



Methamphetamine psychosis, the efficacy of atypical antipsychotics

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ABSTRACT

Worldwide growing methamphetamine abuse is one of the most serious health problems with several different consequences for victims, especially in developing countries. Chronic methamphetamine abuse is associated with several psychiatric problems in all countries which are faced to epidemic methamphetamine abuse. Methamphetamine-induced psychosis is a major medical challenge for clinical practitioner from both diagnostic and therapeutic viewpoints. Stimulant psychosis commonly occurs in people who abuse stimulants, but it also occurs in some patients taking therapeutic doses of stimulant drugs under medical supervision. The main characteristic of meth psychosis is the presence of prominent hallucinations and delusions. Other drugs, such as cocaine and marijuana, can trigger the onset of psychosis in someone who is already at increased risk because they have "vulnerability". The current literature review attends to explain several aspects of MIP epidemiologically and clinically. Investigators proposed pharmacologically treatment based on recently published data.

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Introduction

Amphetamine and methamphetamine are the most abuse substances among the synthetic psychostimulant across the world (1). The overall prevalence of methamphetamine users (excluding amphetamine users) ranges from 10.5 to 28.5 millions people worldwide (0.2% to 0.6% of adults between 15 to 64 years old) (2). Accompanied to amphetamine, these synthetic psychostimulants are ranked as the second illicit drug abuse after cannabis as the first and before cocaine and opiates (1).

Many consequences follow methamphetamine abusers including medical, psychiatric, cognitive, legal and socioeconomic problems. It is unclear why methamphetamine abusers are more in-

involved with legal consequences than all other illicit drug abusers (3).

It might be due to more psychotic symptoms induced by these psychostimulant drugs or flaring of symptoms in a subtle or stable schizophrenia, which could be exacerbated by methamphetamine (4). It has been well-known that such drugs are able to produce psychotic symptoms in persons with no history of previous psychiatric disorders (5,6).

Epidemiology and clinical manifestations of Methamphetamine-induced psychosis (MIP)

There are other substances, which are able to produce psychosis including cocaine, cannabis, alcohol, hallucinogens, heroin and sedatives (7).

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There will be a diagnostic challenge to meet a net diagnosis for drug-induced psychosis if the clinical practitioner cannot establish the presence of psychotic symptoms before initiating drug abuse. In a survey, among 400 cases who admitted in different psychiatric emergency departments for their psychotic symptoms, 44% received a substance-induced psychotic diagnosis and 56% were diagnosed essential psychosis (8). According to DSM-IV criteria, diagnosis of primary psychosis is usually after at least 4 weeks with persisting symptoms without heavy substance use. In addition to the previous history of substance abuse, other factors can lead to drug-induced psychosis including parental substance abuse, dependency to drug (rather than occasional abuse) and visual hallucination. Lower positive and negative syndrome scale with the positive history of drug abuse put in favor of drug-induced psychosis as well as more consciousness to psychotic symptoms and more tendency to suicidal thoughts are another feature of drug-induced psychosis. Generally, reported psychotic symptoms due to methamphetamine (MA) abuse, from USA, Japan, Taiwan, Australia and Iran are the same as each other including (as studied by Fasihpour et al) persecutory delusions (82%), auditory hallucination (70.3%), reference delusion (57.7%), visual hallucination (44.1%), grandiosity delusion (39.6%) and jealousy delusion (26.1%) (9).

Although certain risk factors could not be extracted among documented literature and many conducted studies have been reported more common factors by different authors in involved countries including:

1. Psychosis induction is largely dose-dependent than duration-dependent (5,10,11)
2. Positive family history of psychotic symptoms especially in first-degree relatives (5). Interestingly protracted and more resistant psychosis were occurred in abuser persons, whose one of their first-degree relatives has been involved by schizophrenia (12).
3. Presence of premorbidity in abuser subjects such as schizoid/schizotypal personality traits, alcohol dependency, antisocial personality disorders and major depression, all can induce psychosis by methamphetamine (5).
4. History of sexual abuse experience, recent higher occasion of methamphetamine (MA) abuse plus another illicit substance (13).
5. Childhood Attention Deficit Hyperactive Disorder (ADHD) may be associated frequently with psychosis reports (14).
6. Higher serum level of methamphetamine and amphetamine are associated with more profound psychotic symptoms (4). The route of consumption

(oral, smoking, injection) was not a significant factor in Mc Keit et al. study (6). But according to Matsumoto et al. smoker abuser showed acute psychotic symptoms more quickly than who used the injection form because smokers had poor control of MA consumption. In addition, psychotic syndromes in injection abusers required more medical care to respond to treatment (15).

Other personal characteristics such as age at which abuse is started, education, intelligence quotient (IQ) and the duration of methamphetamine use were not associated significantly with the risk of developing psychosis among abusers (8). Female preponderance for undergoing psychotic symptoms was established among participants in the study of Mahoney and his colleagues (16).

It is noticeable that the results of studies were somewhat inconsistent on MIP characteristics because of different cultural population, different accuracy in the methods of studies and so on. Nevertheless, they provided a general opinion for further investigations and more accurate and localized studies.

Sign and symptoms of MIP

Reported psychotic symptoms among several different studies performed in Japan (17), Taiwan (5), Australia (6), Tailand (18) and Iran (9) are unanimous in obtained results. The most common features included persecutory delusion and auditory hallucination followed by delusion of reference, visual hallucination and thought broadcasting. MIP is initiated with excitation and increased focusing or concentration states following by prepsychotic states and delusions, which may subsequently progress, to overt psychosis with positive symptoms (10). The onset of first psychotic episode from the first occasion of methamphetamine consumption ranges from 1.7 years in smoker abusers to 4.4 years in injectioners (19) and/or 5.2 years without considering route of abuse (10). Individuals with intense eagerness (20), injection of methamphetamine and methamphetamine abusers are at higher risk of experiencing more severe psychosis (21). Although MIP usually has short course duration, longer and persistent episodes of psychosis have been reported even after discontinuation of drug abuse and in abstinence period (17). As protracted MIP frequently occurred in many studies, it remained unclear whether methamphetamine could produce a chronic psychotic disorder or methamphetamine had uncovered a psychotic disorder in a patient with psychotic background (5). The risk factors for developing long lasting MIP include positive family history of first-degree relative involved to schizophrenia, premorbidity

with a personality disorder specially schizoid/schizotypal form, a former neurological disorder like ADHD, head injury and learning disability (2). During the abstinent period, MIP relapse might occur in a previously undergone short MIP as well as any stressor such as insomnia and severe alcohol intake (10,23,24). Methamphetamine and not stress-induced MIP relapse occur with a likelihood of 60% to 80% in less than 1 week to 1 month respectively, after re-exposure to MA (8).

A history of more than 2-year MA abuse makes the person susceptible to spontaneous relapse of psychosis without any methamphetamine reabusing for years (10).

MIP Treatment and pharmacological approaches

No medical agent (s) are approved as therapeutic drug for MIP but a few numbers of pharmacological evaluations have been performed for finding a suitable choice in recent years. According to bio-molecular neurotransmitters influenced by MA, several pharmacologic agents are proposed for treating MA with clinical implications such as dependency and MIP. In this review, a brief review will run to introduce involved pharmacological groups separately.

Dopaminergic agents

Modafinil is a dopaminergic agonist approved essentially for sleep disorders such as narcolepsy, obstructive sleep apnoea/hypopnoea and idiopathic hypersomnia. Modafinil may increase efficacy of cognitive behavioral treatments and decrease craving in methamphetamine dependency (25). It may have beneficial effect in schizophrenia and thereby in MIP (26,27).

Bupropion, a re-uptake inhibitor of dopamine, has demonstrated its effect to decrease methamphetamine use specially in low to moderate dependency (28-30).

Methylphenidate (Ritaline) and dextroamphetamine (d-amphetamine) both increase the releasing of dopamine in synaptic cleft and have high capacity to be abused. They showed strong efficacy in studies to stop or reduce MA abuse in even deep dependency (31-34).

Although the above quoted drugs have not revealed any direct effect for MIP, it seems that appetite decreasing for MA use occurs by these drugs, which can be indirectly effective for MIP managing as well.

Aripiperazole, a dopamine D2-receptore partial agonist and a second generation antidepressant, is proposed for methamphetamine (MA) dependency and MIP.

In a study driven by Sulaiman et al. aripiperazole was effective in diminishing the severity of

psychosis resulted from methamphetamine, but it was failed to increase abstinence duration (35).

In another study, Farnia et al. compared the efficacy of aripiperazole versus risperidone in MIP cases in a double blind randomised control trial. After six weeks trial with aripiperazole 15mg/day or risperidone 4mg/day, they concluded that both drugs were able to significantly decrease the MIP severity. Risperidone showed more reduction on positive symptoms while aripiperazole was more effective on negative symptoms (36). The ability of antipsychotics such as aripiperazole and haloperidol in suppressing the dopamine releasing in amygdala of animal experiments, which caused marked reduction in behavioral sensitivity following MA exposure, may explain its benefits on MIP (37). In another animal model study, it was shown by Futamara et al. that aripiperazole could diminish behavioral sensitization through acting on 5-HT1A receptor (38).

Risperidone was evaluated solely for its ability to prolong abstinent period in 4 weeks administration of 3.6mg/day in an open-label trying. Results demonstrated a decrease in meth consumption in abusers (39). Two separate case reports have considered the dramatic response of MIP to risperidone therapy (40,41).

Despite safety applications of classic antipsychotics, Hatzipetros et al. warned about an unknown toxic effect of conventional antipsychotics such as haloperidol administration to GABAergic cells in subchronic treatment of MIP that might lead to hyperkinetic movement disorder and convulsion (42).

Other antipsychotics such as quetiapine and olanzapine were applied successfully for drug-induced psychosis (43,44).

GABAergic agents

Several different GABA agents such as baclofen (45), gabapantane (45,46), vigabatrine (47,48), topiramate (49) and benzodiazepines were proposed for the treatment of MA dependency and associated psychosis based on their effects on decreasing the dopamine transmission in mesolimbic system by which reinforcing effects of MA is reduced (50,51). But, actually conducted trial studies were somewhat inconsistent to suggest a precise recommendation (49,52). Nevertheless, Ito K et al. showed that clonazepam did not obtain explicating of behavioral sensitization in rats, which were under treatment with MA (53).

Serotonergic agents

No pharmacological trial studies lead to any clinical recommendation of serotonergic agents for MIP in searching the web publish except for two animal experiments in which the role of se-

rotonergic receptors were evaluated in locomotor activating and developing behavioral sensitization. Kaneko et al. studied the inhibitory effect of fluoxetine and paroxetine, two clinically available SSRI agents, on establishing and expression of MA-induced behavioral sensitization and suggested a prophylactic role of SSRIs in preventing the psychotic states such as hallucination and paranoid symptoms due to methamphetamine abuse (54).

Ago et al. demonstrated the critical role of serotonine system in behavioral sensitization formation in mice by osetozotan, a 5-HT_{1A}-receptor agonist, and ritanserin, a 5-HT₂-receptore antagonist, and again suggested a capacity of serotonergic agents for treating methamphetamine psychosis (55).

Opioid antagonist

Naltrexone, a pure antagonist of morphine, have showed successful outcomes in MA-dependency management by decreasing craving, probably because of endogenous opioid system modulating role in reducing of reinforcing effects of metamphetamine (56-61).

Behavioral sensitization produced by frequently exposure to methamphetamine was prevented by induction and expression of naltrexone in mice (56).

Nevertheless, naltrexone plus N-acetylsysteine, an antioxidant, failed to demonstrate priority to placebo group for MA-dependency treatment (62). Although no particular study with emphasis on the effects of naltrexone on MA-induced psychosis was found, it may be associated with precise changes in severity and prevalence of MIP because of its strong effects on abolishing dependency.

Other unclassified treatment

Minocycline, a second generation antibiotic, was proposed for MIP treatment. In two separate case reports minocycline administration were associated with significant results in curing the psychotic symptoms of methamphetamine abuse probably due to its anti-inflammatory effects on micoglia (63,64).

Electroconvulsive therapy (ECT) was mentioned for its high capacity to create a dramatic response in MIP cases whose psychotic symptoms were resistant to conventional pharmacological antipsychotic therapy (65).

Conclusion

Methamphetamine abuse is now going to become an epidemic problem in many countries. Chronic MA abuser underwent many medical psychiatric cognitive and legal consequences. Psychosis in one of the most important complications. Many studies were performed and a plenty of pharmacological drugs were proposed for managing of MA dependency. None of them were approved and a few investigations tried to find drugs targeted on psychosis due to MA. These drugs as reviewed in this article belong

to the different biochemical neurotransmitters such as dopaminergic antipsychotics, serotonergic agents and GABAergic drugs. All the studied drugs failed to obtain approval validity. Nevertheless, according to the results of conducted studies merely all of these agents could subside the MA-associated psychosis. Recognizing neurotransmitter/receptor systems involved and influenced by MA in animal models and human experiments is the best way to overcome MIP pharmacologically and is recommended strongly for future studies that can elevate knowledge about developing MA-induced psychiatric syndromes, especially psychosis.

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Conflict of Interest

The authors declare no conflict of interest.

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