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REVIEW ARTICLE

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Methamphetamine-associated psychosis: Clinical presentation, biological basis, and treatment options

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Abstract

Introduction: Methamphetamine associated psychosis (MAP) represents a mental disorder induced by chronic methamphetamine use in a subset of users. The prevalence of the disorder has increased in several countries in Europe and Asia where methamphetamine use has increased. MAP remains difficult to distinguish from primary psychiatric disorders, especially schizophrenia, creating complications in prescribing treatment plans to patients.

Design: This narrative review sought to summarize difficulties related to MAP diagnosis and highlight the need for a better treatment model. Current best practices are described and potential novel therapies and future research suggested.

Results: Results suggest that clear biological and clinical differences appear between patients presenting with MAP and schizophrenia and that there may exist distinct subgroups within MAP itself. MAP-specific treatment studies have been few and have focused on the use of antipsychotic medication. Antipsychotic treatment has been shown to alleviate the psychotic symptoms of MAP but produce debilitating adverse effects and fail to adequately address methamphetamine use in patients.

Conclusions: Continued identification of subgroups within the heterogenous MAP population may lead to better diagnosis, treatment, and outcomes for patients. Psychosocial therapies should be explored in addressing the cooccurring substance use and psychosis in the treatment of MAP.

KEYWORDS

addiction, methamphetamine abuse, psychosis, schizophrenia, virtual reality (VR)

1 | INTRODUCTION

Methamphetamine represents a heavily abused illicit substance across the globe. Abuse has reached epidemic levels, presenting a serious and growing issue in a many countries across the globe (Alam Mehrjerdi, Barr, & Noroozi, 2013; Chomchai & Chomchai, 2015; Grant et al., 2012; McKetin, Baker, Dawe, Voce, & Lubman, 2017; Sulaiman et al., 2014; Wang et al., 2016). Methamphetamine can be administered orally, intravenously, or nasally to produce a euphoric high. Methamphetamine use causes reduction in appetite, inhibition of fatigue, and enhancement of mental acuity, mood, and social and sexual function (Shin et al., 2017). There are an estimated 24 million methamphetamine users worldwide, down from an estimate of 35 million in 2005 (Chomchai & Chomchai, 2015; Okazaki, Makinodan,

Yamamuro, Takata, & Kishimoto, 2016). Nonetheless, the prevalence of methamphetamine use has increased in both Europe and Asia, in countries such as the Netherlands, China, India, and Iran (Chomchai & Chomchai, 2015; Wang et al., 2016). More significantly, over 57% of the world's methamphetamine abusing population has been reported to reside in South East Asia (i.e., Thailand, Vietnam, Indonesia, Myanmar, Cambodia; Chomchai & Chomchai, 2015). It has been robustly demonstrated to produce psychotic symptoms in a subset of users in a condition known as methamphetamine-associated psychosis (MAP; Glasner-Edwards & Mooney, 2014; Grant et al., 2012).

MAP is often difficult to diagnose. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies a substance-induced psychotic disorder as the presence of hallucinations and delusions developed during, or soon after, intoxication or withdrawal from a substance or medication known to cause psychotic symptoms, such as methamphetamines, and the presence of psychotic symptoms not mediated by another nonsubstance-induced psychotic disorder that persists longer than 1 month after substance intoxication or withdrawal (American Psychiatric Association, 2013). The International Classification of Diseases diagnostic system (ICD-10) offers a similar definition (Organization, 2010). Nonetheless, controversy and confusion remain in distinguishing primary psychotic disorders from MAP (Glasner-Edwards et al., 2008). Many methamphetamine users report symptoms of psychosis. But, for most users, psychotic symptoms do not exist outside of methamphetamine intoxication and cannot be classified as a psychotic disorder (Iwanami et al., 1994). Clinicians can feel forced to decide between diagnosing psychoses arising from a primary psychotic illness or a secondary substance abuse disorder that may result in significantly different treatment plans and subsequent patient outcomes (Glasner-Edwards & Mooney, 2014).

MAP has been estimated to affect between 26 and 46% of people with a methamphetamine dependence (Grant et al., 2012). A recent meta-analysis of 17 studies produced a composite event rate for a methamphetamine-induced psychotic disorder of 36.5%, with the event rate reaching 42.7% when the period of assessment was lifetime and 43.3% when only individuals reaching the criteria for a methamphetamine use disorder were included (Lecomte, Dumais, Dugre, & Potvin, 2018). A recent cross-sectional study (n = 292) of methamphetamine dependent patients in Malaysia measured current and lifetime prevalence of psychosis and recorded a variety of sociodemographic and drug use data. A lifetime instance of psychosis was observed in 48% of subjects with 13% currently experiencing psychotic symptoms. Major Depressive disorder or antisocial personality disorder were both associated with a higher risk of psychosis, as was heavy comorbid drug use (Sulaiman et al., 2014). Variations in the instance rate have been associated with factors including individual vulnerability to psychotic disorder, severity and method of methamphetamine abuse, and significant methodological heterogeneity between studies (Fujii, 2002; Ujike & Sato, 2004).

Prior reviews by Grant et al., (2012) and Glasner-Edwards and Mooney (2014) have provided an effective summary of the body of literature on MAP up to the start of the current decade. Recent studies have worked to elucidate mechanisms controlling the etiology of MAP and to identify specific subgroups (e.g., transient and persistent) within the MAP population itself. A recent comprehensive review by Wearne & Cornish, (2018) has provided an effective comparison of symptom profiles within MAP and between MAP and schizophrenia (Glasner-Edwards & Mooney, 2014; Grant et al., 2012; Wearne & Cornish, 2018). Nonetheless, a paucity of research on the treatment of MAP remains to be addressed.

As such, the present review aims to address key findings and issues related to the diagnosis and treatment of MAP, using the best practices identified in the literature and the recommendations of the authors as experts in the management of psychosis and substance use disorders.

A Pubmed Database search was conducted between June and November 2018 using the search query, "(methamphetamine[mh] OR methamphetamine*[tiab]) AND (psychotic disorders[mh] OR psychosis[tiab] OR psychotic[tiab] OR psychoses[tiab])," and the "Best Match" sorting algorithm to yield 665 results. A secondary search of Google Scholar (n = 56) and the Cochrane Library (n = 36 for search term "methamphetamine psychosis") was also conducted to search for any additional articles. English-language articles describing the presence or treatment of psychoses related to methamphetamine-abuse in human subjects or describing biological mechanisms related to methamphetamine use and psychosis were included. Articles including a focus on addiction to substances apart from amphetamines were excluded. A total of 48 articles related to the etiology, treatment, and outcomes of MAP were identified in the literature search and have been reviewed in the sections below (Figure 1).

2 | CLINICAL PRESENTATIONS OF MAP

2.1 | Symptoms

Symptoms of MAP have been likened to paranoid schizophrenia, with subjects experiencing persecutory delusions, delusions of reference, and auditory hallucinations (C. K. Chen et al., 2003). Psychotic symptoms typically amplify over time with continued methamphetamine use (Ujike & Sato, 2004). Negative symptoms, such as anhedonia, avolition, and affective blunting typical of schizophrenic patients, are less common. The prognosis of MAP can be extremely heterogeneous and outcomes vary greatly.

2.2 | Onset

The onset of the disorder has been reported to range from 1.7 to 5.2 years after the start of methamphetamine use. The wide range in years is thought to be due to variations in the method, age at start, and intensity of methamphetamine use (C. K. Chen et al., 2005; Matsumoto et al., 2002; Ujike & Sato, 2004).

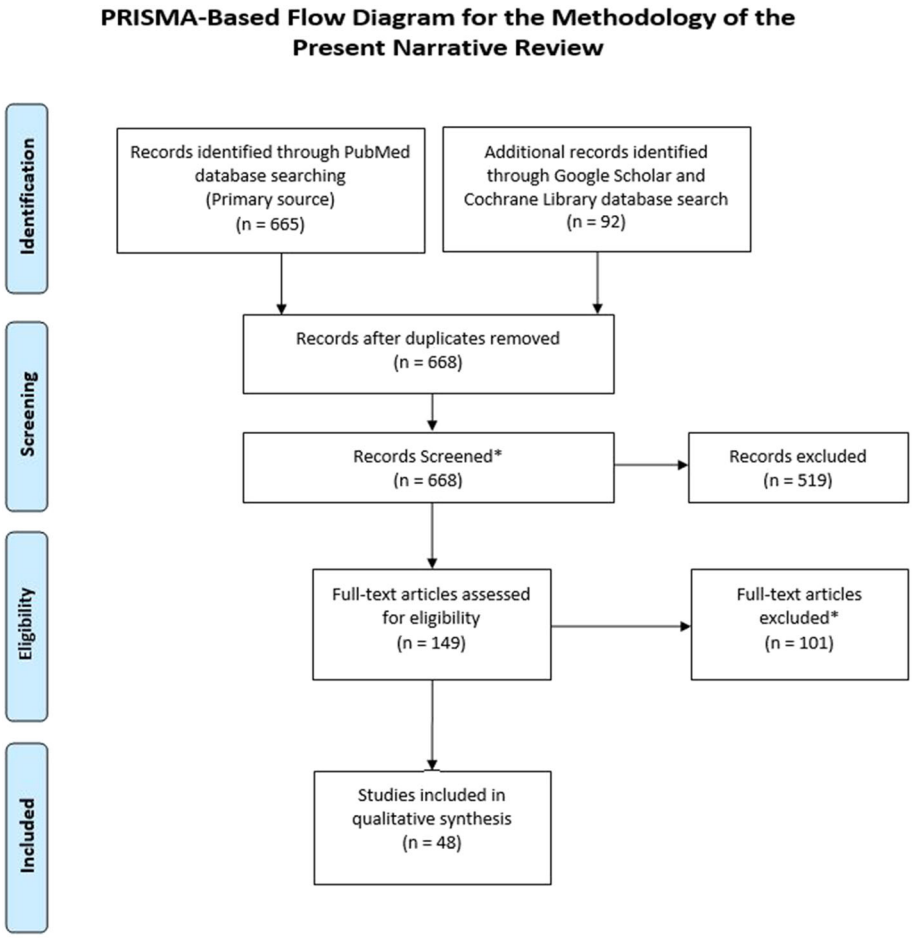

FIGURE 1 As this was not a systematic review, but rather a narrative review, not all articles meeting the inclusion criteria were referenced in the present article (included in qualitative synthesis). Articles similar in content and/or the conclusions reached by other works were considered but not referenced in the present work

2.3 | Risk factors

MAP has been associated with many environmental and genetic risk factors, but higher frequency, severity, and length of abuse represent the most robust risk factors (Arunogiri, Foulds, McKetin, & Lubman, 2018; Lecomte et al., 2018). One cross-sectional study (n = 445) conducted in Taiwan found that methamphetamine users with a lifetime diagnosis of psychosis, compared with users without a diagnosis of psychosis, were younger at first use of methamphetamine, used larger amounts, had significantly higher mean score on the Premorbid Schizoid and Schizotypal Traits scale, and higher rates of major depressive disorder, alcohol dependence, and antisocial personality disorder (C. K. Chen et al., 2003). A previous history of psychotic disorders relates to worse outcomes, and methamphetamine users with a family history of schizophrenia have been shown to be five times more likely to develop a psychosis than those without one (Bramness et al., 2012; Glasner-Edwards et al., 2008). Another cross-sectional study observed that methamphetamine users with psychosis were more likely to have first-degree relatives with schizophrenia compared with users without psychosis (C. K. Chen et al., 2005; C. K. Chen et al., 2003). Risk of psychosis following methamphetamine use has also been shown to be higher in victims of sexual abuse (Christian et al., 2007; Fujii, 2002), transient vs persistent.

It has been suggested that two distinct groups can be observed amongst MAP patients (Glasner-Edwards et al., 2008; McKetin et al., 2017). One group in which patients experience transient psychotic symptoms that abate shortly following abstinence from methamphetamine abuse, and another in which patients experience persistent psychotic symptoms that persist for weeks and months of abstinence (Glasner-Edwards & Mooney, 2014; Iwanami et al., 1994). One cross-sectional study demonstrated that 52% of MAP patients (with no history of non-MAP-related psychosis) psychotic symptoms subsided after a week of sobriety. Twenty-six percent of the patients in the same study had symptoms that continued after a month, and 16% had symptoms that continued past 3 months of abstinence (Iwanami et al., 1994).

Another cross-sectional study went further in comparing differences in symptom profiles between MAP and primary psychotic patients (McKetin et al., 2017). Subjects abusing methamphetamines were selected and divided into four groups: patients with no psychotic symptoms (n=110), transient MAP (n=85), persistent MAP (n=37), and primary psychosis (n=52). The types of hallucinations and delusions experienced by individuals within each group were compared. It was

found that the types of hallucinations and delusions observed in the population could be used to distinguish between a transient, persistent, or primary psychosis. Transient psychosis was associated with persecutory delusions and tactile hallucinations, and persistent psychosis was associated with delusions of reference, thought interference, and auditory hallucinations. The symptom profile associated with primary psychosis was not observed to be statistically different from that of persistent psychosis. It was thought that persecutory delusions, overwhelmingly the most common symptom in transient MAP, could likely be attributed to brain changes directly related to methamphetamine use and the environment that foster it. Nonauditory hallucinations, typical of primary and persistent psychoses, were thought to be reflective of a vulnerability towards psychosis precipitated by drug use. The frequency of nonauditory hallucinations is curious and could potentially also be used to differentiate persistent MAP from another primary psychosis, as auditory hallucinations represent the most common hallucination in schizophrenia spectrum disorder patients. Nonetheless, it was concluded that MAP patients experiencing psychotic symptoms, especially nonauditory hallucinations, outside of persecutory delusions, represent high risk patients for developing a persistent or primary psychosis and thus require greater attention when assessing a management plan (McKetin et al., 2017).

3 | MAP AND SCHIZOPHRENIA

Numerous authors, citing connections between MAP and schizophrenia, have suggested that MAP may represent a stress-vulnerability model of psychosis (Bramness et al., 2012; Glasner-Edwards & Mooney, 2014). In this model, methamphetamine abuse represents a stressor that can trigger an acute psychosis in vulnerable individuals. Amount and frequency of drug use needed to induce psychosis vary based on genetic vulnerability for psychosis and/or schizophrenia. Chronic methamphetamine abuse works to elevate vulnerability, increasing susceptibility to psychosis even following abstinence (Bramness et al., 2012).

Furthermore, MAP and schizophrenia have been characterized by many of the same symptoms and comparisons between MAP and paranoid schizophrenia remain common (C. K. Chen et al., 2003). Antipsychotic medications used to treat schizophrenia have been popular and effective in treatment of the positive psychotic-type symptoms of MAP (Glasner-Edwards & Mooney, 2014; Samiei, Vahidi, Rezaee, Yaraghchi, & Daneshmand, 2016; Wang et al., 2016).

In a novel attempt to differentiate symptoms and outcomes of MAP from primary psychotic disorders, a recent cross-sectional study (n=165) compared the severity of symptoms and general functioning of inpatients diagnosed with MAP, affective psychosis, and nonaffective psychosis at the time of psychiatric hospital admission and at 12-month follow-up. Patients with nonaffective psychosis were found to have the most severe negative symptoms; affective psychosis was associated with the greatest positive symptoms (Hajebi, Amini, Kashani, & Sharifi, 2016). The MAP group was related to the highest rates of suicide attempts and hospital readmissions, demonstrating a worse expected outcome for MAP compared with other psychotic disorders. Worse outcome was thought to be produced by frequent relapses and other drug-related comorbidity in the MAP population. Overall, the study found the course of MAP to be most similar to that of nonaffective psychosis, further demonstrating an association of MAP with schizophrenic-like patients.

Studies have shown that prefrontal cortex (PFC) dysfunction seems to exist for both MAP and schizophrenia, but that distinct differences appear to exist between both groups (Hajebi et al., 2016; McKetin, Hides, Kavanagh, Saunders, & Dawe, 2018; Okada et al., 2016). A recent cross-sectional study using multichannel near-infrared spectroscopy demonstrated that MAP and schizophrenia patients both had reduced inhibition control activity in the bilateral ventrolateral PFC, when compared with healthy controls, but that reductions in inhibition control in the frontopolar PFC were only visible in MAP (Okada et al., 2016). Another study found comparable reductions in PFC activity, between MAP patients and controls, but did not have a schizophrenia comparison group (Yamamuro et al., 2016).

One cross-sectional study noted that differences in symptom profiles could be observed between patients with a lifetime diagnosis of a substance induced psychosis compared with a primary psychiatric disorder. Using retrospective reports, it was found that patients with a lifetime primary psychiatric disorder were more likely to experience Schneiderian auditory hallucinations and grandiose delusions and were hospitalized for substantially longer periods of time following their first episodic break. It was suggested that patients presenting with a symptom profile more typical of a primary psychotic disorder should be considered for early psychosis intervention, and patients presenting with other symptom profiles may only require clinical monitoring (McKetin et al., 2018).

A cross-sectional study comparing cognitive functioning in patients with schizophrenia and MAP noted that although clear deficits in test scores were observed for tests of cognition (visual search and attention test and Rey-Osterrieth complex figure) for both MAP and schizophrenia patients, performance on tests of cognition could not significantly differentiate patients with MAP or schizophrenia (Khalkhali, Golshahi, Hasandokht, Kafie, & Zare, 2018).

A recent comparative review of positive and negative symptoms and cognition in acute and chronic MAP and schizophrenia by Wearne and Cornish (2018) summarized that despite differences being observed between chronic MAP and schizophrenia, the gross similarities between the two conditions, as well as inconsistencies related to methodology and results between studies, continue to prevent conclusive evidence of chronic MAP representing a separate primary psychiatric disorder with schizophrenia (Wearne & Cornish, 2018).

4 | BIOLOGICAL BASIS OF MAP

4.1 | Neurotransmitter dysregulation

The metabolism of methamphetamine works to effect dopamine (DA) transmission in the central nervous system through the inhibition of

the DA transporter and the vesicular monoamine transporter (VMAT2). Inhibition of these proteins results in increased and potentially neurotoxic concentrations of DA. Increased DA concentrations then work to affect the polysynaptic interactions of different dopaminergic systems (i.e., mesolimbic, nigrostriatal, and mesocortical) that result in increased glutamate and DA signaling (Bramness et al., 2012; Hsieh, Stein, & Howells, 2014). Chronic methamphetamine use subsequently leads to changes in dopaminergic receptor density and function, especially in the mesolimbic system and striatum, that plays on feed-forward systems and results in sensitization and addiction (Bramness et al., 2012).

Excessive DA signaling may work to overwhelm GABAergic interneurons, leading to the dysregulation of DA systems and possible psychotic symptoms (Hsieh et al., 2014). Damage to cortical interneurons, through impairment of NMDA receptors, and increased neurotoxicity may cause this glutamate dysregulation and result in damage to the cortex, thereby triggering psychotic and MAP-related symptoms (Grant et al., 2012; Hsieh et al., 2014). Nonetheless, the actual mechanisms underlying the etiology of MAP remain poorly understood.

4.2 | Inflammation, oxidative stress, and neurodegeneration

In the striatum, decreased DA signaling, tyrosine hydroxylase, and DA transporter have been shown to be most pronounced in the caudate nucleus and putamen. Even so, striatum markers of DA signaling can recover following extended periods of abstinence (Shin et al., 2017).

Although only a limited number of studies have observed the effects of oxidative stress and inflammation in methamphetamine abuse, preliminary studies have demonstrated that both may play a role in the pathology of MAP. Evidence exists that neuroinflammation-related breakdown of the blood–brain barrier and the influx of inflammatory cytokines, chemokines, and macrophages into the brain related to methamphetamine abuse precipitates cognitive deficits and addiction (Chang, Alicata, Ernst, & Volkow, 2007; Kohno et al., 2018). Methamphetamine use has been shown to result in decreased anti-inflammatory cytokines and increased pro-inflammatory cytokines through the hypertrophic transformation of microglia (Shin et al., 2017). Similarly, elevated oxidative stress markers have been found in the post-mortem brain/plasma of methamphetamine users. It is thought that excessive DA triggers mitochondria and relevant enzymes to overproduce reactive oxygen species that exacerbate neurodegeneration (Shin et al., 2017). Methamphetamine itself carries a positive charge that can offset the electrochemical gradient in cells and result in the production of damaging superoxide radicals. Antioxidant molecules such as glutathione peroxidase and superoxide dismutase have been shown to exert a protective role against MA-induced neurotoxicity. Animal knockout studies targeting oxidative stress molecules such as NOS or pro-inflammatory markers such as IL-6 have been demonstrated protective effects against MA abuse (Shin et al., 2017).

In sum, oxidative stress and inflammation have not been studied in MAP specifically, but studies of related conditions suggest that these processes may play a major role in the brain abnormalities observed in MAP. Future studies must explore the role of oxidative stress, inflammation, and neurodegeneration in the pathology and etiology of MAP.

4.3 | Genetics

Grant et al. (2012) compiled a list of susceptibility genes thought to mediate vulnerability in high-risk individuals for MAP. Genes were identified based on biological function, differential expression in disease, relation to schizophrenia, and animal models. Seven susceptibility genes were selected from over 50 studies conducted in the past two decades (Grant et al., 2012). Of the genes identified, all held implications with schizophrenia, four were related to glutamatergic signaling, two with neural development, and one with serotonergic signaling. A study measuring the potential epigenetic dysregulation caused by methamphetamine use observed specific changes in LINE-1 partial methylation patterns in methamphetamine using subjects (Kalayasiri, Kraijak, Maes, & Mutirangura, 2018). Methamphetamine use was found to be associated with increased % mCuC and % mCuC + uCmC levels when compared with controls. In particular, methamphetamine-induced paranoia was strongly associated with a change to a specific partial methylation profile (increased % mCuC and decreased % uCmC). LINE-1 regulates gene expression in cis, and the study suggests that dysregulation of LINE-1 methylation patterns could have a significant effect on both gene expression and dysregulation of DNA repair genes, thus effecting the pathophysiology of paranoid psychosis through neuro-oxidative and immune pathways in these patients.

4.4 | Imaging studies

Neuroimaging studies have found methamphetamine associated changes in serotonergic systems, glucose metabolism, and gross structural anatomy (Chang et al., 2007; Tang et al., 2018). Lower levels of cortical thickness in brain regions related to affective regulation has been observed in MAP as compared with nonpsychotic methamphetamine users, and healthy controls (Uhlmann et al., 2016). Ingroup analysis demonstrated that deficits in emotional regulation was associated with reduced cortical thickness in the lateral orbitofrontal cortex, inferior frontal, and temporal gyrus in MAP. Bilateral hippocampal volume was also found to be significantly lower in the MAP than in methamphetamine users without psychosis. The study noted that all the brain regions mentioned were previously found to be reduced in psychotic and schizophrenic populations as well (Uhlmann, Fouche, Koen, et al., 2016).

A multimodal brain imaging study observed that methamphetamine users (MAP and nonpsychotic methamphetamine user groups) demonstrated decreased glucose metabolism in the left insula, left precentral gyrus, and the anterior cingulate cortex when compared

with healthy controls (Vuletic et al., 2018). Moreover, participants in the MAP group demonstrated decreased glucose metabolism in the left precentral gyrus and left inferior frontal gyrus and both increased glucose metabolism and cerebral perfusion in the putamen and pallidum. The study noted that the increased regional activity of glucose metabolism in the putamen and palladium for the MAP group was consistent with findings from neuroimaging studies for schizophrenia and suggests that the deficits in these regions may be a cause, consequence or even a compensatory effect of psychosis.

It has been shown that abnormalities in gray matter volume exist in both MAP and schizophrenia (Aoki et al., 2013; Li et al., 2018). One study demonstrated that similar gray matter deficits appear to exist within the left perisylvian region of brain in the posterior inferior frontal gyrus and anterior superior temporal gyrus in both MAP and schizophrenia (Aoki et al., 2013). However, a study by Zhang et al., 2018 revealed that functional and structural deficits associated with gray matter MAP significantly differed from those observed in the schizophrenia group. Gray matter deficits unique to MAP, such as those in the orbitofrontal area or the frontopolar BA 10 cortices, have been implicated in contributing to the symptoms of MAP unique to the disorder (Aoki et al., 2013). Additionally, regional homogeneity was observed to be negatively correlated with positive symptoms in the left orbital interior frontal gyrus in MAP, and regional homogeneity was found to be negatively correlated with negative symptoms in the right superior frontal gyrus in schizophrenia patients (Zhang et al., 2018).

MAP patients have been shown to exhibit globally diminished white matter integrity (Breen et al., 2017; Uhlmann et al., 2016). Uhlmann (2016) et al. observed lower fractional anisotropy in MAP compared with healthy controls. Moreover, the study found increased mean, axial, and radial diffusivity values in MAP compared with both methamphetamine users without psychosis and healthy controls. Decreases in fractional anisotropy signal a general decrease in white matter integrity, and increased radial and axial diffusivity has been related to decreased myelination and axonal integrity, respectively (Breen et al., 2017). Mean diffusivity has been correlated with the intercellular space and compactness of white matter, and greater mean diffusivity values were significantly correlated with negative psychotic symptoms in the study (Uhlmann, Fouche, Lederer, et al., 2016). High levels of self-report impulsivity was associated with decreases in regional frontal white matter integrity measures in both MAP and methamphetamine users without psychosis (Uhlmann, Fouche, Lederer, et al., 2016). Another study found significant colinear relationships between serum protein levels and diffusion tensor imaging markers (i.e., white matter measures) in healthy controls that was disrupted in MAP and MA users (Breen et al., 2017).

4.5 | Biomarkers

Two functional biomarkers related to ubiquitin-mediated proteolysis downregulation and upregulation of a circadian clock-related psychoticism have been found to be associated with MAP (Breen et al., 2016). A study analyzing the levels of 43 serum proteins related to inflammation, lipid metabolism, and psychiatric illnesses in MAP found differential regulation of apolipoprotein C-II (APOC2) and apolipoprotein H (APOH) in MAP patients when compared with methamphetamine users without psychosis and controls (Breen et al., 2017). Altered APOH and APOC2 levels have been previously observed in schizophrenia and other psychiatric disorders, and APOH has been identified as one of 26 serum protein biomarkers for the classification of schizophrenia (Breen et al., 2017; Chan et al., 2015). It has been suggested that apart from lipid metabolism, APOH and APOC2 may be important to regulation of inflammation and healthy brain functioning, but more research remains needed on the role of these proteins in psychiatric disorders (Breen et al., 2017).

Moreover, machine-learning analysis of 25 blood-related biomarker genes was demonstrated to be able to distinguish between healthy controls and methamphetamine dependents with 87% accuracy. The analyzer differentiated between MAP patients and methamphetamine dependents with 95% accuracy (used 20 genes, 14 overlapping with first analysis; Breen et al., 2016).

Future biological research should focus on elucidating if differences can be observed in the brain morphologies of the persistent and transient MAP subpopulations. More research comparing the connections between MAP and schizophrenia could aid in these determinations. Additional studies identifying genes families and epigenetic markers and their function in the pathology and etiology of MAP remain necessary.

5 | TREATMENT OF MAP

The treatment of methamphetamine users presenting with psychotic symptoms must focus on eliminating addition, drug use, and relapse as it will be beneficial in preventing the recurrence of psychotic symptoms and syndromes. Transient psychosis in many patients will subside after a few weeks to a month of abstaining from methamphetamine abuse and prescribing more serious antipsychotic interventions to these patients could cause undue stress from the serious mental and physical side effects associated with the medications (McKetin et al., 2017). Nonetheless, the difficulty of discerning a MAP diagnosis from a primary psychiatric disorder makes treatment of the disorder highly situational (McKetin, 2018). Although a standardized treatment for MAP has yet to be developed, much clinical practice has demonstrated that various antipsychotic medications are effective at alleviating the psychotic symptoms induced by MAP (Shoptaw, Kao, & Ling, 2009; Wang et al., 2016). A comprehensive treatment plan for individuals presenting with recurrent and persistent psychosis, even in the absence of methamphetamine use, may include psychotherapy and behavioral treatments to prevent resumption of methamphetamine use and pharmacological treatment for psychotic symptoms. Treatment of cooccurring psychiatric disorders including depression and anxiety may also be important in preventing relapse to methamphetamine use, which is often triggered by affective symptoms.

5.1 | Antipsychotics

A 2009 review on treatment approaches for amphetamine related psychosis found only one study to meet their inclusion criteria for review (Shoptaw et al., 2009).

The randomized control trial (RCT) compared the use of haloperidol (most common typical antipsychotic) with olanzapine (atypical psychotic) and demonstrated that although most patients (n=58) experienced clinically improved outcomes (olanzapine, 93%; haloperidol, 80%) by the conclusion of the 4-week trial, olanzapine was preferred outcomes due to its reduced extrapyramidal side effects (frequency and severity). No statistical difference in psychotic symptoms was measured between the treatments at endpoint (Leelahanaj, Kongsakon, & Netrakom, 2005).

A decade later, we have identified only four additional studies exploring antipsychotic treatment methods in MAP populations.

The first study (n=68) compared haloperidol with a different atypical antipsychotic, quetiapine (Verachai et al., 2014). The study hypothesized that the hypodopaminergic effects associated with methamphetamine abuse would be exacerbated by typical antipsychotics, such as haloperidol. DA blocking effects related to typical antipsychotics would then work to increase cravings and anhedonia in MAP patients, resulting in increased relapse. Thus, quetiapine, unique for its low D2 receptor affinity, was selected to circumvent these hypothesized hypodopaminergic effects. Additionally, the study noted that atypical antipsychotics, which specifically block dopaminergic D2 and serotonergic 5-HT2A receptor systems, induce fewer side effects, reduce cravings, and improve cognitive function in schizophrenic populations. Nonetheless, the study found that quetiapine and haloperidol treatment exhibit comparable therapeutic and adverse effects.

A recent study demonstrated that atypical antipsychotics vary greatly in their efficacy and effects in MAP (Wang et al., 2016). The study, conducted on patients from two inpatient wards in China, tested the effects of aripiprazole and risperidone, the two atypical antipsychotic drugs most commonly administered to MAP patients in China (n=42). Aripiprazole represents a partial agonist at both DA and serotonin receptors, and risperidone represents an antagonist of the same two receptor systems. Risperidone demonstrated a much higher tolerability, as 33% (7/21) of the aripiprazole treated patients dropped out before the end of the 22-day trial (0% drop out for risperidone, 0/21). Treatment with aripiprazole resulted in significantly more akathisia and agitation in patients, contradicting biologically expected results, but consistent with a growing body of literature (Ono et al., 2012; Samiei et al., 2016). Surprisingly, although both risperidone and aripiprazole reduced cravings, the effect was significantly greater in risperidone-treated subjects. Improvements in psychotic symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) were similar for both treatments (Wang et al., 2016). The findings of the study were consistent with the results of earlier studies testing the efficacy and safety of aripiprazole against placebo in MAP patients (Sulaiman et al., 2013; Sulaiman et al., 2014).

Another RCT comparing haloperidol (n=22) and risperidone (n=22) in MAP subjects found both medications to be equally effective at eliminating positive symptoms (i.e., delusions, hallucinations, and bizarre behaviors) following 1 month of treatment as measured by the Persian validated version of the Scale of Assessment of Positive Symptoms (SAPS; Samiei et al., 2016).

A report of two MAP patients, each with mild intellectual disability, in Japan demonstrated that blonanserin, an atypical antipsychotic targeting DA D2 and serotonin 5-HT2A receptors, was effective for treating the positive and negative symptoms of MAP and for alleviating cognitive impairments in the two patients. Blonanserin was shown to be well tolerated and recommended for patients deemed to be more vulnerable towards the negative side effects associated with other antipsychotic medications (Okazaki et al., 2016). Nonetheless, clinical trials remain needed to corroborate the findings of the case report.

Treatment studies using both first and second generation antipsychotic drugs have demonstrated the efficacy of many antipsychotic medications in the treatment of psychotic symptoms for MAP. However, the debilitating side effects associated with many of these medications mandate the continued need for the comparison of different antipsychotics. Future studies should continue to develop or examine antipsychotic medications effective at eliminating not only the psychotic symptoms but also addiction (cravings) and other damaging effects related to MAP.

5.2 | Cognitive behavioral therapy

Psychological-based treatment for methamphetamine use has been common and has focused on the development of contingency management, behavioral therapy, and cognitive behavioral therapy (CBT) to reduce substance-abuse/addition and risky behaviors associated with drug use. Studies have shown efficacy in psychological treatment for methamphetamine use, but retention in psychological therapies from methamphetamine using patients has been an issue (Stuart et al., 2017).

Psychotherapeutic treatment for MAP has primarily used CBT to target addiction. Abstaining from methamphetamine abuse stands as an essential step towards recovery regardless of MAP classification or diagnosis. The Matrix Model of CBT, family education, and self-help participation has been successfully used to help drug abusers reduce their drug use through avoidance, identification of triggers, and drug refusal (Glasner-Edwards & Mooney, 2014). Although no studies have been conducted on the efficacy of CBT for MAP patients, CBT represents a promising treatment method for medication resistant patients. CBT treatment methods such as the Matrix Model should be adjusted and applied for use in MAP populations (Glasner-Edwards & Mooney, 2014).

5.3 | Novel treatment approaches

5.3.1 | Electrocompulsive therapy and electro-acupuncture

Results from three separate case studies have suggested electrocompulsive therapy (ECT) to produce a dramatic benefit for

patients with MAP (Ahmadi, 2016; Ahmadi, Ekramzadeh, & Pridmore, 2015; Grelotti, Kanayama, & Pope, 2010). The case reports each describe the treatment of a different MAP patient presenting with positive and negative symptoms of psychosis following methamphetamine use unresponsive to antipsychotic medications (e.g., olanzapine/risperidone). All three case reports highlight immediate improvement to psychotic symptoms, cravings, withdrawal, and mood following adjunctive ECT treatment. Two of the three patients were shown to be symptom-free at a 1-month follow-up (hospital discharge).

A recent novel RCT of electro-acupuncture for patients (n=68) diagnosed with amphetamine dependence (DSM-V) and PANSS $\geq$60 points observed that a 4-week trial of electro-acupuncture resulted in a significant improvement to positive and negative PANSS scores after one-week of treatment that continued to improve until the end of the four-week trial (Zeng, Tao, Hou, Zong, & Yu, 2018). Moreover, the study noted that acupuncture has been shown to improve PANSS scores, quality-of-life, and sleep in patients with schizophrenia in related trials and deserves to be studied further.

Although the biological mechanisms for ECT and electro-acupuncture therapies remain undetermined, electroshock therapy is known to promote striatal DA function in animal models, suggesting a possible restorative effect. Future studies should seek to determine the biological mechanisms associated with electro-shock-based therapies for MAP.

5.3.2 | Computer/digital-based therapies

Virtual reality (VR)-based therapy has received increasing attention as the technology rapidly improves in customizability, affordability, realism, and accessibility (X. J. Chen et al., 2018; Culbertson et al., 2010). Used to treat a variety of substance use disorders, VR-based therapy has been observed to reduce craving and increase coping mechanisms. It is thought that VR therapy works on a number of cognitive processes related to substance use disorders by allowing patients to experience highly controlled and highly interactive three-dimensional environments where they can work through personalized real-life drug and addiction related situations. These environments work similarly to supportive counseling roleplaying activities and offer a novel solution to many of the problems present in traditional exposure-based therapies (Pot-Kolder et al., 2018). Although there have yet to be any VR-based therapy for MAP patients, a growing number of pilot studies have tested VR-based therapy for psychosis and methamphetamine use independently (Culbertson et al., 2010).

One RCT for psychosis (n=116) revealed that VR-CBT was able to lead to significant reductions in momentary paranoia, paranoid ideation, and anxiety (Pot-Kolder et al., 2018). These symptoms represent the most commonly observed positive symptoms in MAP. A review of 50 studies for VR-based treatment for psychosis concluded that although VR-based therapies remain in its infancy, they appear a safe and well-tolerated method for treating auditory hallucinations, paranoia, depression, anxiety, and social and cognitive functioning in psychotic patients (Rus-Calafell, Garety, Sason, Craig, & Valmaggia, 2018).

The RCT of VR therapy for methamphetamine use demonstrated that methamphetamine cues in an online VR environment was able to increase self-reported craving in methamphetamine users when compared with traditional methamphetamine and neutral cues. The result of this rudimentary study was consistent with findings of similar VR interventions for substance use disorders and suggests that VR-based therapies used for other substance use disorders should be tested for methamphetamine using populations (X. J. Chen et al., 2018).

Computerized cognitive addiction therapy (CCAT) represents another computer/digital-based therapy with potential therapeutic benefit for treating methamphetamine addiction (Zhu et al., 2018). Previous findings demonstrate cognitive function and decision making as predictors of long-term prognosis in methamphetamine use. CCAT methods have been shown to produce cognitive benefits for both schizophrenia and substance use disorders. A pilot RCT of a novel mobile-based CCAT app for methamphetamine use found that CCAT therapy improved performance on both cognitive function (Chinese version of CogState Battery) and impulse control tasks (e.g., Balloon Analog Risk Task, Delay Discounting Task, Iowa Gambling Task) when compared with treatment as usual controls (d'Amato et al., 2011; Zhu et al., 2018).

5.3.3 | Mindfulness-based relapse prevention

Mindfulness-based relapse prevention (MBRP) denotes another novel therapeutic technique with potential use for MAP patients. MBRP embodies a combination of CBT and mindfulness medication techniques and aims to help improve coping mechanisms and decrease risk of relapse for patients with methamphetamine and other substance use disorders (X. J. Chen et al., 2018). MBRP methods have been shown to decrease craving and depressive symptoms for comorbid substance use in depressive disorders (Zemestani & Ottaviani, 2016). A meta-analysis of mindfulness-based interventions for psychosis revealed that the intervention resulted in significantly reduced positive and negative psychotic symptoms when compared with TAU controls (Louise, Fitzpatrick, Strauss, Rossell, & Thomas, 2018). Nonetheless, mindfulness-based intervention produced a nonsignificant difference in symptom scores when compared with active control groups.

MBRP may provide benefit for addressing both the addiction and psychotic effects related to MAP. However, it has been suggested that poor concentration and interoception common in methamphetamine use and MAP patients may prevent them from fully benefiting from MBRP therapy. For these individuals, engagement in MBRP therapy could be considered after they have abstained from drug use for a period of time and have regained drug-induced deficits to attention. Even so, one study protocol seeks to combine the benefits of a VR cue exposure technique with MBRP in the treatment of methamphetamine abuse to help address these concerns and observe the potential

benefit of the combination therapy for anxiety, depression, regulatory self-efficacy, mindfulness, and attention bias in participants (X. J. Chen et al., 2018).

5.3.4 | Exercise-based therapies

Exercise-based therapies have been shown to result in improvements to both positive and negative symptoms in schizophrenia and help ameliorate the damaging metabolic side effects associated with antipsychotic medications (Archer & Kostrzewa, 2015; Morris et al., 2018). Exercise-based therapies have also been associated with benefits to body image, coping, anxiety, independence, working memory, and overall quality-of-life. Although the biological mechanisms of exercise for schizophrenia remain poorly understood, preliminary studies have found exercise to benefit many of the biological systems disrupted in MAP, such as neurotransmitter dysfunction, apoptosis, BDNF signaling, inflammation, and oxidation (Archer & Kostrzewa, 2015). Exercise therapy has been shown to reduce anxiety and depression and improve physical health for individuals with a methamphetamine use disorder. The benefits of exercise therapy for methamphetamine use were related to many of the same biological mechanisms noted for schizophrenia (i.e., neurochemical imbalance, oxidative stress, inflammation, and impaired neurogenesis; Morais, Pita, Fontes-Ribeiro, & Pereira, 2018; Morris et al., 2018).

Overall, new therapies and treatment plans for MAP patients must aim to both combat the psychotic symptoms and substance use present in MAP. Controversy over diagnosis and complexities in the heterogeneity of the disease has prevented standardized systems of care for MAP patients from being developed. Future studies should focus on refining methods used for the short- and long-term treatment of MAP in transient and persistent MAP patients respectively. Noting the limited evidence used to guide clinicians in prescribing an appropriate management plan for MAP patients, one group has suggested an assertive and integrated approach that states careful assessment of family and personal risk factors, and past subclinical symptoms stand necessary in providing proper personalized care (Lappin, Sara, & Farrell, 2017). Following their recommendations, treatment should be prescribed immediately following the development of non-transient symptoms and involve flexible and integrated coordinated specialty care to share knowledge and resources between mental health, substance use, and primary care services in treating the multifaceted nature of the disorder.

6 | CONCLUSION

MAP represents a complex disease in which genetic and environmental susceptibility seems to precipitate a persistent psychosis in vulnerable individuals and transient psychosis in others. It remains difficult for clinicians to distinguish the various forms of MAP and MAP itself from a primary psychiatric disorder. Much work has been conducted on the treatment of biological markers related to methamphetamine abuse, but biological studies in humans and animals specific for psychosis and related to methamphetamine abuse remains lacking. It remains to be seen if underlying biological differences and markers can be identified in differentiating transient, persistent, and primary psychoses in MAP patients and should represent a major aim of future research. Novel and alternative treatment methods for MAP that build upon standardized methods for psychosis and addiction care should be explored further.

CONFLICT OF INTEREST

X. F. has received research support or honoraria from Alkermes, Neurocrine, Avanir, Allergen, Otsuka, Lundbeck, Boehringer Ingelheim, and Janssen. Other authors report no competing interests.

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