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Pharmacotherapy treatment of stimulant use disorder

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Abstract

Stimulant use disorder (SUD) is a public health problem in the United States that is associated with increased morbidity and mortality. Psychosocial interventions, such as cognitive behavioral therapy and contingency management, are the main treatment modality for SUDs and no pharmacotherapy is currently FDA approved for this indication. Although some medications show promising data for the treatment of SUD, the evidence remains inconsistent, and the clinical application is limited due to the heterogenicity of the population and the lack of studies in patients with various comorbidities. Selection of pharmacotherapy treatment for methamphetamine intoxication, persistent methamphetamine-associated psychosis with methamphetamine use disorder, and cocaine use disorder in patients with co-occurring OUD are discussed in 3 patient cases.

Keywords: methamphetamine, cocaine, amphetamine, stimulant use disorders, pharmacotherapy

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Introduction

Stimulant use disorders (SUDs) include the use of cocaine, amphetamine-type substances, and other stimulants with similar effects, such as methylphenidate and khât.[1] Amphetamines refer to both amphetamine and the structurally similar methamphetamine. Methamphetamine is a more potent derivative of amphetamine with a longer duration of action and increased ability to cross the blood-brain barrier.[2] Although prescription stimulants, such as amphetamines, are FDA approved for the treatment of attention-deficit hyperactivity disorder and narcolepsy, patients with SUD misuse prescription and illicit stimulants to produce effects of euphoria, increased energy, confidence, wakefulness, and reduced hunger.[1,3] It is estimated that the global prevalence of cocaine and amphetamine use disorders was 0.4% and 0.7%, respectively.[4] According to the 2018 National Survey on Drug Use and Health, the misuse of stimulants has significantly increased since 2015, and overdose deaths linked to stimulants have increased more than 3-fold over the past 5 years.[3,5] The presence of fentanyl in methamphetamine and cocaine increases polysubstance use and could contribute to accidental overdose and death as opioids are involved in more than 50% of all stimulant-related overdose deaths.[3]

Acute intoxication of stimulants is associated with increases in heart rate and body temperature, vasoconstriction, panic attacks, hostility, paranoia, psychosis, and

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Take Home Points:

1. Up to a quarter of methamphetamine users can experience clinically significant psychotic symptoms during methamphetamine intoxication. Withdrawal symptoms associated with methamphetamine are usually transient and resolve within 1 week after last use although some patients can experience persistent psychosis lasting for longer than 1 month. Treatment with an antipsychotic medication demonstrates efficacy for methamphetamine-associated psychosis, and long-term treatment and follow-up maybe necessary for these patients.
2. Methylphenidate, bupropion, topiramate, and naltrexone have limited data to support their efficacy in the maintenance treatment of methamphetamine use disorder. A recent study supports the use of combination therapy with bupropion and extended-release naltrexone intramuscular injection in reducing methamphetamine use.
3. Approximately one-third of patients with OUD report concurrent use of stimulants. No specific pharmacotherapy treatment is shown to be effective in this patient population. Antidepressants and disulfiram demonstrate the ability to decrease treatment retention, so they should be used with caution unless warranted in patients with additional psychiatric diagnoses.

violent behavior.[3,6] Tolerance occurs with repeated stimulant use, and patients can experience withdrawal symptoms, such as fatigue, depression, insomnia, and increased appetite.[1,3] Chronic use of stimulants is a public health concern as it can increase the risk of human immunodeficiency virus infections, hepatitis C infections, cardiovascular events, cognitive impairment, and worsening of mental health.[3,4]

Psychosocial interventions, such as cognitive behavioral therapy, contingency management (CM), and a community reinforcement approach are used for the treatment of SUD.[2,3,7] CM provides reinforcement, such as prizes or cash, to incentivize patients to remain engaged in treatment in community-based substance use or mental health clinics.[3] With the exception of CM, most psychosocial interventions have limited benefit in the treatment of SUD.[4,8] The effects of psychosocial interventions may not be sustainable after their cessation, and they are less effective for severe disorders.[2] The lack of access and availability of psychosocial interventions can be a barrier for patients to obtain treatment.[3,4]

Unlike OUD, no medications are approved to treat cocaine use disorder (CUD), amphetamine, or methamphetamine use disorder (MUD). Most clinical trials for SUD have a small sample size, inconsistency in design and outcome assessment, and high attrition rate, which makes it difficult to evaluate the literature as a whole.[9] For example, some trials utilize urine drug screens (UDS) as indicators for stimulant use, but the frequency of UDS assessment varies. The results of UDS may not be reliable due to the short detection time depending on the frequency of stimulant use.[1] Definition of abstinence ranges from 2 to 3 or more consecutive weeks with negative UDS.[10] Patients with other comorbidities are often excluded from clinical trials. Clinical trials often combine patients with amphetamine use disorders and MUD, which makes it difficult to discern if there are differences in the pharmacotherapy treatment efficacy rate between the 2 stimulants.[2,10]

In this article, 3 cases are discussed to evaluate the use of pharmacotherapy for patients with methamphetamine intoxication, persistent methamphetamine-associated psychosis (MAP) and maintenance treatment of MUD, and the treatment of CUD in patients with concurrent OUD.

Cases

Case 1: Methamphetamine Intoxication

A 20-year-old is brought in by the police to the emergency department (ED) for possible methamphetamine intoxication with symptoms of agitation, paranoia, and hallucinations. The patient refuses to be examined; claims the police, hospital staff, and a family member are all part of a government conspiracy theory; and tries to leave the ED. Lorazepam 2 mg IM injection is administered with minimal response after 20 minutes. After additional lorazepam 1 mg and haloperidol 5 mg IM injections are administered, the patient appears calmer and agrees to be examined. Vital signs include heart rate (HR) at 137 beats per minute, blood pressure at 148/112 mm Hg, and a temperature of 101.8°F. The UDS is positive for amphetamines, electrocardiogram reveals a QTc of 487 msec, and laboratory results of a comprehensive metabolic panel (CMP) and CBC are within normal limits. A family member reports that the patient had been using an unknown amount of methamphetamine intravenously for the past 2 years, and the last use of amphetamine was approximately 4 hours prior to admission. The patient continues to be agitated and occasionally threatening, consistently ruminating about government conspiracies, and lorazepam 1 mg, haloperidol 5 mg, and diphenhydramine 50 mg IM injections are administered 5 hours later. Hospital psychiatrists are contacted to determine if transfer to the psychiatric unit is warranted.

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Patients with methamphetamine intoxication can present with symptoms of agitation, hypertension, tachycardia, hyperthermia, and dysrhythmias.[11-13] Severe complications, such as rhabdomyolysis, acute kidney injury, seizure, intracranial bleeds, and myocardial infarction, are also reported.[12,13] The use of amphetamine and methamphetamine can lead to the development of an acute psychotic disorder that requires hospitalization in the emergency room or psychiatric unit.[6,14] Although most patients require less than 24 hours in the ED, some patients may need inpatient psychiatric treatment for ongoing psychosis, suicidality, and depressive symptoms.[13] It is estimated that approximately 23% of methamphetamine users may experience clinically significant psychotic symptoms.[15,16] Benzodiazepines are often used as first-line therapy for the treatment of severe agitation or aggression during methamphetamine intoxication.[11,12] Addition of antipsychotics may be considered if benzodiazepines are not sufficient or symptoms of hallucinations and delusions are present.[11] Antipsychotics are generally reserved as a second-line treatment option due to the risk of adverse reactions, such as lowering seizure threshold, QT interval prolongation, and hyperthermia.[12]

There is a lack of randomized clinical trials (RCTs) on the safety and efficacy of antipsychotics for methamphetamine intoxication because patients often present to the ED unable to provide information on substance ingestions. In a retrospective chart review[13] of ED patients with acute behavioral disturbances from methamphetamine intoxication, successful sedation (sedation assessment tool $\leq$1) was achieved in 180/226 patients (80%) who received oral medications, such as diazepam (68%), a combination of diazepam and olanzapine (29%), and olanzapine alone (3%). In 107 patients (46 of whom failed oral medications previously) who received parenteral medications, such as droperidol and ketamine, 95% were able to achieve successful sedation. Overall, successful sedation was achieved in 98% of patients using oral and/or parenteral medications. No improvement in sedation rate was observed in patients who received the combination of diazepam and olanzapine. No information on adverse reactions related to medications was discussed.[13] A systematic review (SR) was conducted by Conner et al[12] to evaluate the use of antipsychotics in the management of stimulant toxicity. The most common antipsychotics studied were haloperidol and chlorpromazine, and 330 patients were included in the analysis. Rare instances of adverse reactions were reported with the use of chlorpromazine and haloperidol.[12] However, the heterogeneity of the data with different dosing regimens, age, study designs, and use of concurrent medications, such as benzodiazepines, limits the clinical significance of this data.

Patients with acute agitation from methamphetamine should be approached in a calm manner, and treatment should be provided in a quiet, low-stimulus environment. Vital signs, CBC, CMP, UDS, creatine phosphokinase, and electrocardiogram should be evaluated.[11] In this patient case, lorazepam IM injection was given due to agitation and the refusal of care. Haloperidol IM was added when benzodiazepine monotherapy was insufficient, and the patient continued to exhibit symptoms of paranoia and delusion. Haloperidol is the most studied antipsychotic for MAP during the intoxication phase. However, second-generation antipsychotics (SGAs) maybe preferred for their lower incidence of extrapyramidal symptoms (EPS), and first-generation antipsychotics may worsen symptoms of dysphoria and anxiety.[11] Although there is no robust evidence of any safety issue with antipsychotics, there is also no evidence of significant benefit over benzodiazepines for the acute treatment of agitation due to methamphetamine intoxication. Clinicians should tailor the treatment based on specific circumstances and characteristics of the individual patients.[12,13]

Case 2: Persistent MAP and MUD

The patient from Case 1 is transferred to the inpatient psychiatric unit due to symptoms of persistent paranoia and hallucinations. The patient appears less agitated but continues to ruminate that the relatives are imposters sent by the government to control those who disagree with them. Vital signs have improved with HR = 83 beats per minute, blood pressure = 127/93 mm Hg, and the electrocardiogram reveals normal sinus rhythm with a QTc of 452 msec. The patient has no prior psychiatric or medical history and reports occasional use of alcohol approximately 1 to 2 times a week at social gatherings and the IV methamphetamine 3 to 4 times a week. The psychiatrist wants to initiate an antipsychotic for the psychotic symptoms and MUD.

Although withdrawal symptoms associated with stimulant use are usually self-limiting and resolve within 1 week after last use, 8.75% to 31.6% of patients may experience persisting MAP lasting for longer than 1 month.[1,6] The prevalence of psychosis may be related to the dose and frequency of methamphetamine use, severity of methamphetamine dependence, and polysubstance use.[17,18] Psychotic symptoms commonly associated with MAP include persecutory delusions, auditory or visual hallucinations, referential delusions, grandiose delusions, and jealous delusions.[6,19] Compared with patients with transient MAP, persistent MAP is more likely to be associated with delusions of reference; thought interference; and tactile, visual, complex auditory, and olfactory hallucinations.[20] No significant differences have been found in the type of positive symptoms seen in patients with persistent MAP and those with primary psychotic disorders, such as

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TABLE 1: Results from randomized clinical trials[16,24-29] of antipsychotics for methamphetamine-associated psychosis

Study	Treatment		Duration, d	Outcome
Leelahanaj et al[24] N = 56	Olanzapine 5 to 20 mg/d n = 29	Haloperidol 5 to 20 mg/d n = 27	28	• Clinical improvement in 93% of olanzapine patients and 79.3% of haloperidol patients ($P = .25$) • Higher rate of EPS reported in haloperidol group
Farnia et al[25] N = 53	Aripiprazole 15 mg/d n = 27	Risperidone 4 mg/d n = 26	42	• Significant reduction in SAPS and Scale for Assessment of Negative Symptoms scores by the end of study in both groups ($P < .001$) • Significant reduction in SAPS score in risperidone group compared to aripiprazole ($P < .001$) • No major side effects reported during treatment in either group
Verachai et al[26] N = 80	Quetiapine 100 to 300 mg/d n = 36	Haloperidol 2 to 6 mg/d n = 44	28	• Remission rate of 89% and 84% in quetiapine and haloperidol groups, respectively ($P = .779$) • No difference in rate of EPS, anticholinergic, antihistamine, and adrenergic blockade
Samiei et al[27] N = 44	Haloperidol 5 to 20 mg/d n = 22	Risperidone 2 to 8 mg/d n = 22	21	• Compared with baseline, clinical improvement seen in both haloperidol and risperidone groups ($P < .05$) • No statistically significant differences in effectiveness between the treatment groups • No mention of adverse reactions in the trial
Wang et al[28] N = 42	Aripiprazole 5 to 15 mg/d n = 21	Risperidone 4 to 6 mg/d n = 21	25	• Compared with baseline, patients in both aripiprazole and risperidone groups showed significant reductions in psychotic symptomatology ($P < .001$) • No statistically significant differences in effectiveness between the treatment groups • Aripiprazole group had a significantly lower retention than risperidone group ($P = .007$) • Higher rate of akathisia and agitation in aripiprazole group than risperidone group ($P = .03$ and $P = .02$, respectively)
Wang et al[29] N = 120	Paliperidone 3 to 9 mg/d n = 60	Risperidone 3 to 6 mg/d n = 60	25	• Compared with baseline, improvement in Positive and Negative Syndrome Scale total score, Clinical Global Impressions-Severity, and methamphetamine craving score were seen in both paliperidone and risperidone groups ($P < .01$) • No statistically significant differences in effectiveness between the treatment groups • EPS increased from baseline during treatment in both groups ($P < .01$) • Higher rate of hypermyotonia, salivation, and dizziness in the risperidone group ($P < .05$)

EPS = extrapyramidal symptoms; SAPS = Scale for Assessment of Positive Symptoms.

schizophrenia. Approximately one-third of patients with primary psychosis have concurrent SUD, and this may pose a diagnostic dilemma between MAP and primary psychosis.[18,20] Because up to one-third of patients with MAP may transition to a diagnosis of primary psychosis over time, long-term treatment and follow-up may be necessary for patients with MAP.[18,21,22]

An antipsychotic medication is indicated for patients with persistent MAP beyond the intoxication or withdrawal period. An SR of 6 RCTs with 314 patients concluded that haloperidol, aripiprazole, olanzapine, quetiapine, and risperidone are effective for the treatment of MAP with no major adverse events. One RCT[23] found aripiprazole was more efficacious than placebo but no medication was clinically superior to the others. In a network meta-analysis by Srisurapanont et al[16] comparing the treatment effects of risperidone, haloperidol, aripiprazole, paliperidone, quetiapine, and olanzapine for MAP, 6 RCTs[24-29] with 395 patients were included (Table 1). All of the trials were conducted outside of the United States, and 5 of the trials were conducted in an inpatient setting. Mean age ranged from 25.2 to 38.8 years and the majority of participants were male (range 54.6% to 100%).[16] Although the network meta-analysis[16] found low-quality evidence that olanzapine and quetiapine were superior to risperi-

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done and aripiprazole, the results of the individual trials found no significant difference between each pair of antipsychotics in reducing the main psychotic symptoms. The adverse reactions reported are consistent with the well-known profile associated with the antipsychotics, and no significant adverse reaction, such as neuroleptic malignant syndrome was reported.[16,24-29] For example, higher rates of EPS were reported with haloperidol, increased incidence of akathisia with aripiprazole, weight gain with olanzapine, and sedation with olanzapine and quetiapine.[11,16,23] Given the limited data, SGAs are preferred over first-generation antipsychotics due to the lower risk of EPS, but no specific SGA is recommended for the treatment of MAP.[11,23] The choice of antipsychotic should be based on the risks and benefits of the medication for the individual patient.[23]

In this patient case, the symptoms persisted for >1 week since the last methamphetamine ingestion, and residual paranoia and hallucinations remained, so risperidone 1 mg by mouth twice daily was started. The patient's symptoms improved with risperidone, and the dose was increased to 3 mg by mouth once daily at bedtime. Risperidone was initiated because it was evaluated in more clinical trials for MAP than other antipsychotics (4 trials, N = 129), and it shows positive symptom benefit in patients with MAP and first-episode psychosis.[11,23,30-32] The optimal antipsychotic treatment duration for MAP is unclear.[4,11,16] MAP is a self-limiting disorder for most patients, and some authors suggest that antipsychotics should be tapered off after the resolution of psychotic symptoms and discontinued after 4 weeks of methamphetamine abstinence.[16] The guideline for the pharmacologic management of methamphetamine-related disorders by Wodarz et al[11] recommends maintaining patients on the antipsychotic for approximately 6 months because residual symptoms may persist in some patients. Nevertheless, periodic monitoring by out-patient providers is important to determine the optimal duration of antipsychotic treatment and provide psychosocial interventions, such as evidence-based CM, to improve abstinence and prevent relapse.

Treatment to prevent relapse on methamphetamine use is another issue that needs to be addressed in this patient. Antidepressants (selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]), gabapentin, baclofen, aripiprazole, varenicline, modafinil, and atomoxetine had no significant effects on abstinence, use, or treatment retention.[2,9] Prescription stimulants as a class are found to have no benefit on abstinence and treatment retention for amphetamine use disorder.[10,33] An SR on 2 RCTs on methylphenidate found low-strength evidence that it may reduce methamphetamine/amphetamine use (N = 97, dosing ranges from 54 to 180 mg/d).[2,9,10,34,35] However, the clinical applicability of the benefit is limited because 1 of the trials was rated with a high risk of bias due to incomplete outcome data and the high methylphenidate dose studied.[10,35] The use of prescription stimulants should be implemented with caution due to the potential for euphoric effects and the risk of misuse and diversion.[33,36] Topiramate 200 mg/d may be more effective in reducing methamphetamine use in patients with recent abstinence as indicated by the negative UDS at study randomization.[9,10,37] Naltrexone has mixed findings on reducing methamphetamine use and no effect on abstinence or treatment retention.[2,10] One 12-week RCT of naltrexone 50 mg/d showed fewer amphetamine-positive UDS in the naltrexone group compared with placebo (47.7% vs 65.2%, $P < .05$).[38] Two RCTs[39,40] on naltrexone extended-release injection (380 mg every 4 weeks) and 1 RCT on naltrexone implants (1000 mg every 10 weeks) showed no difference in methamphetamine use, abstinence, or treatment retention.[41]

In a 12-week, double-blind, randomized, placebo-controlled study[42] among 60 participants who were methamphetamine-dependent, sexually active men who have sex with men, mirtazapine 30 mg/day shows benefit in reducing methamphetamine use (relative risk [RR] 0.57; 95% confidence interval [CI] 0.35, 0.93; $P = .02$). A similar outcome is observed in a mirtazapine trial[43] of cisgender males and transgender females who had sex with men. Sustained-release bupropion (300 mg/d) may be more effective than placebo for reducing methamphetamine use in patients who have less severe use (≤2 methamphetamine-positive UDS in 2 weeks) at baseline (odds ratio 2.81; 95% CI 1.61, 4.93; $P < .001$).[2,9,10,44] In a double-blind, placebo-controlled study[45] comparing sustained-release bupropion 300 mg/d to placebo, a subgroup analysis finds bupropion is more effective in increasing methamphetamine-negative weeks in males but not females. This benefit in male patients is not observed in another bupropion trial[46] with the same dose, and no difference is seen between patients with or without comorbid depression.

Given the limited evidence on the effectiveness of monotherapy treatment for MUD, combination medications may offer more diverse pharmacologic effects or additive benefits.[36] Trivedi et al[47] conducted a 12-week, randomized, double-blind, two-stage, sequential parallel comparison design trial in 403 adult patients with MUD. Patients were included in the study if they were opioid-free at the time of randomization and had two or more positive methamphetamine UDS within 10 days prior to randomization. Patients were randomized into the combination of extended-release bupropion (450 mg/d) plus extended-release naltrexone IM injection (380 mg every 3 weeks) group or the placebo group. The study participants were mostly male (68.7%) and White (71.2%) with an average age of 41 years and average methamphetamine use on 27 out of 30 days prior to consent. The overall

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weighted response rate, defined as at least 3 methamphetamine-negative UDS out of a possible 4 samples taken during weeks 5 and 6 of each treatment phase, was 13.6% and 2.5% ($P < .001$) at the end of the study in the naltrexone/bupropion treatment and placebo groups, respectively. The most common adverse effects reported with the treatment group include nausea, vomiting, constipation, dry mouth, dizziness, decreased appetite, and hyperhidrosis.[47]

In this patient case, naltrexone 50 mg by mouth once daily and extended-release bupropion 150 mg by mouth once daily were initiated for MUD, and the patient was scheduled for out-patient appointments for further treatment and evaluation for transitioning to extended-release naltrexone IM injection. The results on the use of combination therapy with extended-release naltrexone injection plus bupropion are promising. The applicability of the result in clinical practice is unclear due to the high rate of treatment dropout, and the cost of extended-release naltrexone IM injection maybe a barrier for some patients.

Case 3: CUD With Co-occurring OUD

A 34-year-old patient with OUD presented to an outpatient clinic requesting treatment for CUD. The patient had a motor vehicle accident 14 years ago, was initially prescribed oxycodone for pain, and the opioid use escalated over time. The patient was started on buprenorphine/naloxone 1 year ago for opioid maintenance therapy with a current daily dose of 12 mg/3 mg. The patient also reported using cocaine recreationally since the patient's early 20s, but cocaine use became more frequent (4 to 5 times a week) in the past 2 years. Last use of cocaine was 1 day prior to the appointment, and UDS was positive for cocaine. Medical history was otherwise negative; CMP and CBC were normal. The patient expressed interest in starting medication for treatment of CUD.

Although the opioid epidemic is an ongoing public health crisis, there has been an increase in the number of patients with comorbid OUD and stimulant use disorders. A survey[48] conducted in 2018 with 15 741 participants finds that 33.2% of patients seeking treatment for OUD reported crack/cocaine use within the past month. Although patients with polysubstance use disorders are more likely to have poorer outcomes, earlier treatment discontinuation, and increased hospitalizations, many studies on the treatment of stimulant use disorder exclude patients with co-occurring OUD.[49]

Several SRs[8,9,50] on pharmacotherapy for CUD find SSRIs, TCAs, anticonvulsants, dopamine agonists, n-acetylcysteine, opioid agonist therapy, and disulfiram to have insufficient data to demonstrate benefits on abstinence, cocaine use, or treatment retention. Adverse effects associated with SSRIs may increase the risk of dropout.[9,49] Disulfiram is associated with worsening rates of treatment retention.[9,50] Antipsychotics, such as haloperidol, aripiprazole, olanzapine, quetiapine, and risperidone, may increase treatment retention but no benefit on improving abstinence or reducing cocaine use.[8,9,50] Bupropion, topiramate, and high-dose psychostimulants (ie, FDA maximum recommended doses or higher) have low-strength evidence that they may increase continuous abstinence at 2 weeks or more.[8,9,33,50]

Chan et al[49] conducted a meta-analysis of 34 RCTs to address the benefit of pharmacotherapy on abstinence, cocaine use, and treatment retention in patients with OUD and CUD. Trials with abstinence defined as cocaine-negative in UDS for $\geq$3 consecutive weeks were included. Cocaine use was defined by the proportion of negative UDS, and retention was defined by the proportion of patients who completed treatment. This meta-analysis excludes trials in patients with comorbid psychotic spectrum or bipolar disorder, thus limiting the applicability of the result in these populations. Sixteen of the clinical trials include patients who were already receiving opioid maintenance treatment (OMT). Nine trials enrolled patients who had not recently received OMT. Nine trials enrolled patients with a mix of treatment stabilized, treatment naïve, or OMT information unavailable (Table 2).[49,51-78] Key findings from the trials included in this meta-analysis are summarized below.

Ten RCTs[51-60] studied patients who were on stable dose of methadone maintenance treatment and received antidepressants, such as desipramine, bupropion, and fluoxetine. Overall, they[49,51-60] had a lower treatment retention and higher withdrawal rate due to adverse events that are known to antidepressants compared with placebo groups (N = 1006; RR for dropout 1.22; 95% CI 1.05, 1.41). Studies[49,61-63] on anticonvulsants (topiramate, tiagabine, gabapentin) also find lower treatment retention (N = 292; RR 0.86; 95% CI 0.76, 0.97) and no effects on cocaine use or abstinence compared with placebo. Two antipsychotics, risperidone (2 to 4 mg/d) and aripiprazole (15 mg/d), were studied and no difference in time to relapse, abstinence, or retention is found when comparing aripiprazole with the placebo group. Patients in the risperidone group had fewer dropouts compared with the placebo group, but the difference was not statistically significant, and no difference in cocaine use is found.[49,64,65]

Three RCTs[58,68,69] compared the efficacy between methadone (20 to 85 mg/d) and buprenorphine (4 to 16 mg/d) on CUD. Two of the trials[68,69] with low risk of bias were included in the meta-analysis, and greater abstinence rates from cocaine in patients taking methadone 65 to 80 mg/d than buprenorphine 12 to 15 mg/d are found (RR

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TABLE 2: Results from meta-analysis on randomized clinical trials[49,51-78] of CUD in patients with comorbid OUD

Medications, No. of Trials	No. of Patients; Treatment Duration; Dose per Day	Summary of Outcome on CUD
Antidepressants		
Bupropion, 2 trials[51,52]	N = 255; 12 to 25 wk; 300 mg/d	• No information on antidepressants effect on cocaine abstinence for ≥3 consecutive wk
Desipramine, 6 trials[53-58]	N = 585; 12 to 13 wk; 150 to 300 mg/d	• No difference on cocaine use with bupropion compared with placebo • Results on treatment retention favor placebo over antidepressants; RR for dropout 1.22 (95% CI 1.05, 1.41)
Fluoxetine, 2 trials[59,60]	N = 166; 8 to 16 wk; 20 to 60 mg/d	• Antidepressants had higher rate of study withdrawal due to adverse events; RR of 2.42 (95% CI 1.03, 5.90)
Anticonvulsants		
Gabapentin, 1 trial[61]	N = 76; 10 wk; 2400 mg/d	• No difference on cocaine abstinence for ≥3 consecutive wk or cocaine use with topiramate compared with placebo
Tiagabine, 2 trials[61,62]	N = 121; 10 wk; 12 to 24 mg/d	• Results on treatment retention favor placebo over anticonvulsants; pooled RR 0.86 (95% CI 0.76, 0.97)
Topiramate, 1 trial[63]	N = 171; 18 wk; 300 mg/d	
Antipsychotics		
Aripiprazole, 1 trial[64]	N = 18; 12 wk; 15 mg/d	• No information on antipsychotic effect on cocaine abstinence for ≥3 consecutive wk
Risperidone, 1 trial[65]	N = 96; 26 wk; 2 to 4 mg/d	• No difference on cocaine use, treatment retention, or harm with aripiprazole compared with placebo • No difference on treatment retention with risperidone compared to placebo
Dopamine Agonists		
Amantadine, 3 trials[54,55,66]	N = 175; 9 to 12 wk; 200 to 300 mg/d	• No information on dopamine agonist effect on cocaine abstinence for ≥3 consecutive wk
Bromocriptine, 1 trial[67]	N = 50; 5 wk; 5 mg/d	• No difference on cocaine use, treatment retention, or harm with dopamine agonists compared with placebo
Medications for OUD		
Buprenorphine, 3 trials[58,68,69]	N = 458; 13 to 24 wk; 4 to 16 mg/d	• Higher rate of cocaine abstinence for ≥3 consecutive wk with methadone compared with buprenorphine; RR 1.85 (95% CI 1.25, 2.75)
Buprenorphine/naloxone, 1 trial[70]	N = 302; 24 wk; 4 to 16 mg/d	• No difference on cocaine abstinence for ≥3 consecutive wk with buprenorphine/naloxone compared with placebo
Methadone, 3 trials[58,68,69]	N = 458; 13 to 24 wk; 20 to 85 mg/d	• Results on cocaine use favor high-dose buprenorphine/naloxone (16 mg/4 mg/d) compared with placebo; OR 1.09, $P = .022$. • No difference on treatment retention or harm with methadone compared with buprenorphine • No difference on treatment retention with buprenorphine/naloxone compared with placebo
Medications for Other Substance Use Disorder		
Disulfiram, 6 trials[71-76]	N = 605; 10 to 12 wk; 62.5 to 250 mg/d	• No difference on cocaine abstinence for ≥3 consecutive wk with disulfiram compared with placebo
Varenicline, 1 trials[77]	N = 31; 12 wk; 2 mg/d	• No difference on cocaine use with varenicline compared with placebo • Results on treatment retention favor placebo over disulfiram; RR 0.86 (95% CI 0.77, 0.95) • No difference on treatment retention with varenicline compared with placebo • No difference on harm with disulfiram and varenicline compared with placebo
Psychostimulants		
Dexamphetamine, 1 trial[65]	N = 120; 26 wk; 15 to 60 mg/d	• No information on psychostimulant effect on cocaine abstinence for ≥3 consecutive wk
Methylphenidate, 1 trial[78]	N = 62; 12 wk; 30 mg/d	• No difference on cocaine use, treatment retention, or harm with psychostimulants compared with placebo

CI = confidence interval; CUD = cocaine use disorder; OR = odds ratio; RR = relative risk.

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1.85; 95% CI 1.25, 2.75). However, no significant difference in treatment retention with methadone is found when all 3 studies are combined.[49,58,68,69] One trial[70] compared the efficacy between placebo and buprenorphine/naloxone at high (16 mg/4 mg) and low (4 mg/1 mg) doses. No difference in retention or abstinence is found for either of the buprenorphine/naloxone groups compared with placebo. However, the higher dose buprenorphine/naloxone group (16 mg/4 mg) had significantly less cocaine use (UDS negative odds ratio 1.71, $P = .02$).[49,70] No RCT data is available on naltrexone for patients with concurrent cocaine and OUD.

Six RCTs[71-76] study disulfiram in patients with CUD and with comorbid OUD. Meta-analysis[49] indicates there is moderate-strength evidence that disulfiram can worsen treatment retention compared with placebo (RR 0.86; 95% CI 0.77, 0.95). Disulfiram does not have any effect on abstinence and has conflicting evidence on reducing cocaine use.[49,71-76] RCTs[49,54,55,65-67,77,78] on psychostimulants, dopamine agonists, and varenicline show no effect on treatment retention or cocaine use in patients with comorbid OUD.

In this patient case, buprenorphine/naloxone dose is increased from 12 mg/3 mg daily to 16 mg/4 mg/d for the treatment of CUD. No specific pharmacotherapy treatment is shown to be effective in patients with concurrent OUD and CUD. There is limited data indicating that a higher dose of methadone might increase abstinence from cocaine although buprenorphine/naloxone at 16 mg/4 mg/d may reduce cocaine use. However, more research is needed to confirm if there is a dose-related benefit. Given that SSRIs, TCAs, and disulfiram are shown to decrease treatment retention in CUD patients with or without OUD, these medications should be used with caution unless warranted for additional psychiatric diagnoses.[9,49]

Limitations of Literature

In addition to the inconsistent outcomes assessment and trial design, the underrepresentation of populations such as patients with comorbid psychiatric diagnoses or female patients also makes the clinical applicability of the current literature more challenging.[2] In a recent systematic review[2] of pharmacologic treatment for patients with MUD/amphetamine use disorder, less than 30% of study participants are female, and almost 80% of clinical trials exclude patients with depression or psychotic disorders or those taking an antidepressant or antipsychotic medication. More research is needed in female patients and in patients with comorbid psychiatric or substance use disorders.

Conclusion

Limited clinical trials exist to delineate the place in therapy of antipsychotics for the treatment of psychosis during methamphetamine intoxication. For patients with persistent MAP, continuing antipsychotic treatment for up to 6 months may be warranted. There is no FDA-approved pharmacotherapy for the treatment of SUDs and no robust, consistent data to support the routine use of pharmacotherapy. Although medications such as methylphenidate, bupropion, topiramate, and naltrexone have limited data to support their efficacy in the treatment of SUD, the clinical application and generalizability of the existing data is unclear due to the limitations of small sample sizes, low treatment retention, and inconsistency in trial designs and outcome measures in clinical studies. Furthermore, there is little evidence-based research guiding the management of SUDs in female patients and in patients with co-occurring psychiatric or substance use disorders. Clinicians should make treatment decisions based on patient-specific factors and coordinate care between the SUD and mental health services, whenever possible.

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