major study using MRI and new computational brain-mapping techniques to determine the pattern of structural brain alterations associated with chronic methamphetamine abuse and deficits in cognitive impairments in humans. This is the first study to use these techniques to document cerebral deterioration.

- 45** McCann U, Ricaurte G. Amphetamine neurotoxicity: accomplishments and remaining challenges. *Neurosci Biobehav Rev* 2004; 27:821–826.

This article is a review of the history of amphetamine neurotoxicity research and the progress that has been made toward defining its characteristics. The remaining challenges for this line of investigation are outlined and suggested avenues to address these challenges are provided.

- 46** Rawson R, Gonzales R, Brethen P. Treatment of methamphetamine use disorders: an update. *J Subst Abuse Treat* 2003; 23:145–150.

This article is one of the key contributions to the literature. It clearly summarizes the problems faced in treating methamphetamine users and should be required reading for all clinicians.

- 47** Shoptaw S, Reback C, Peck J, *et al.* Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend* (in press).

This controlled trial randomly assigned methamphetamine-dependent gay and bisexual men to one of four treatment conditions to measure reductions in methamphetamine use and sexual risk behaviors.

- 48** Volkow N, Fowler J, Wang G. The addicted human brain: insights from imaging studies. *J Clin Invest* 2003; 111:1444–1451.

While this article is not specifically about methamphetamine, it provides a very thoughtful model explaining the effects of drugs on the brain. It details the need for a multi-prong approach to treatment that targets decreasing the rewarding properties of drugs, increasing the rewarding properties of alternative reinforcers, interfering with conditioned-learned associations, and strengthening cognitive control in treatment of addiction.

- 49** Rawson R. Treatment of stimulant abuse. CSAT Tip #33 (Chair, CSAT Consensus Panel). Department of Health and Human Services, Rockville, MD; 1998.

- 50** Rawson R, Marinelli-Casey P, Anglin M, *et al.* A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction* 2004; 99:708–717.

This article presents the results of the largest randomized clinical trial of treatments for methamphetamine dependence to date. It compares the Matrix Model with 'treatment as usual' in eight community outpatient settings in the western US.

- 51** Grabowski J, Shearer J, Merrill J, Negus S. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. *Addict Behav* 2004; 29:1439–1464.

This is a major contribution to replacement medication for stimulant dependence. It discusses the research to date and is very thoughtful in laying out the scientific, clinical, social, and legal issues involved in stimulant replacement.