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Current research on the epidemiology, medical and psychiatric effects, and treatment of methamphetamine use

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Abstract

Methamphetamine (MA) is a drug that is widely used in many parts of the world. It has multiple neurobiological impacts on the nervous system, some of which are transitory and some more long lasting. MA activates the reward system of the brain and produces effects that are highly reinforcing, which can lead to abuse and dependence. Routes of administration that produce rapid onset of the drug's effects (i.e., smoking and injection) are likely to lead to more rapid addiction and more medical and psychiatric effects. The medical effects of MA use are extensive, and chronic use of MA can produce significant neurological damage as well as damage to cardiovascular, pulmonary, and other organ systems. Both acute and chronic MA use can lead to extreme paranoia, anxiety, and depression, and following discontinuation of MA use, cognitive deficits and anhedonia can persist for months. No effective pharmacotherapies have been developed for the treatment of MA dependence, although this is an area of very active research. Several behavioral treatments have been shown to reduce MA use, but better treatments are needed. The research agenda for MA is substantial, with development of effective pharmacotherapies as one of the most important priorities.

Keywords

methamphetamine use; medical effects; psychiatric effects; treatment

1. Introduction

Worldwide, as many as 52 million individuals aged 15–64 are estimated to have used amphetamine-type stimulants for non-medical purposes at least once in the past year. Methamphetamine (MA) is the second most widely abused illicit drug in the world (following cannabis); its users nearly outnumber heroin and cocaine users combined. About two-thirds of the world's MA/amphetamine users reside in East and Southeast Asia, followed by approximately one-fifth in the Americas (specifically the United States and northern Mexico). Methamphetamine is a substantial problem in many Asian countries, including Brunei, Cambodia, Japan, and Thailand, which report MA as their No. 1 drug

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problem, and indicators of abuse, production, and trafficking of MA show signs of increased use in several other Asian countries, including China and Vietnam.

2. Pharmacology of Methamphetamine

Methamphetamine increases activation of the dopamine, norepinephrine (NE), and serotonin systems. Methamphetamine use causes release of dopamine into the synaptic cleft, increasing dopamine concentration. Furthermore, MA inhibits transport of dopamine into the storage vesicles, thus increasing the synaptic dopamine concentration. This abnormally high concentration of dopamine contributes to the severe neurotoxicity of MA. Heavy daily MA use and high dosages over a long duration result in neurobiological deficits that do not resolve until many months following cessation of use [1–3].

Besides the acute dopaminergic stimulation, MA produces NE effects such as mild elevation of pulse and blood pressure and cutaneous vasoconstriction. Higher doses increase central nervous system stimulation, manifested as increased alertness and compulsive or repetitive behavior. Methamphetamine users have increased sympathomimetic effects such as dizziness, tremor, hyperreflexia (rapid reflexes), pyrexia (fever), mydriasis (dilated pupils), diaphoresis (sweating), tachypnea (rapid breathing), tachycardia (rapid heartbeat), and hypertension (high blood pressure) [4]. The drug has a prolonged half-life (10–12 hours) and long duration of action. The reinforcing effects of MA are mediated through the mesolimbic dopamine (DA) reward system, which includes dopaminergic projections from the ventral tegmental area of the brain to the nucleus accumbens and other forebrain structures. Elevated levels of dopamine in the central nervous system are associated with the reinforcing and highly addictive properties of MA.

3. Route of Administration

Methamphetamine can be used orally or intranasally, or it can be smoked or injected intravenously. Injection and smoked administration of MA carry higher risk for acute toxicity as well as greater potential for the development of addiction. In general, the rapid onset of euphoria provided by these routes of administration provides a powerful stimulus for re-administration of the drug to maintain the euphoria. When injected intravenously, MA reaches cerebral circulation in 10–15 seconds. When smoked, it reaches the brain in 6–8 seconds; smoking can achieve blood levels comparable to those reached through intravenous injection [5,6]. These routes also have the most potential for toxicity due to rapid dose escalation. Intranasal insufflation (“snorting”) of MA produces euphoria in 3–5 minutes [6]. Absorption of orally administered MA occurs more slowly from the intestines, with peak plasma levels being reached 180 minutes after dosing [7]. Clinical reports recount dependence-level users taking 50 mg to 1,000 mg of MA daily.

4. Symptoms of MA Use, Misuse, and Dependence

Methamphetamine use increases blood pressure, body temperature, heart rate, and breathing rate. Continued use is common because of rewarding effects such as euphoria, reduced fatigue, reduced hunger, increased energy, increased sex drive, and increased self-confidence. Negative acute effects include abdominal cramps, shaking, high body

temperature, bruxism (teeth grinding), stroke, and cardiac arrhythmia, as well as increased anxiety, insomnia, aggressive tendencies, paranoia, and hallucinations.

The acute subjective effects of MA use depend on the amount used and route of administration. The effects of injection and smoking are rapid and intense, often described as a “rush,” followed by euphoria and a sense of increased energy, wakefulness, alertness, and increased libido. Heart rate, blood pressure, and breathing rate increase, and many users will grind their teeth and pick at their skin. Effects of MA can last up to 12 hours. Due to the development of tolerance, chronic MA users repeat dosing every few hours in “binging” episodes, which can result in paranoia, hallucinations, delusions, mood disturbance, and formication (tactile hallucination of bugs crawling on the skin).

After prolonged or heavy use of MA, a withdrawal syndrome may emerge characterized by dysphoric mood, anhedonia, fatigue, increased appetite, sleep disturbance, and slowing or acceleration of psychomotor activity [8]. The severity of withdrawal is related to the duration and intensity of recent MA use [9]. MA-dependent individuals have reported remission of the most severe withdrawal symptoms within several days to three weeks, although there have been numerous clinical observations of more subtle symptoms (i.e., anhedonia) lasting for several months [10,11]. Apathy has been reported more frequently than depressed mood, suggesting that anhedonia may be more problematic than major depressive disorder following cessation of MA use [12].

5. Psychiatric Considerations

Methamphetamine-associated psychiatric impairment may occur in several domains: cognitive, intellectual, or affective. The drug’s contribution to impairment may be acute, delayed, or cumulative/residual. Psychiatric impairment appears to correlate with duration of use as well as total and peak amounts of MA absorbed. Neurocognitive deficits associated with chronic MA use include impairments in episodic memory, executive functions, and psychomotor tasks related to frontostriatal and limbic circuits. Methamphetamine use may also be associated with deficits in attention, memory, and language [13]. Neurocognitive impairment may persist for nine months or longer following cessation of MA use, but recovery in dopamine transporter activity and improvement in cognitive functioning is possible with sustained abstinence [14,15].

Psychiatric symptoms have been well-documented in MA users [16]. Anxiety, depression, insomnia, and psychosis are among the most commonly reported symptoms associated with MA dependence, and individuals presenting to the emergency department in the context of MA intoxication may be agitated, violent, or suicidal [17,18]. Though minor agitation may be treated by placing the individual in a quiet, less stimulating environment, benzodiazepines or neuroleptics may be required for more severe MA-related agitation or psychosis [18].

Psychiatric symptoms may vary as a result of individual differences in sensitivity to MA, amount and/or frequency of use, and route of administration [19]. Individuals who use intravenously and who have a family history of psychotic symptoms are at heightened risk for the development of MA-related psychosis, which may mimic schizophrenia. Clinical

symptoms of MA-induced psychosis include paranoia, delusions, and hallucinations [20,21]. Psychosis occurs at least intermittently in a significant proportion of MA users, with wide variation in the severity and clinical course of symptoms [20]. Although the majority of MA-related psychiatric symptoms typically remit within a week of abstinence [12], a subset of MA users experience prolonged psychiatric symptomatology, even in the absence of a prior reported history of mental illness [22,23].

6. Medical Considerations

Chronic use of MA results in a variety of medical consequences, including:

- *cardiovascular disease*—arrhythmia and coronary artery damage are particularly prevalent, occurring at a much younger age among MA misusers than in the general population [24].
- *pulmonary problems*—including pneumonia are common, particularly among individuals who smoke MA.
- *liver disease*—found in 40% of MA misusers by autopsy [24].
- *strokes*—may occur in even young MA misusers by all routes of administration, resulting in long-term neuronal damage [25,26]; hemorrhage or ischemia typically occurs in frontal lobes [24].
- *pregnancy complications*—use of MA by pregnant women endangers the fetus; for example, use of MA has been associated with a 3.5 times greater likelihood of reduced birth weight compared to non-MA-using controls [27].
- *neurological complications*—MA use can produce movement disorders [28], tonic-clonic seizures, and cerebrovasular accidents [29], hyperkinetic movements including repetitive or stereotyped behaviors [28,30] and choreoathetoid movement disorders [31,32].
- *dental complications*—an emerging body of literature suggests an association between MA dependence and dental pathology, including rampant caries (cavities), missing and fractured teeth, and periodontal disease [33–35].

Long-term MA use is associated with elevated rates of infectious diseases, including human immunodeficiency virus (HIV), hepatitis B and C, and endocarditis [18]. Factors mediating the relationship between MA use and infectious diseases include increased risky sexual behaviors occurring in the context of MA intoxication, as well as injection drug use and associated risk behaviors (e.g., needle sharing) [36].

7. Clinical Considerations

The groups disproportionately impacted by MA have been women as well as men who have sex with men. Unlike with cocaine and heroin, where a very high proportion of users are male, women use MA at rates almost equal to men. Surveys among women suggest that they are more likely than men to be attracted to MA for weight loss and to control symptoms of depression. Over 70% of MA-dependent women report histories of physical and sexual abuse and are more likely than men to present for treatment with greater psychological

distress. Methamphetamine has been a popular drug among men who have sex with men (MSM) since the 1980s. Men who have sex with men report using MA to combat feelings of loneliness and isolation and to promote sexual desire and sexual behavior [37,38]. In addition to the appeal of its sexual effects, MA serves as a coping tool for many MSM with HIV or AIDS. MSM with HIV report using MA to manage symptoms of HIV disease, such as fatigue, or to remedy HIV-related “burn out” and depression [37].

Methamphetamine’s dramatic effect on sexual desire and sexual behavior has been a major public health concern, as it has been associated with increasing risk for transmission of HIV [37,39]. Sexual practices associated with MA use include increased numbers of casual and anonymous sexual partners, increased anal intercourse, decreased condom use, sex trading, group sex, and more frequent and longer episodes of sexual activity [40–42]. The Multicentre AIDS Cohort Study and several other studies found a high correlation between MA use and HIV seroconversion [40] and other sexually transmitted infections, such as syphilis, gonorrhea, and hepatitis [43–45]. Treatment of MA dependence may be one of the most effective strategies in reducing the spread of HIV and other associated sexually transmitted infections.

8. Pharmacotherapy Treatments

To date, there is limited literature on evidence-based pharmacological treatment approaches for MA withdrawal. Antidepressants and anxiolytics may be used to ameliorate depressive and anxiety symptoms, though research suggests only limited benefits of antidepressants in reducing withdrawal symptoms [46]. Neuroleptics may be used to treat MA-induced psychotic symptoms in the context of intoxication or recent use [47], and a recent study demonstrated the equivalent efficacy of olanzapine (Zyprexa), an atypical neuroleptic, and haloperidol (Haldol), a typical neuroleptic, in improving psychotic symptoms related to amphetamine use [48].

The research literature lacks substantiation of efficacy of any medication as a treatment for MA dependence. Past work has failed to determine efficacy of compounds such as selegilene (Eldepryl), sertraline (Zoloft), gabapentin (Neurontin), rivastigmine (Exelon), risperidone (Risperdal), and ondansetron (Zofran) [49] as potential treatments for MA dependence.

Medication development for MA addiction generally strives to address deficits caused by MA use or associated with withdrawal. The target of therapeutic development has focused on initiation of abstinence and prevention of relapse. Bupropion (Wellbutrin), modafinil (Provigil), naltrexone, mirtazapine (Remeron), and baclofen (Lioresal) have exhibited limited utility in treating MA addiction. Other medications (e.g., lobeline, vigabatrin) are under consideration, but evidence for efficacy is lacking and the scant data that do exist contain no information regarding suitability for various populations. Also of interest is a “replacement” or “substitution” approach with other stimulants such as methylphenidate [50,51], akin to methadone for opioid addiction. As with methadone, however, such a pharmacotherapy enables the patient to rehabilitate in other life areas but does not lead to near-term abstinence from stimulants.

Matrix Model of Cognitive Behavioral Therapy (CBT)

The Matrix Model incorporates principles of CBT in individual and group settings, family education, motivational interviewing, and behavioral therapy that employs CBT principles. This manualized therapy has been proven effective in reducing MA use during the 16-week application of the intervention, in comparison to a "treatment as usual" condition [52,53]. The Matrix Model has been evaluated as a stand-alone treatment for subgroups of methamphetamine abusers (e.g., gay and bisexual men and heterosexuals) and as the behavioral treatment platform in pharmacotherapy trials for MA dependence [54].

Contingency management

Contingency management (CM) therapy for treatment of stimulant use disorders employs principles of reinforcement for demonstration of desired behaviors. Drug use can be brought under control if desired behaviors that replace or compete with drug use are followed by rewards to increase the frequency of these behaviors. Thus, CM combined with a pharmacotherapy, such as modafinil, that potentially enhances cognition or restores memory/learning processes impacted by methamphetamine dependence could be a potent approach. Contingency management and CBT have been assessed for comparative effectiveness in treating stimulant dependence with a group of cocaine- and methamphetamine-dependent individuals—participants who received CM were retained in treatment significantly longer than those who received only CBT and they provided more stimulant-negative urine samples [53].

9. Summary

Methamphetamine, a drug that is widely used in many parts of the world, produces significant acute and chronic medical and psychiatric conditions. Currently, there are no medications that have shown evidence of efficacy in the treatment of MA dependence. Several behavioral treatments have been shown to reduce MA use, but additional treatments are needed to provide a sufficient set of clinical tools to adequately treat the majority of MA-dependent individuals. The development of effective treatments that can reduce the use of MA as well as its consequent medical and psychiatric comorbidities is an important priority for future research.

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