Current Research on Methamphetamine: Epidemiology, Medical and Psychiatric Effects, Treatment, and Harm Reduction Efforts

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Review Article

Abstract

Background: Methamphetamine (MA) which is known as "shisheh" in Iran is a drug that widely is used in many parts of the world and it is near to a decade that is available for the most drug users and has a considerable prevalence of use. Due to high abuse prevalence and very new challenging phenomenon, it is very important that researchers and treatment providers become more familiar with different aspects of MA.

Discussion: It has multiple neurobiological impacts on the nervous system, some of which are transitory and some longer 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. 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.

Conclusion: Harm reduction strategies for non-treatment seeking MA users are needed to reduce the risk of human immunodeficiency virus and other medical risks. The research agenda for MA is substantial, with development of effective pharmacotherapies as one of the most important priorities. Appropriate and effective response for prevention, treatment and harm reduction services due to increasing problems regarding MA in Iran and some other countries in the region.

Keywords: Methamphetamine, Epidemiology, Side-effects, Treatment, Harm reduction, Iran

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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).

Iran has a special situation in Asia and Middle East, with regard to amphetamine type stimulants (ATS) availability and use. Prior to 2004, there were no reported seizures of ATS in Iran. The first reported of ATS seizure was in 2005,¹ followed by an increasing number of seizures, year by year.²-7 The amount of MA seized qualified Iran for ranking 5th in ATS seizures in 2010 and 2011.6.7 There was a 400% increase in the amount of ATS seized in Iran between 2010 and 2011, this 1 year rate of increase compares to increases of 238% in Mexico 166% in Thailand, 153% in USA and 140% in China, put Iran in 1st ranking for an increase in seizure.

Discussion

Pharmacology of MA

MA increases activation of the dopamine, norepinephrine, and serotonin systems. MA use causes the release of dopamine into the synaptic increasing dopamine concentration. Furthermore, MA inhibits transport of dopamine into the storage vesicles, thus increasing the dopamine concentration. 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.8-10

Besides the acute dopaminergic stimulation, MA produces norepinephrine effects such as mild elevation of pulse and blood pressure and cutaneous vasoconstriction, but it is important to know that some chronic users shows a unpredictable hypotension during general anesthesia in operation rooms, which one of the

possible cause is down-regulation of endogenous catecholamine receptors.¹¹

Higher doses increase central nervous system stimulation, manifested as increased alertness and compulsive or repetitive behavior. MA users have increased sympathomimetic effects such as dizziness, tremor, hyperreflexia, pyrexia, mydriasis, diaphoresis, tachypnea, tachycardia, and hypertension. The drug has a prolonged half-life (10-12 h) and long duration of action. Elevated levels of dopamine in the central nervous system are associated with the reinforcing and highly addictive properties of MA.

Route of administration

MA can be used orally or intranasal, 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 s. When smoked, it reaches the brain in 6-8 s; smoking can achieve blood levels comparable to those reached through intravenous injection.^{13,14} These routes also have the most potential for toxicity due to rapid dose escalation. Intranasal insufflation (snorting) of MA produces euphoria in 3-5 min.14 Absorption of orally administered MA occurs more slowly from the intestines, with peak plasma levels being reached 180 min after dosing.15 Clinical reports recount dependencelevel users taking 50 to 1000 mg of MA daily.

MA injection in Iran is reporting recently in different cities with high rate of injection and shared injection both in closed and open setting, which is an alarming sign for human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) prevention programs in Iran. 16-18

Symptoms of MA use, misuse, and dependence

MA 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 h. 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.19 The severity of withdrawal is related to the duration and intensity of recent MA use.²⁰ MA-dependent individuals have reported remission of the most severe withdrawal symptoms within several days to 3 weeks; although, there have been numerous clinical observations of more subtle symptoms (i.e., anhedonia) lasting for several months.^{21,22} 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.23

Psychiatric considerations

MA-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 MA absorbed. Neurocognitive associated with chronic MA use impairments in episodic memory, executive functions, and psychomotor tasks related to frontostriatal and limbic circuits. MA use may also be associated with deficits in attention, memory, and language.24 Neurocognitive impairment may persist for 9 months or longer following cessation of MA use, but recovery in DAT activity and improvement in cognitive functioning is possible with sustained abstinence.²⁵⁻²⁷

Psychiatric symptoms have been well-documented in MA users.²⁷ 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.^{28,29} 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.²⁹

Psychiatric symptoms may vary as a result of individual differences in sensitivity to MA, amount and/or frequency of use, and route of administration.30 Individuals who 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 delusions, and hallucinations.^{31,32} Psychosis occurs at least intermittently in a significant proportion of MA users, with wide variation in the severity and clinical course of symptoms.31

majority Although the of MA-related psychiatric symptoms typically remit within a week of abstinence,²³ a subset of MA users prolonged psychiatric experience symptomatology, even in the absence of a prior reported history of mental illness.33,34 Although MA is one of the most famous drugs in a druginduced psychosis, but recent studies finding suggest that designer drugs may have severe sideeffects in this domain than MA.35

Medical considerations

Chronic use of MA results in a variety of medical consequences, including cardiovascular disease, pulmonary problems, neurological problems, and dental disease. Long-term MA use is associated with elevated rates of infectious diseases, including HIV, hepatitis B and C, and endocarditis.²⁹ 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

Clinical considerations

The groups disproportionately impacted by MA have been women and men who have sex with men (MSM). 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. MA has been a popular drug among MSM since the 1980s. MSM 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

MA'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 multicenter AIDS cohort study and several other studies found a high correlation between MA use and HIV seroconversion⁴⁰ 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.

Pharmacotherapy treatments

Until 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), atypical 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 the efficacy of compounds such as selegiline (Eldepryl), sertraline (Zoloft), gabapentin (Neurontin), rivastigmine (Exelon), risperidone (Risperdal), ondansetron (Zofran),⁴⁹ and Abilify (Aripiprazole)⁵⁰ 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, especially in conjunction with behavioral therapy. 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 the suitability for various populations. Also of interest is a "replacement" or "substitution" approach with other stimulants such as methylphenidate,^{51,52} 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. There is at least one clinical trial in Iran, which recently compared aripiprazole with risperidone for treatment of MA induced psychosis, based on findings of this study risperidone is better choice for patients with positive psychosis symptoms and vice versa aripiprazole is better for patients with negative psychosis symptoms.⁵³

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 employ 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.⁵⁴⁻⁵⁷ The matrix

model has been evaluated as a stand-alone treatment for subgroups of MA abusers (e.g., gay and bisexual men and heterosexuals) and as the behavioral treatment platform in pharmacotherapy trials for MA dependence.⁵⁷

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 MA dependence could be a potent approach. CM and CBT have been assessed for comparative effectiveness in treating stimulant dependence with a group of cocaine- and MA-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.⁵⁵

Another approach is empowering patients and their families by empower based interventions which could be effective for Iranian patients.⁵⁶

Harm reduction

Some MA users who do not want treatment and cannot stop using MA should be considered as a target group of harm reduction services.⁵⁸ Harms of MA use includes:

- Direct medical harms such as cardiovascular disease, pulmonary problems, liver disease, strokes, pregnancy complications, neurological/mental complications, and dental complications.
- Indirect medical harms such as HIV and hepatitis B and/or C because increase in high risk sex behaviors and sharing behaviors.⁵⁹⁻⁶² Even in non-injecting MA users we can see an increase in the rate of hepatitis C because of pipe sharing.⁶³
- Indirect social harms such as increase in minor and major crimes^{64,65} and violence.^{66,67}

Current harm reduction strategies have been established in the context of heroin injecting drug users (IDUs) and have been shown to be effective for controlling HIV epidemic among these opiate using IDUs.⁶⁸ Many of the harm reduction strategies developed for IDUs are likely to be useful for injecting MA users. Needle exchange has been shown to be an effective harm reduction

strategy with opiate injectors, but there is evidence that MA injectors prefer to take, but avoid engagement with service providers resulting in less opportunity for patient education.⁶⁹ Establishment of harm reduction facilities that are accepting, non-stigmatizing and provide food, and support services could be useful for engaging MA users into a safe environment. Furthermore, there is some evidence that the availability of smoking equipment such as pipes may provide some benefit in reducing injection use.

MA use increases sexual risk behaviors⁶¹ Condom promotion programs as well as safer sex education and safer sex negotiation for both male and female MA users can be part of harm reduction activities for MA users. In countries such as Iran that already have established harm reduction strategies for IDUs, MA harm reduction activities should be integrated with current activities to expand the impact of the programs. Consideration should be given to employing communication tools including mobile phones, virtual social networks, and text messaging to expand outreach activities.⁷⁰⁻⁷²

Conclusion

MA, 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. Integration of MA harm reduction strategies in current harm reduction programs as well as tailoring new innovative methods for better access to harm reduction assistance for both injecting and non-injecting MA users should be considered as a priority. Iran and many other developing countries in the region are newly facing problems with MA, rapidly and widely, it highly recommended that responsible authorities and scientific communities try to establish appropriate and effective response for prevention, treatment and harm reduction services, which specially should be tailored considering local resources and characteristics.

Conflict of Interests

The Authors have no conflict of interest.

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پژوهشهای اخیر درباره متامفتامین: همه گیر شناسی، اثرات جسمی و روانی، درمان و تلاش در جهت کاهش آسیب

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مقاله مروري

چکیده

مقدمه: متامفتامین (با نام مصطلح شیشه در ایران) ماده روان گردانی است که در دنیا به گستردگی در حال استفاده میباشد و در ایران نیز نزدیک به یک دهه است که در دسترس عموم مصرف کنندگان قرار گرفته است و شیوع مصرف بسیار بالایی دارد. به همین دلیل شناخت بیشتر آن موردنیاز درمانگران و پژوهشگران این حیطه میباشد.

بحث: مصرف متامفتامین عوارض متعددی بر سیستم عصبی مرکزی به جای میگذارد که بعضی قابل برگشت و بعضی برای مدتهای طولانی گریبانگیر فرد مصرف کننده به وجود میآورد که وی را به شدت به مصرف مکرر آن ترغیب میکند و در نهایت این فرایند میتواند به اعتیاد و وابستگی ختم گردد. شیوه مصرف تدخینی یا تزریقی این ماده باعث می شود تا تأثیرات آن بلافاصله بعد از مصرف در فرد مصرف کننده حس شود و این امر باعث افزایش احتمال اعتیادآوری آن و عوارض جسمی و روان پزشکی بیشتری میگردد. تاکنون درمان دارویی مؤثری برای وابستگی به متامفتامین در دسترس نیست. اگرچه در این حیطه پژوهشهای گستردهای در جریان میباشد. چندین مدل درمان رفتاری تأثیر خود را در کاهش میزان مصرف متامفتامین نشان دادهاند، اما نیاز به درمانهای بهتری در این زمینه احساس میگردد.

نتیجه گیری: باید راهبردهای کاهش آسیب برای مصرف کنندگانی که به دنبال قطع مصرف متامفتامین نیستند مدنظر قرار گیرد تا احتمال بروز (Human immunodeficiency virus) HIV و دیگر آسیبهای جسمی در این گروه کاهش یابد. دامنه پژوهش در این حیطه با توجه به نیاز به درمانهای مؤثر دارویی (به عنوان یکی از مهمترین اولویتها) بسیار گسترده میباشد.

واژگان کلیدی: متامفتامین، همه گیر شناسی، عوارض جانبی، درمان، کاهش آسیب، ایران

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