Risperidone for methamphetamine induced psychotic disorder

On the efficacy of risperidone for the treatment of methamphetamine induced psychotic disorder, a dose ranging study

Induced psychosis, diagnosis and treatment

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 (MIP) 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, including epidemiologically, clinically and investigators proposed pharmacologically treatment based on recently published data.

Introduction

Amphetamine and methamphetamine have the most substances for abuse among the synthetic psychostimulant across the world1. The overall the prevalence of methamphetamine users (excluding amphetamine users)

ranges from 10. 5 to 28. 5 million 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 2nd abuser illicit drugs after cannabis as the 1st and before cocaine and opiates1.

Many consequences follow methamphetamine abusers including medical, psychiatric, cognitive, legal and socioeconomic problems. It is unclear why methamphetamine abusers are more involved with legal consequences than all other illicit drug abusers3. 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 methamphetamine4. 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 MIP

There are other substances able to produce psychosis including cocaine, cannabis, alcohol, hallucinogens, heroin and sedatives7. 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 psychosis diagnosis and 56% were diagnosed essential psychosis8. 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 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 th 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 by different authors in involved countries have been reported more common factors include: 1. Pyschosis induction is largely dose-dependent than duration-dependent5, 10, 11 2. Positive family history of psychotic symptoms especially in first degree relatives5. Interestingly protracted and more resistant psychosis was occurred in abuser persons, whose one of their first degree relatives has been involved by schizophrenia12. 3. Presence of premorbidity in abuser subjects, such as schizoid/schizotypal personality traits, alcohol dependency, antisocial personality disorders and major depression, all can be psychosis induced by methamphetamine5. 4. History of sexual abuse experience, recent higher occasion of MethAmphetamine(MA) abuse plus another illicit substance13. 5. Childhood Attention Deficit Hyperactive Disorder (ADHD) may be associated frequently with psychosis reports14. 6. Higher serum level of methamphetamine and amphetamine are associated with more

profound psychotic symptoms4. The route of consumption (oral, smoking, injection) was not a significant factor in Mc Keit et al study6. But according to Matsumoto et al. smoker abuser show more quickly acute psychotic symptoms than who use the injection, because smokers have poor control on MA consumption. In addition psychotic syndromes in injection abusers require more medical care to respond to treatment15.

Other personal characteristics such as age at which abuse is started, education, IQ, and duration of methamphetamine use were not associated significantly with risk of psychosis developing among abusers8. Female preponderance for undergoing psychotic symptoms was established among participant persons in the study of Mahoney and his coleagues16.

It is noticeable to mention that the results of studies on MIP characteristics are somewhat inconsistent because of different cultural population, different accuracy in methods of studies and so on. But they provide 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 Japan17, Taiwan5, Australia6, Tailand18 and Iran9 all are unanimous in obtained results. The most common features include 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 symptoms10. 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 injectioners19 and or 5. 2 years without considering route of abuse10. Individuals with intense eagerness20, injection of methamphetamine and methamphetamine abusers are at higher risk for experiencing more severe psychosis21. Although MIP usually have short courses duration but longer and persistent episodes of psychosis have been reported even after discontinuation of drug abuse and in abstinence period17. As protracted MIP frequently occurred in many studies, it remains unclear whether methamphetamine can produce a chronic psychotic disorder or methamphetamine has uncovered a psychotic disorder in a patient with psychotic background5. 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 disability2. During the abstinent period, MIP relapse might occur in a previously undergone short MIP, as well as any stressor like 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 1week to 1 month respectively, after re-exposure to MA8.

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

MIP Treatment pharmacological approaches

Although no medical agent(s) are approved as therapeutic drug for MIP yet, due to a few numbers of pharmacological evaluations which have been proformed 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 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 dependency25. It may have beneficial effect in schizophrenia and thereby in MIP. 26, 27

Bupropion, a re-uptake inhibitor of dopamine has demonstrated its effect as decreasing methamphetamine use specially in low to moderated dependency. 28, 29, 30

Methylphenidate (Ritaline) and Dextroamphethamine (d-amphethamine) both increase releasing of dopamine in synaptic cleft and have high capacity to be abused. They show 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, but it seems that appetite decreasing for MA use occur by these drugs, which can be indirectly effective for managing MIP 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 for 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 are able to significantly decrease the MIP severity, however rispridone causes showed more reduction on positive symptoms while aripiperazole was more effective on negative symptoms. 36 The ability of antipsychotics like 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 can diminish behavioral sensitization through acting on 5-HT1A receptor. 38

Risperidone is evaluated solely for its ability to prolong abstinent period in 4 weeks administration of 3. 6mg/day in an open-label trying. Results demonstrate 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 like administrating the haloperidol to GABAergic cells in subchronic treatment of MIP might lead to hyperkinetic movement disorder and convulsion42.

Other antipsychotics like quetiapine and olanzepine were applied successfully for drug– induced psychosis. 43, 44

GABAergic agents

Several different GABA agents like baclofen45, gabapantine45, 46, vigabatrine47, 48, topiramate49 and benzodiazepines were proposed for treatment of MA dependency and associated psychosis based on their effects on decreasing the dopamine transmission in mesolymbic system by which reinforcing effects of MA is reduced. 50, 51 But , actually conducted trial studies are somewhat inconsistent to suggest a precise recommendation. 49, 52 Nevertheless Ito K et al. showed that clonazepam in animal model experiments 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 found in web published searching except for two animal experiments in which the role of serotonergic receptors are evaluated in locomotor activating and developing behavioral sensitization. Kaneko et al. studied the inhibitory effect of fluoxetine and paroxetin, 2 clinically available SSRI agents, on establishing and expression of MA induced

behavioral sensitization and suggested a prophylactic role of SSRIs for preventing of psychotic states like 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 osemozotan a 5-HT1A-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 is prevented by induction and expression of naltrexone in mice. 62

But naltrexone plus N-acetylsysteine, an antioxidant, fail to demonstrate priority to placebo group for MA dependency treatment. 63 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. 64, 65

Electroconvulsive therapy (ECT) is mentioned for its high capacity to create a dramatic response in a MIP cases whose psychotic symptoms were resistant to conventional pharmacological antipsychotic therapy. 66

Discussion

Methamphetamine abuse is now going to become an epidemic problem in many countries. Chronic MA abuser underwent many medical psychiatric cognitive and legal consequences. One of the most important complications is the psychosis. Many studies were performed and a plenty of pharmacological drugs were proposed for managing of MA dependency, although none of them were approved yet, but only a few investigations tried to find drugs targeted on psychosis due to MA. These drugs as reviewed in this articles belongs to different biochemical neurotransmitters like dopaminergic antipsychotics, serotonergic agents and GABAergic drugs. All the studied drugs failed to obtain approval validity, although 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 that can elevate knowledge about developing MA-induced psychiatric

syndromes, especially psychosis, is the best way to overcome MIP pharmacologically and is recommended strongly for future studies.