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Methamphetamine Psychosis: Epidemiology and Management

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Abstract

Psychotic symptoms and syndromes are frequently experienced among individuals who use methamphetamine, with recent estimates of up to approximately 40% of users affected. Though transient in a large proportion of users, acute symptoms can include agitation, violence, and delusions, and may require management in an inpatient psychiatric or other crisis intervention setting. In a subset of individuals, psychosis can recur and persist and may be difficult to distinguish from a primary psychotic disorder such as schizophrenia. Differential diagnosis of primary versus substance-induced psychotic disorders among methamphetamine users is challenging; nevertheless, with careful assessment of the temporal relationship of symptoms to methamphetamine use, aided by state-of-the art psychodiagnostic assessment instruments and use of objective indicators of recent substance use (i.e., urine toxicology assays), coupled with collateral clinical data gathered from the family or others close to the individual, diagnostic accuracy can be optimized and the individual can be appropriately matched to a plan of treatment. The pharmacological treatment of acute methamphetamine-induced psychosis may include the use of antipsychotic medications as well as benzodiazepines, although symptoms may resolve without pharmacological treatment if the user is able to achieve a period of abstinence from methamphetamine. Importantly, psychosocial treatment for methamphetamine dependence has a strong evidence base and is the optimal first-line treatment approach to reducing rates of psychosis among individuals who use methamphetamines. Prevention of methamphetamine relapse is the most direct means of preventing recurrence of psychotic symptoms and syndromes. Long-term management of individuals who present with recurrent and persistent psychosis, even in the absence of methamphetamine use, may include both behavioral treatment to prevent resumption of methamphetamine use and pharmacological treatment targeting psychotic symptoms. In addition, treatment of co-occurring psychiatric disorders including depression and anxiety is important as a means of preventing relapse to methamphetamine use, which is often triggered by associated symptoms.

1. Introduction

Studies of drug abuse trends in the Western U.S. indicate that methamphetamine (MA) use is a significant public health concern. According to the 2012 National Household Survey on

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Drug Abuse approximately 1.2 million people (0.4 percent of the population) reported past-year use of MA, and 440,000 (0.2 percent) reported using it in the past month [1]. Moreover, MA use is not only a problem in the United States, but is a growing concern in the global population. According to the World Drug Report set forth by the United Nations Office on Drugs and Crime, approximately 0.7% of individuals aged 15–64 years old worldwide (33.8 million people) reported using an Amphetamine Type Stimulant (ATS) in 2010, with MA being the most frequently used substance in its class [2], MA production and supply also appears to be on the rise [2], with more potent forms of MA increasingly available at lower cost [see 3]. Although rates of MA use have decreased from previous years (e.g., 0.3 percent reported past-month use in 2006), important vulnerable subgroups remain at risk for the development not only of MA use disorders but the severe and potentially debilitating psychiatric complications associated with MA use. Among the characteristics associated with heightened risk of MA use disorders are: residence in rural areas [e.g 4], Hispanic and Asian ethnicities [5], and, among males, gay or bisexual sexual orientation [6].

MA-related psychiatric symptoms are common, and include irritability, anxiety, psychosis, and mood disturbances [7]. Prominent psychotic symptoms among MA users include auditory and tactile hallucinations, ideas of reference, and paranoid delusions [7,8], and violent behavior is frequently linked with the latter [see 9]. Such symptoms and associated syndromes often produce progressive social and occupational deterioration as well as poor treatment outcomes [e.g., 10,11]. Because of the various etiologies that can give rise to psychotic symptoms and syndromes among individuals using MA, the clinical diagnosis and conceptualization of psychosis in MA users can be quite challenging. While psychotic symptoms are among the known possible consequences of MA use irrespective of any prior history of psychosis [8,12], use of MA among those with genetic vulnerability to psychosis or pre-existing psychotic disorders such as schizophrenia can lead to the onset or exacerbation of such conditions, respectively [see 13]. In light of these findings, coupled with research demonstrating greater levels of impairment, disability, and health service utilization among stimulant users with concomitant psychotic disorders [e.g., 14] clinical guidelines to facilitate accurate diagnosis and inform treatment considerations for MA-induced and substance-independent psychotic illnesses among MA users may have great utility. In this article, we explore the risk factors, clinical features, and differential diagnostic considerations for understanding MA psychosis. We then highlight important prevention and treatment implications for individuals whose psychosis is transient (but who remain at risk for persistent psychosis) as well as those with a more pervasive, recurrent, or chronic presentation of psychotic symptoms.

Articles for inclusion in this review were identified through an extensive literature search conducted in April 2014 (and repeated in September of 2014) in PubMed and national survey databases. Search terms included “methamphetamine (or “amphetamine,” when appropriate),” “psychosis,” and domain specific terms such as “epidemiology,” “treatment,” “genetics,” “diagnosis,” and “risk factors.” Extant diagnostic and other clinical guidelines available in the U.S. and internationally were reviewed. Efforts were made to incorporate the most recent reports and reviews in the field to provide an updated summary of the current knowledge about diagnosis and treatment of MA psychosis.

2. Clinical Features of Psychosis in Methamphetamine Users

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [15], an episode of psychosis that occurs in the context of MA (or other substance) use can be considered a primary psychotic disorder (eg., schizophrenia) under the following conditions: (1) symptoms are substantially in excess of what would be expected given the type or amount of substance used or the duration of use; (2) there is a history of psychotic episodes that are not substance-related; (3) psychotic symptom onset precedes the onset of substance use; (4) psychotic symptoms persist for at least one month after the cessation of intoxication or acute withdrawal [15]. By contrast, the presence of a substance-induced psychotic disorder is diagnosable when the following symptoms are present: (1) Presence of prominent hallucinations or delusions; (2) Hallucinations or delusions develop during, or soon after, intoxication or withdrawal from a substance or medication known to cause psychotic symptoms; (3) Psychotic symptoms are not actually part of a psychotic disorder (such as schizophrenia, schizophreniform disorder, schizoaffective disorder) that is not substance-induced (i.e., if psychotic symptom onset was prior to substance or medication use, or persists longer than one month after substance intoxication or withdrawal, then another psychotic disorder is likely); (4) Psychotic symptoms do not only occur during a delirium. Likewise, the criteria used outside of the U.S., based upon the International Classification of Diseases diagnostic system (ICD-10), distinguish substance-induced psychotic symptoms from schizophrenia as follows: “Schizophrenia is a disorder that is characterized by at least one psychotic symptom (or two symptoms if not clear cut) that last for more than a month, and is not related to drug intoxication or withdrawal” [16]. Despite the tendency in some countries to avoid assigning a diagnosis of schizophrenia in certain cases of long-term psychosis with onset in the context of MA use (e.g., Japan), the international diagnostic approach to distinguishing these syndromes is similar to that utilized in the United States. Importantly, according to both criteria sets, a psychotic disorder is not diagnosed when the observed symptoms are consistent with the expected effects of intoxication or withdrawal from a given substance; as such, transient psychotic symptoms, observed in up to 40% of MA users [17] do not constitute a diagnosable psychotic disorder. A MA-induced psychotic disorder is diagnosed when the observed psychotic symptoms exceed the known and expected effects of intoxication or withdrawal from MA. Given that MA use has been associated with longer-term, persistent psychosis in some users, this diagnostic entity has been a source of clinical controversy [18,19]. Nevertheless, as discussed further below, even transient psychotic symptoms may require pharmacological management when accompanied by acute agitation, violent behavior, or otherwise severe distress and impairment in functioning.

2.1 Relevance of discerning clinical features for developing a plan of care

Clinically, distinguishing between individuals with primary psychotic disorders and substance-induced psychotic syndromes may have important implications for treatment planning. Although a psychotic clinical presentation may be explained by numerous possible etiologies (i.e., primary psychosis triggered or exacerbated by substance abuse, substance-induced psychosis in the absence of an underlying primary psychosis), the signs and symptoms that correspond to these different etiologies are often identical. Nevertheless, a

plan of care to effectively treat a patient with a primary diagnosis of psychosis who uses MA will be markedly different than that for a MA user who developed acute and transient psychosis exclusively in the context of use. For an individual with primary psychotic disorder, core components of treatment will include: (a) longer-term neuroleptic medication use, and (b) comprehensive case management and other psychosocial services to stabilize and optimize functioning, such as vocational rehabilitation, psychotherapy, family interventions, and housing [20]. For a MA user with acute and transient psychosis, the intervention approach will be more focused on psychosocial treatment for the MA use disorder, preventing relapse and recurrence of psychotic symptoms, and psychoeducation concerning the MA use-psychosis relationship. Likewise, accurate diagnosis, particularly during the early stages of psychotic disorder onset, can have a profound impact on treatment outcome and, importantly, minimizes the likelihood of medical mismanagement [see 21,22], including unnecessary exposure to neuroleptics or other antipsychotic medications [e.g., 23] or failure to treat potentially harmful withdrawal syndromes due to the effects of another substance, such as alcohol [e.g. 24].

Although the course and outcomes of MA users with co-occurring psychosis is highly variable, it is clear that behavioral treatment addressing stimulant use is indicated for any psychotic patient with a MA use disorder. This recommendation is supported by recent evidence of a dose-response relationship between MA use and psychotic symptoms, with a five-fold increase in the odds of psychotic symptoms in the presence of MA use [25]. In light of the robust finding of a MA use-psychotic symptom association, it has been argued that behavioral treatment for MA dependence comprises the optimal first-line treatment approach to reduce rates of psychosis in MA using populations. Evidence-based behavioral interventions targeting stimulant addiction, such as the Matrix Model (which combines cognitive behavioral therapy [CBT] with family education and self-help participation), effectively engage psychotic MA users in treatment, and reductions in MA use among individuals with psychotic disorders are comparable to those observed among MA dependent adults without psychosis [10]. In terms of treatment outcomes, MA users with psychosis appear to differ most notably from those without psychosis in their high rates of health service utilization, including costly hospitalizations [10,14]. As such, matching diagnosis with treatment is likely a means of effectively addressing both acute and chronic forms of psychosis among MA users, and concurrently minimizing costs associated with health service utilization.

3.-Clinical Correlates of Methamphetamine Psychosis

Research into the nature of the relationship between amphetamines and psychosis has spanned more than 40 years, with many unanswered questions remaining concerning etiology, chronicity, and determinants of clinical course. Nevertheless, a combination of observational, experimental, and clinical research studies have advanced our fundamental understanding of the clinical features, risk factors, and course of psychosis among MA users. The earliest observational studies of amphetamine psychosis described predominant symptoms including paranoid ideation, ideas of reference, delusions of persecution, auditory and visual hallucinations [26,27]. Subsequent studies, in which amphetamine psychosis was experimentally induced via laboratory administration in healthy subjects, showed that

psychosis could develop anywhere from 1 to 5 days following initiation of hourly intravenous administration of d-amphetamine [28]; among individuals with a history of intravenous amphetamine use, oral administration of amphetamine at 6 hour intervals produced psychotic symptoms within 36 hours [29]. Notably, in subsequent replications of these studies in which the dosing schedules, substance administered (i.e., amphetamine versus MA), route of administration (oral versus intravenous), and populations (i.e., healthy volunteers versus individuals with a history of amphetamine use disorders) varied, the most consistent observations were that (1) some, but not all participants developed symptoms of psychosis; (2) the dose that triggered psychosis onset was variable; and (3) the most frequently observed psychotic symptom was paranoia, accompanied by ideas of reference which progressed, in some individuals, to well-formed delusions [30–32].

The observation that a subset of individuals who use amphetamines may develop psychotic symptoms, coupled with the variability in dose-related effects of amphetamine use on psychosis [33,34], raises important questions about the factors that confer risk or vulnerability to psychotic symptoms in MA users. Likewise, despite evidence that binge use of MA is associated with psychosis [33,35], as suggested in a recent review [19], this may be explained by characteristics of the binge episode (e.g., quantity used, binge duration), individual risk factors for psychosis, or some combination thereof. Studies of putative risk factors have examined psychological, genetic, and drug use variables, each of which has been shown to contribute to the variability in psychotic symptom onset and duration.

In a series of studies, life history of MA use was examined in relation to MA psychosis among over 200 inpatients. The researchers concluded that years of lifetime MA use may distinguish two forms of MA psychosis, with a more persistent subtype lasting more than one month (i.e., the “delayed lasting type”) associated with 5 or more years of MA use history [36,37]. Similarly, Sato [38] described two psychotic subgroups, Type A and Type B with those in the more persistent category, “Type B,” experiencing symptoms of longer duration, putatively mediated by the neurobiological effects of chronic MA use across dopaminergic and non-dopaminergic neural systems. Indeed, the onset and persistence of psychosis have been linked not only with the effects of amphetamines on dopaminergic activity [39,40], but serotonergic activity and neurotoxicity [41].

3.1 Psychiatric and Genetic Risk Factors

Apart from chronicity of MA use patterns, a number of studies have shown that psychological vulnerability predisposes some individuals to develop acute psychotic symptoms and syndromes in response to MA. Not surprisingly, individuals with schizophrenia, schizoaffective disorder, and schizotypal personality have been found to be at heightened risk for the development of MA psychosis [41–44]. Nevertheless, the contribution of a MA use disorder to the user’s risk for psychosis remains significant; even after controlling for history of schizophrenia and other psychotic disorders, MA users who meet criteria for dependence are 3 times more likely to experience psychotic symptoms, relative to MA users who are non-dependent [41]. Likewise, a review of recent studies of the MA use-psychosis association reported that between 26% and 46% of individuals with MA dependence have MA psychosis [45]. Other risk factors for MA psychosis include polydrug

use [41] and additional psychiatric comorbidities, particularly affective disorders and antisocial personality disorder, as well as family psychiatric history [12,41,45–48]. Among those who develop psychosis, route of administration of MA has been found to impact the latency from first use of MA to the onset of psychosis, with one study reporting a latency of 1.7 years among MA smokers, relative to a 4.4 year latency among injectors [49]. Although injection use of MAs is more commonly associated with greater severity of psychiatric complaints and disorders, as noted by Matsumoto and colleagues, smoking MA does not appear to be protective in regards to the risk of precipitating psychosis, relative to injection use.

Sleep deprivation, which is commonly associated with MA binge episodes and may exacerbate psychiatric symptoms, has also been cited as a putative contributory factor in MA psychosis [19].

There is generally good consensus that MA psychosis shares so many clinical features with paranoid schizophrenia that the two conditions are often indistinguishable. Indeed, factors associated with susceptibility to schizophrenia appear to similarly predict MA psychosis. Moreover, the degree of familial loading for schizophrenia is predictive of MA psychosis onset and duration [47]. According to this line of research, first-degree relatives of individuals with MA psychosis are more than 5 times more likely to have schizophrenia, relative to MA users who did not develop psychosis. In addition, individuals with underlying primary psychotic disorders have substantially higher rates of illicit drug use, including amphetamines [50,51].

To date, seven candidate genes have been identified that may be associated with MA psychosis [see 44]. These genes appear to confer susceptibility not only to MA psychosis but also to poorer clinical course in the context of this diagnosis. Notably, evidence suggests substantive overlap between markers of genetic vulnerability to MA psychosis and schizophrenia (which is considered to be pharmacologically similar to MA psychosis), further complicating the distinction between these two conditions.

3.2 Duration

In the earliest observational and experimental studies of MA psychosis, the recovery period on average was reportedly within one week [28,30,52,53]. Nevertheless, in a sizable subset of individuals, what is initially diagnosed as a MA-induced psychosis “converts” over a period of years into a primary psychotic disorder, with symptoms present over periods of 6 months or longer, even in the absence of MA use [54–56]. The DSM–5 defines substance-induced psychosis as that preceding the onset of substance use or persisting for less than one month after acute substance withdrawal or intoxication [15]; as such, a primary diagnosis of psychotic disorder (e.g., schizophrenia, Psychotic Disorder NOS) would be assigned to any individual for whom symptoms are sufficient to meet the threshold for a psychotic syndrome diagnosis. However, based on emerging Japanese literature, a rigid 1-month cutoff may not be applicable in some cases of MA-related psychosis that may be longer in duration, yet not appropriate for classification as a schizophrenia-spectrum disorder. In a large sample of over 1,000 MA users in Thailand who had experienced at least a single episode of MA-induced psychosis, within 6 years of the first reported episode, nearly 40% had been diagnosed with

schizophrenia due to persistent psychosis [57]. Notably, two smaller studies reported very similar rates of persistent psychosis in the absence of MA use (i.e., 16% and 17% of MA users continued to experience psychosis after 1 and 3 months of abstinence, respectively) [12,47]; in both of these studies, those with persistent psychosis had no prior episodes of psychosis nor any family history of schizophrenia. Two competing theories have been posited to explain the robust finding that psychosis can become chronic and persistent among MA users: either a pre-existing schizophrenia may be unmasked or triggered by MA use, or MA psychosis may share a very similar clinical course to that of schizophrenia [58]. While the latter is supported largely by Japanese studies, in which investigators describe a prolonged MA psychosis observed even among individuals without psychiatric risk factors or history, the notion of "latent schizophrenia," expressed in response to MA use as a triggering event, is increasingly recognized as a Western theory [18]. A third, more recently proposed integrated theory contends that MA psychosis and primary psychosis are not distinct diagnostic entities, but rather fall along a continuum of psychosis. According to this model, the MA-psychosis association is understood within the framework of a stress-vulnerability paradigm; as such, the potential for an individual to develop psychosis both in the context and absence of MA use (for those with prolonged psychotic symptoms following cessation) is a function of one's vulnerability [19]. The clinical implications of each of these theories are quite similar, nevertheless, necessitating the following practices: (a) close monitoring for the development of chronic or recurrent psychosis among those who present transient symptoms; (b) possible pharmacological management of acute symptoms, and (c) behavioral treatment and psychoeducation addressing MA use and its association with psychosis.

3.3 Recurrence

The recurrent nature of MA psychosis is another feature that is similar to the clinical course of schizophrenia. In a review of studies relating to the first and second epidemics of MA abuse in Japan, Sato [59] reported that during the second epidemic, nearly 50% of those admitted to the hospital for MA psychosis had experienced this condition previously with the most extreme cases having been readmitted for treatment of MA psychosis more than 10 times. A number of studies have examined risk factors for recurrent MA-induced psychoses, with identified triggers including MA use or resumption of use [38], even in relatively small amounts following protracted abstinence [60], other substance use [61], including heavy alcohol use, even in the absence of MA use [54,59,62]; sleep deprivation [63], and psychosocial stressors [62,64]. When MA use triggers re-currence of psychosis, the symptom presentation tends to remain the same as in prior episodes [59]. Moreover, under these conditions, the latency from MA use to psychosis onset can be remarkably brief (i.e., within less than a week), relative to that observed in the initial MA-induced psychosis episode [38,59]. The propensity for MA use to trigger psychosis among individuals who have previously experienced psychotic symptoms can persist for years [54], and has been described as a MA "sensitization" or "reverse-tolerance" effect.

4. Differential Diagnosis

Clinically, the most straightforward means of distinguishing substance-induced psychosis from another (i.e., substance-independent) psychotic disorder is through careful assessment of the temporal relationship of substance use and the onset of psychosis. Among the most common reasons for diagnostic uncertainty when evaluating the differential diagnosis between a primary psychotic disorder and a stimulant-induced psychosis are: an insufficient period of abstinence from which to evaluate the role of stimulant use in the symptom presentation, inconsistencies in patient reports, and poor recall [65]. As such, diagnostic accuracy can be bolstered by the use of multiple sources of clinical data, including interviews with collateral sources of information (e.g., family or other individuals with whom the patient is close) concerning patterns of stimulant use and psychosis onset, review of medical records, collection of objective indicators of stimulant use (i.e., urine tests), clinical observations, and structured interview assessments with the patient (in which information is gathered concerning lifetime history as well as current substance use, detailed description of presenting symptoms, and temporal relationship between current substance use and psychotic symptoms). Optimally, these sources can be combined to enable the clinician to understand the timing and course of stimulant use and psychotic symptoms. Given the complexity of the MA use-psychosis association, however, there are inherent limitations to diagnostic certainty even when collateral sources are available. For example, the outcome of a urine drug screen does not confirm the etiology of psychosis [66]. Moreover, given that a subset of MA using individuals will experience longer lasting psychotic symptoms even after cessation of use, collateral data concerning patterns of use and remission from MA are useful, but not necessarily confirmatory concerning etiology diagnostic process.

The Psychiatric Research Interview for Substance and Mental Disorders (PRISM), a well-validated semi-structured interview that was developed to optimize the accuracy of differential diagnostic assessment of substance-induced versus substance-independent or “primary” psychiatric disorders [67], has been found to have excellent reliability for psychotic disorder diagnoses among individuals with alcohol and/or drug use disorders. The features of this state-of-the-art assessment instrument are described here to exemplify clinical methodology that can be used to facilitate diagnostic accuracy when evaluating a MA user who presents with psychosis. First, prior to probing patients concerning specific psychotic symptoms, the interviewer develops a timeline of drug and alcohol use history, detailing periods of use of substances and abstinence. Among the timeline follow-back methods used to establish an accurate history is the use of major life events, holidays, treatment episodes, and other meaningful temporal anchor points from which to support recall. Second, using an a priori definition of heavy alcohol or drug use (i.e., 4 or more use episodes per week), primary psychiatric disorders are defined as those that occur in the absence of heavy substance use. As such, a primary psychotic disorder such as schizophrenia can: (1) occur exclusively and entirely during a period of abstinence or less than heavy substance use; (2) begin prior to a period of heavy substance use; or (3) begin during a period of heavy substance use and persist beyond the withdrawal period (i.e., for more than 4 weeks following cessation of use). If psychotic symptoms occur exclusively

during a period of heavy alcohol or drug use or withdrawal, and are sufficiently severe to fulfill DSM-IV-TR criteria for the disorder, then a substance-induced psychosis is diagnosed.

Apart from examining the temporal relationship of psychotic symptoms to MA use based upon patient self-report combined with collateral family/significant other interview data, urine toxicology data can be useful, particularly for clinicians who do not routinely work with MA users. Objective diagnostic instruments, other than the PRISM, that may be used to differentiate between primary and MA-induced disorders include the Diagnostic Interview Schedule (DIS) [68] and the Composite International Diagnostic Interview (CIDI) [69], both of which probe the patient directly concerning the potential role of substance use in psychiatric symptoms. By contrast, like the PRISM, the Structured Clinical Interview for DSM-IV (SCID) [70] relies upon clinician judgment concerning the role of substance use in the etiology of psychotic symptoms. Importantly, both of these well-validated and reliable instruments operationalize the concept of symptoms that are greater than the expected effects of MA (or other substance) use. Samet and colleagues [71] provide a comprehensive discussion and comparison of structured interview approaches to diagnosing comorbidity. Of note, though the practice of gathering and interpreting temporal data concerning the concurrence of psychotic symptoms with MA use is a strength of the structured clinical interview approaches described in this section, a limitation that is common to these instruments is their reliance on self-report.

Though determining psychosis etiology among MA users is challenging and can be uncertain even with careful assessment, accurate matching of psychosis diagnosis and treatment plans or services optimizes outcomes; as such, gathering and synthesizing clinical information to arrive at the most accurate differential diagnosis possible is important.. Schizophrenia can be easily misdiagnosed among individuals with metamphetamine-induced psychosis, with potentially harmful consequences of the resulting treatment approach; namely, prolonged or unnecessary exposure to neuroleptics [72,73]. Ideally, treatment of individuals with co-occurring psychosis and MA use should address both the psychotic symptoms or disorder (i.e., including ongoing psychiatric evaluation and treatment as indicated) and the MA use disorder, to facilitate sufficient periods of abstinence to facilitate the clinician make an informed differential diagnosis.

5. Treatment

5.1 Treatment for acute methamphetamine psychosis

Because large randomized clinical trials of pharmacotherapeutic regimens for the treatment of acute MA psychosis have not been conducted, recommendations are not sufficiently conclusive to form evidence-based clinical guidelines. Guidance for clinical practice can be drawn from case studies, a number of which report the use of antipsychotics including risperidone and olanzapine for management of acute MA-induced psychotic symptoms [38,74–76]. Likewise, laboratory-induced psychotic symptoms in response to amphetamine administration have been shown to be effectively blocked by antipsychotics [e.g., 77]. Though only one clinical trial met criteria for inclusion in the 2009 Cochrane review of treatments for amphetamine psychosis [78], this small randomized trial (N=58) found both olanzapine and haloperidol to be efficacious in treating psychotic symptoms, with

significantly better tolerability and fewer extrapyradimal symptoms associated with the use of olanzapine [79]. Likewise, in a more recent randomized clinical trial comparing haloperidol to quetiapine for MA psychosis, both neuroleptics were tolerable and efficacious, with remission of psychosis observed in a significant majority of the participants, regardless of the particular neuroleptic administered [80]. As recently pointed out by Bramness and colleagues [19]; however, the increased anhedonia putatively produced by antipsychotic action of blocking the DRD2 receptor may heighten vulnerability to MA relapse, a premise with some supportive clinical evidence [81–83]. Moreover, at least one preclinical study identified a potential MA-haloperidol interaction producing GABAergic cell death, which in turn, could heighten the risk of seizures and hyperkinetic movement disorders [84]. On the other hand, there may be some protective effects of neuroleptics against MA-induced toxicity [85,86]. As such, while there is some limited support for the use of antispsychotics to manage acute agitation and psychosis among stimulant users, the associated risks must be taken into account and weighed against the benefits of this approach [see 87]. Moreover, the remission of psychotic symptoms within 1 week of abstinence from MA has been reported across a number of studies, suggesting that for a large majority of those who present with these symptoms, they may resolve without pharmacological intervention.

Of note, little is known about the safety and efficacy of antipsychotics for children and adolescents with MA-induced psychosis, and a sizable subgroup of those who present with first-episode MA psychosis fall into this age range [88]. Adolescents and children appear to be especially vulnerable to adverse effects of antipsychotic medications, and evidence suggests that they experience these effects more frequently and in a more severe form than that observed among adults [89]. As such, it is imperative that careful consideration of the risks and potential benefits of the use of these medications be undertaken prior to prescribing them to youth with psychotic disturbances secondary to MA use.

MA-related psychosis is commonly accompanied by other psychiatric symptoms including anxiety, agitation and insomnia. When a MA user presents to medical or ED setting with evidence of intoxication and agitation, a common initial approach is to provide calm reassurance and “talk down” the individual in a quiet environment to minimize stimulation. If clinically indicated, short-term anxiolytics (i.e. benzodiazepines) or sleep medications may be prescribed to target anxiety and agitation, or insomnia, respectively. Benzodiazepines may be used in conjunction with antipsychotics to reduce severe symptoms of agitated psychosis [e.g., 78,79]. Medication doses may have to be administered every several hours until acute symptoms remit. Of note, clinical guidelines concerning the use of pharmacological interventions for MA-related psychosis as described here are consistent both in and outside of the U.S [90].

5.2 Psychosocial treatment for methamphetamine psychosis

Research studies have demonstrated the benefits of CBT in the treatment of both psychotic disorders and MA use disorder. The Matrix Model incorporates principles of CBT in individual and group settings to reduce MA use and facilitate abstinence through implementation of relapse prevention skills including drug avoidance, identification of

triggers, and drug refusal [91,92]. The Matrix Model has been evaluated both as a stand-alone 16-week treatment for MA users and as the behavioral treatment platform in medication trials for MA dependence [93]. The results of these clinical trials indicate that both as a primary treatment approach and as an augmenting strategy to potentiate the effects of addiction pharmacotherapy, the Matrix Model intervention has strong evidence of efficacy for MA users in reducing substance use and improving functional outcomes.

CBT principles may be adapted to target multiple psychiatric disorders and symptoms, and emerging evidence supports the use of CBT to manage psychotic symptoms associated with schizophrenia; according to a recent meta-analysis, CBT targeting psychosis confers benefits over and above the effects of antipsychotic medications, particularly for those who are medication resistant [94]. Though the use of CBT has not been formally studied as a treatment for MA-induced psychotic disorder, CBT principles used to ameliorate or cope with psychotic symptoms associated with other psychotic disorders, such as self-monitoring of psychotic symptoms, thought challenging, and pleasure predicting, may also be applied to MA-associated psychosis.

5.3 Long-term treatment

Long-term treatment of individuals with MA-induced psychosis should focus on abstinence from MA to prevent future episodes of psychosis. Psychosocial treatment in the form of CBT may be a valuable tool to strengthen relapse prevention skills. Other evidence-based psychosocial treatments, including contingency management (CM) to reduce MA use may also be considered. CM involves the use of rewards, such as cash payment or vouchers, to reinforce desired behaviors such as MA-negative urine drug screens or treatment attendance and has been demonstrated to significantly reduce MA use, with optimal efficacy associated with longer intervention duration [95]. Attendance at 12-step meetings (e.g., Alcoholics Anonymous, Narcotics Anonymous) may be beneficial to strengthen one’s support network and promote motivation for abstinence. If clinically indicated, psychiatric medications may be prescribed to manage comorbid conditions such as major depression, anxiety disorders, or persistent psychotic disorders. Given that negative affect states, such as depression or anxiety have been demonstrated to increase relapse risk and worsen treatment outcomes among MA users (see Glasner-Edwards, [11,96]), amelioration of persistent symptoms with psychosocial treatment or pharmacotherapy is important in individuals with co-occurring addiction and mental health disorders. Lastly, though no medications have been FDA approved for the treatment of MA use disorder, several medications have shown preliminary benefit in reducing MA use in some studies, including bupropion[93] naltrexone [97], mirtazapine [98], and methylphenidate [99].

6. Conclusions

Psychosis is commonly associated with MA use. In this article, we highlight core issues in the clinical conceptualization of psychotic symptoms and syndromes among MA using populations, for whom transient psychotic symptoms are commonly observed. Key considerations in clinical conceptualization are summarized as follows. The presence of transient psychotic symptoms, observed in a sizable proportion of MA users, does not

constitute a psychotic disorder. A diagnosable psychotic *disorder*, whether or not it is considered to be MA-induced, must comprise symptoms that *exceed* the expected effects of intoxication or withdrawal from MA. Differential diagnostic questions concerning the etiology of a psychotic syndrome among MA users most typically arise when psychotic symptoms with onset in the context of MA use persist for longer than a month following cessation of MA use or when symptoms recur in the absence of MA use. One of the central questions in the debate about how to conceptualize persistent psychosis among individuals with current or past MA use concerns the diagnostic categorization of such syndromes. Whereas the Japanese scientific literature refers to observations of persistent psychosis among MA users as a prolonged MA psychosis observed in a subset of users, U.S.-based studies point to a possible latent, and primary schizophrenia diagnosis that may be activated, via a stress-diathesis process, in the presence of MA use. Regardless of etiology, several genetic, psychosocial, and drug use variables discussed in this review can act as risk factors for the onset and persistence of MA psychosis.

Though arriving at an accurate diagnosis is often challenging, several considerations and approaches to the psychodiagnostic process warrant mention. First, understanding the temporal relationship of MA use to psychotic symptoms is a powerful technique to aid diagnostic accuracy. To achieve this, gathering information from multiple sources is recommended, including patient self-report using a calendar or timeline method, obtaining collateral data from family or other loved ones with knowledge of substance use patterns and psychotic symptoms, review of medical records, and objective data concerning MA use (e.g., from urine assays). To facilitate a systematic approach to this diagnostic process, several validated structured and semi-structured interviews are recommended, including the PRISM and other temporally sensitive instruments.

Treatment implications of MA-related symptoms and syndromes will vary depending on the persistence of symptoms, chronicity of clinical course, and the extent to which symptoms are temporally anchored to MA use. For individuals with transient symptoms, though pharmacological intervention may or may not be indicated, psychoeducation around the MA use-psychosis association and psychosocial treatment addressing the MA use disorder are important as a means of preventing recurrent psychotic symptoms that may emerge if MA use persists. Determination of the need for pharmacological intervention for short-term psychosis will depend upon the extent of impairment, including agitation, associated violence, and other psychiatric symptoms including insomnia and anxiety. Neuroleptics may be used for short-term or long-term management of psychotic symptoms, with or without the use of benzodiazepines to control acute agitation. In the long term, whether the psychosis is diagnosed as a MA-induced psychotic disorder or the individual has co-occurring schizophrenia and a MA use disorder, evidence-based psychosocial treatments such as CBT should be utilized to facilitate abstinence and prevent relapse to MA use. When compared to an individual whose psychotic symptoms or syndrome is temporally related to MA use (i.e., a syndrome which resolves in between episodes of MA use), a core difference in the treatment of an individual with co-occurring MA use disorder and schizophrenia is the need for integrated treatment of both disorders, which should include intensive case management, comprehensive services including vocational rehabilitation, housing, individual psychotherapy, relapse prevention, and psychiatric services in efforts to prevent the

functional decline that is commonly observed among individuals with schizophrenia. Finally, treatment of co-occurring psychiatric disorders is important to prevent dysphoria, anxiety, and other symptoms that may predispose MA users to relapse.

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Key points

- Psychotic symptoms are among the known possible psychiatric consequences of methamphetamine (MA) use, can occur irrespective of any prior history of psychosis, and may, among vulnerable subgroups of MA users with risk factors for psychosis or pre-existing schizophrenia, lead to the onset or exacerbation of these conditions.
- Though challenging to diagnose accurately, differentiating between MA-related psychosis and primary psychotic disorders has important treatment implications, and may be aided by the use of temporally sensitive diagnostic interviewing procedures and collateral clinical information to understand the clinical course of the symptoms in relation to MA use.
- Because the use of MA greatly increases the risk of transient and recurrent psychosis, behavioral treatment for MA dependence is considered to be an optimal first-line treatment approach to reduce rates of psychosis in MA using populations.
- Clinical recommendations for current or chronic psychosis among MA users, regardless of etiology, will involve pharmacological treatment using neuroleptics, coupled with behavioral management and/or case management.