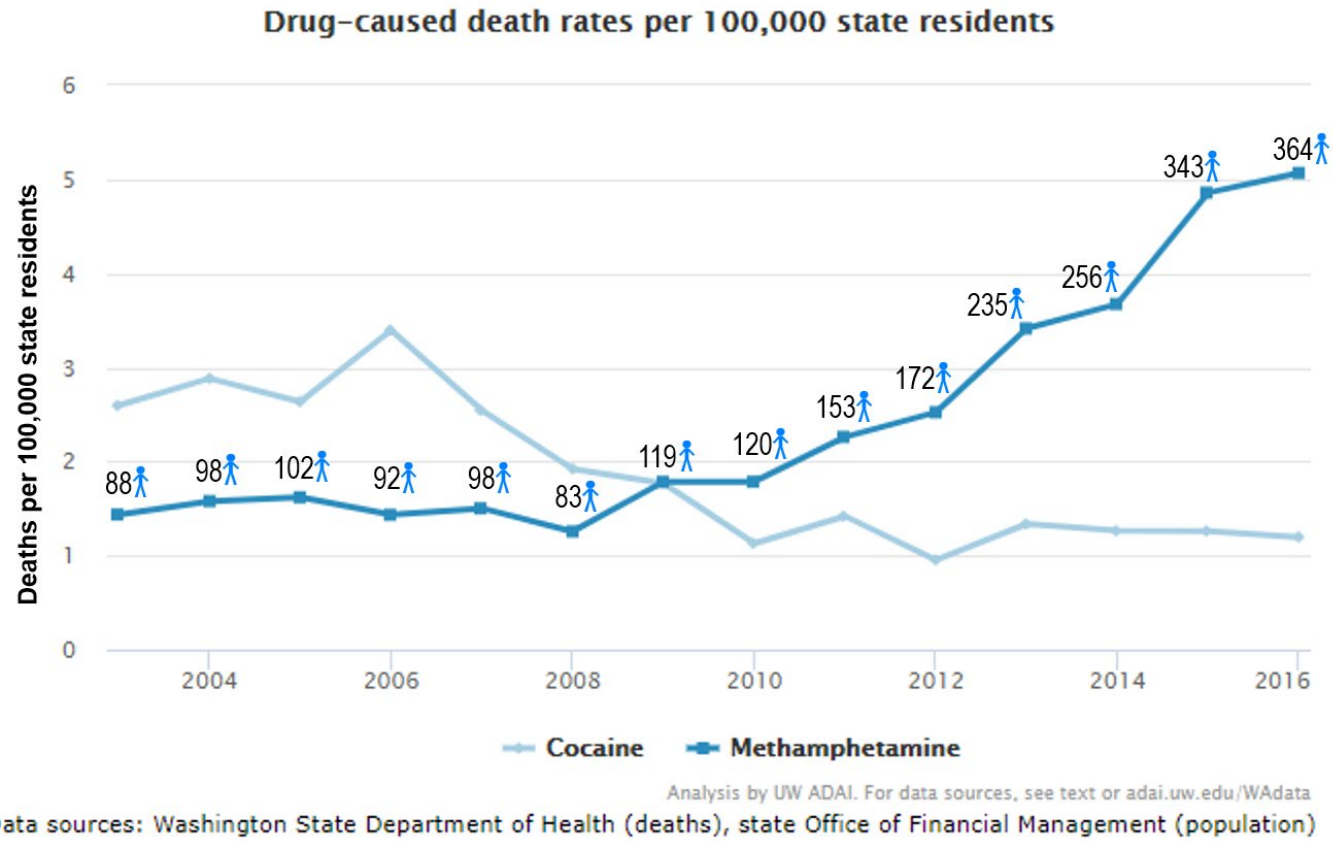
Effective Treatments for Methamphetamine Use Disorder: A Review

ADAI | ALCOHOL & DRUG ABUSE INSTITUTE

Susan A. Stoner, PhD, Research Consultant

Introduction

Methamphetamine (MA) use is a significant and growing problem in the state of Washington. From 2003-2004 to 2015-2016 the statewide number of deaths per year per 100,000 residents attributed to MA poisoning increased by 228% from 1.51 to 4.96. The largest increases were observed in Pierce (460%), Okanogan (475%), and Yakima counties (517%), and both King (285%) and Spokane (236%) also posted large increases. From 2003 to 2016, the number of deaths per year grew from 88 to 364.[1]



In 2015, MA accounted for the second highest number of publicly funded drug treatment admissions in the state of Washington (7,611), second only to heroin (11,614), and far exceeding the number of admissions for cocaine (804).[1] Statewide, the number of admissions for MA per year per 100,000 residents decreased from 2003-2004 to 2014-2015 from 115.4 to 107.9 In 2003-2004, approximately 35% of treatment admissions for MA were first-time admissions while only about 21% were in 2014-2015.[1] Thus, over time, the trend has been for a greater proportion of admissions to be for those presenting for repeat treatment.

While many MA users do not see a personal need for drug treatment services[2] and estimates suggest that only a third of those with MA dependence ever receive such treatment,[3] findings from a large study of substance abuse treatment effectiveness with 6 months post-treatment outcomes, conducted in 19 states,[4] including Washington, indicated that both rural and urban MA users who received treatment experienced significant improvements in abstinence from MA use, employment status, and independent living, and a significant decrease in arrests.[5]

With increasing emphasis in Washington State on the use of evidence-based and research-based practices in behavioral health[6] and substance use disorder treatment, an important question is what evidence exists for treatments for MA use disorders. To that end, this review will summarize the evidence for pharmaco-therapeutic and behavioral/psychosocial treatments.

Method

An extensive literature search was conducted for research articles in English published since 2003 using PubMed (Medline), Google Scholar, and the Cochrane Collaboration databases. Search terms included "methamphetamine", "amphetamine," "stimulant," "treatment," "RCT," "randomized," "effectiveness," and "efficacy." Articles were excluded from consideration if they were not a review article or did not include a randomized controlled trial (RCT). Only review articles were included for pharmacotherapeutic treatments. This search revealed 12 reviews and 26 original research articles that met criteria. In addition, clinicaltrials.gov was searched for candidate pharmacotherapeutic treatments for MA use disorder, studies of which may currently be underway or may not have been published.

Pharmacotherapeutic Treatments

A wide range of pharmacotherapeutic approaches have been tried in the treatment of MA use disorders. The most common classes of attempted pharmacotherapies have included antidepressants, antipsychotics, and substitution/replacement therapies.[7] Table 1 lists a number of drugs that have been or are being examined for MA use disorders, as identified in the present literature review.

As of the date of this writing, the most recent systematic review of pharmacotherapeutic treatment approaches for MA dependence was published by Morley et al. in 2017.[8] It concluded that there were currently no approved medications for the treatment of MA dependence, nor were there any medications on the horizon with scientific literature sufficient to demonstrate a robust treatment effect. Studies included in the review by Morley et al. examined aripiprazole, baclofen, bupropion, d-amphetamine, gabapentin, ibudilast, methylphenidate, mirtazapine, modafinil, n-acetylcysteine, naltrexone, perindopril, rivastigmine, topiramate, and varenicline. The authors noted that the atypical antidepressants mirtazapine and bupropion have shown some promise. In a double-blind, randomized, controlled trial involving 60 men who have sex with men, mirtazapine, which acts on serotonergic and noradrenergic receptors, reduced urine-positive drug screens from 73% to 44% with a corresponding decrease in high risk sexual activity.[9] Studies have suggested that bupropion, a selective norepinephrine and dopamine uptake inhibitor with nicotinic receptor effects FDA-approved as a smoking cessation aid, may be efficacious for a subset of those with MA dependence who use MA less than daily and are highly adherent to the treatment.[10]

> ***Table 1*** *(page 15) lists drugs that have been examined for treatment of methamphetamine use disorders and their mechanism of action.*

Additionally, Morley et al.[8] noted that attention deficit drug, methylphenidate-SR, and anticonvulsant, topiramate, have shown some efficacy in post hoc analyses depending on baseline levels of MA use. A review of combination pharmacotherapies for stimulant use disorders published by Stopps and Rush in 2014[11] included two blinded, randomized controlled trials of combination therapies in MA dependent subjects that were not included in the Morley et al. review. The two trials evaluated the primary constituents in a heavily promoted proprietary treatment for substance use disorders called Prometa® that consists of the antihistamine hydroxyzine, the GABA agonist gabapentin, and the benzodiazepine receptor agonist flumazenil. Reduced MA use was observed in only one of the two studies.

Substitution therapies for MA dependence deserve particular mention due to existence of FDA-approved substitution therapies for opioid and nicotine dependence. Studies of substitution therapies for MA dependence have provided mixed results.7 A 2013 Cochrane review of the efficacy of stimulant drugs for amphetamine abuse or dependence by Pérez-Mañá et al.[12] identified 11 randomized clinical trials with 791 participants investigating four drugs with psychostimulant effects. The review concluded that neither psychostimulants as a group nor any single drug was found to reduce amphetamine use (as evidenced by urinalysis), attain sustained amphetamine abstinence, or improve treatment retention. The authors noted only two studies showed a favorable result for a single outcome: retention was found to improve with dexamphetamine[13] and self-reported use improved with modafinil.[14] Further examining safety and conducting subgroup analysis, Pérez-Mañá et al.[12] concluded that the available data did not support substitution therapy for amphetamine dependence.

Frontiers of pharmacotherapeutic treatment development for MA use disorders include novel functionally-selective serotonin 5HT2 drugs (phenylaminotetralin analogs), drugs selectively binding synaptic glycoprotein 2C (which plays an important role in dopamine neurotransmission) or the trace amine-associated receptor 1 (TAAR1), nonpeptide small molecule compounds for the neurotensin receptor system (NTR1 and NTR2), drugs targeting the cannabinergic and oxytocinergic systems, and immunotherapies.[8,15]

Behavioral/Psychosocial Treatments

Behavioral and psychosocial interventions are the mainstay of treatment of MA use disorders. Ciketic et al.[16] reviewed the literature on behavioral and psychosocial treatment for MA dependence in 2012. The researchers noted that that psychosocial treatment provided for MA abuse and dependence is provided in both inpatient and outpatient treatment settings with an emphasis on abstinence (especially in residential inpatient settings) but also pursuing aims of drug use reduction and harm minimization (particularly in outpatient settings). Beyond these primary aims they pointed out that common goals of psychosocial interventions are to engage and retain dependent MA users in the treatment process, to promote treatment compliance, and to help them avoid relapse into harmful MA use. Treatment approaches differ in whether they are delivered to individuals, families, or groups of unrelated individuals and may differ substantially in terms of frequency and duration. After surveying the literature, the researchers concluded that the evidence base for psychosocial interventions was quite limited for psychostimulant-related disorders with insufficient controlled trials to support one intervention over another. However, they indicated an overall impression is that psychosocial interventions are moderately effective in reducing drug use and associated problems.

A more recent systematic review of behavioral and/or psychosocial treatments for stimulant dependence published in 2016 came to a similar conclusion. In their review, Minozzi et al.[17] considered "textbook-recognized, standardized psychosocial interventions," consisting of cognitive behavioral therapy (CBT), contingency management, motivational interviewing (MI), interpersonal therapy (IPT), psychodynamic therapy (PDT), and 12-step facilitation. Clinical management, case management, and "drug counseling" (i.e., supportive treatment) were considered treatment as usual (TAU) when compared to one of the other treatments. Without differentiating between treatment for cocaine, amphetamine, and methamphetamine use disorders, the review identified 52

studies (a large majority of which focused on cocaine) with 6923 participants: contingency management (27 studies), CBT (19 studies), MI (5 studies), twelve step facilitation (4 studies), interpersonal therapy (3 studies – all on cocaine), and psychodynamic therapy (1 study on cocaine). The authors concluded that the addition of any psychosocial treatment to TAU probably reduces dropout rate and increases the longest period of abstinence and may also increase the number of persons with continuous abstinence at the end of treatment though treated persons may not be able to maintain abstinence over long periods of time. Similarly, the authors concluded that compared to TAU any psychosocial treatment probably improves adherence, but it may not improve abstinence at the end of treatment nor increase the longest period of abstinence. It should be noted that the Minozzi et al. review did not differentiate between psychosocial approaches nor address the clinical question regarding which is the most effective psychosocial approach for stimulant use disorders in general, much less MA use disorders in particular.

Given that MA users tend to present for treatment with greater medical and psychiatric disorders, researchers have questioned whether there is a differential treatment effect for MA and cocaine users and whether MA use disorders should have a specialized treatment. Vocci and Montoya[18] examined the research literature to address this question in 2009 and concluded that, despite the worse medical and psychiatric condition of MA users, there was no evidence for a differential treatment effect of any psychosocial treatment for MA users compared to cocaine users in treatment. A 2007 study in Washington state similarly concluded that patients addicted to MA responded to treatment as positively as those addicted to cocaine and other hard drugs.[19] Vocci and Montoya[18] asserted that the efficacy of psychological and behavioral treatments may be improved by providing treatments for a longer time and developing efficacious relapse prevention strategies, consistent with a chronic disease approach. Furthermore, they argued that while abstinence from MA use may be the ultimate goal of treatment, interventions aimed at reducing drug use and minimizing harm from drug use should be investigated.[18]

Behavioral and psychosocial treatments disseminated by the Addiction Technology Transfer Center (ATTC) network of the Substance Abuse and Mental Health Services Administration (SAMHSA) as effective for MA use disorders include the Matrix Model, other forms of cognitive-behavioral therapy (CBT), contingency management (CM), motivational interviewing (MI), mindfulness-based approaches, and exercise.

Matrix Model

One of the most commonly used psychosocial treatments for stimulant use disorders in general and MA use disorders in particular is the Matrix Model (MM).[20] Developed in response to the cocaine epidemic of the 1980s by the Matrix Institute in Los Angeles, California, MM sought to incorporate empirically-supported treatment elements into a manualized, nonconfrontational, structured program that is considered to be primarily cognitive-behavioral in nature. Standard MM treatment generally spans 16 weeks and consists of group CBT (36 sessions), individual counseling (4 sessions), family education groups (12 sessions), group social support (4 sessions) and urine and weekly breath alcohol testing. Weekly (at least) attendance at 12-step meetings such as Crystal Meth Anonymous is also encouraged. In the late 1990s, the MA epidemic combined with a funding requirement that providers use evidence-based treatments resulted in a high demand by training programs in the use of MM. For training delivery, the Matrix Institute developed standard training curricula, fidelity instruments, and quality assurance protocols. Training procedures consist of an initial 2-day, core training session followed by more intensive training with the person designated to be the "Key Supervisor" at the site. Sites are certified after passing a site visit and review of audiotaped sessions. The developers indicate that certified programs exist across the US and in South Africa, Nicaragua, Guam, Spain, New Zealand and Abu Dhabi.[21]

In spite of the fact that MM has been widely used, it has not been extensively evaluated for effectiveness with regard to MA users. Although it is often used as the treatment platform onto which additive interventions (such as contingency management or pharmacotherapeutic agents) are superimposed, the full MM treatment has only once been compared to TAU, i.e., supportive counseling, in a single RCT. Rawson et al.[22] randomized 978

treatment-seeking, MA-dependent individuals (60% White/non-minority) at 8 sites with 8 different types of TAU to TAU or the 16 session MM treatment. Overall MA use by study participants in both groups was substantially reduced during treatment. Controlling for covariates, MM participants, compared to TAU participants, were 38% more likely to stay in treatment (odds ratio = 1.4), 31% more likely to have MA-free urine test results during treatment (odds ratio = 1.3), and had longer mean periods of abstinence. Differences between groups were lost at follow-up; at the discharge and 6-month follow-up data collection points, participants in both conditions demonstrated nearly a threefold reduction compared to baseline in mean self-reported days of MA use in the past 30 days and a rate of 66–69% MA-negative urine samples at discharge and follow-up.

In a study of long-term outcomes of MM treatment for MA dependence,[23] all 437 clients who were treated for MA dependence at the Matrix Institute in the preceding 5 years were attempted to be contacted for the study. Just over a quarter (N = 114, 84% White/non-minority) were reached. A large majority (83%) reported no MA use in the 30 days prior to the follow up interview. A similarly large number (78%) reported no drug use (not counting MA) in the preceding 30 days. Almost two thirds (62%) were reportedly employed full time (compared to 26% at treatment admission). It should be noted that those who were able to be reached and completed the long-term follow up had been more significantly engaged in treatment, received more treatment sessions, and showed better treatment performance compared to those lost to follow-up (N = 323). Thus, these results reflect outcomes of those who were most engaged in treatment.

In a related study examining in-treatment performance and post-treatment outcomes in MA users among those who received MM treatment (N = 420, 56% White/non-minority),[24] poor treatment engagement was associated with being female, using MA for ≥ 15/30 days prior to intake (high frequency baseline MA use), life-time MA use of < 2 years (long-term MA use), smoking route of MA administration, and reported depression at intake. Shorter retention was associated with MA high frequency baseline MA use, injection route of MA administration, and MA use during treatment. MA use during treatment was associated with being female, high frequency baseline MA use, and smoking or injection route of MA administration. Not completing treatment was associated with long-term MA use; smoking or injection route of MA administration; and MA use during treatment. Poor post-treatment outcome was associated with high frequency baseline MA use, long-term MA use, injecting MA, baseline depression, MA use during treatment, not completing treatment, and being of Asian ethnicity. Those who maintained abstinence and successfully completed treatment were less likely to use MA after discharge.

Other Forms of Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy is an umbrella term that applies to encompasses a range of interventions that may be quite different in application and focus.[25] In general, the term is applied to approaches that derive from principles of learning and classical conditioning and emphasize the role of thoughts in behavior change. Skill acquisition and strengthening is a major focus, and CBT seeks to provide and strengthen skills to reduce or stop drug use and sustain abstinence (relapse prevention). In 2008, Lee and Rawson[25] reviewed the literature on CBT for MA dependence and noted that relapse prevention and coping skills therapy are the most widely known and commonly practiced approaches. They concluded that while there was only a small number of studies examining interventions for MA users, those that have been conducted with CBT (with and without MI) have shown some evidence of efficacy. They noted that studies are difficult to compare because many of the studies had only a brief description of the intervention that was conducted, despite having fidelity checks built in to their methods.[25]

Baker et al.[26,27] have examined a 4-session form of CBT consisting of individual sessions, starting with MI and then focusing on relapse prevention skills. They found modest effects when they examined outcomes in terms of amount of treatment received rather than from an intent-to-treat perspective. The researchers found an overall decrease in MA use across the groups and a significant increase in abstinence in the treatment groups compared

to the control groups. In their larger second study, the researchers also found a short-term beneficial effect on depression.

Smout et al.[28] compared a 12-session individual CBT intervention, expanded from the manual used by Baker et al.[26,27], to a 12-session intervention derived from Acceptance and Commitment Therapy (ACT), a mindfulness-based approach. The investigators found that ACT and CBT showed comparable attendance and reductions in self-reported MA use, consequences, and dependence symptoms, but only the CBT group showed a significant improvement in objectively assessed MA use.

Reback and Shoptaw[29] developed and evaluated a gay-specific CBT intervention for gay and bisexual men who abused MA. Their intervention consisted of 24 group sessions over 8 weeks patterned after the group CBT component of MM with content tailored to men who have sex with men (MSM) and supplemented with a low-cost CM component. A previous study by Shoptaw et al.[30] examined a 48-session gay-specific intervention CBT intervention also patterned after the group CBT of MM but lacking CM. Reback and Shoptaw found that the shorter gay-specific intervention was comparably effective to the longer intervention, which Shoptaw et al. showed was superior in terms of drug use and sexual risk-taking outcomes to standard MM CBT with gay and bisexual men during treatment but not after.

Efforts to adapt CBT to a web-based format have been less successful. Tait et al.[31,32] developed a 3-module web-based CBT intervention, called "Breaking the Ice," patterned after the CBT content of Baker et al.[26,27] Examining both 3-month and 6-month outcomes, the researchers found that the CBT intervention did not reduce MA use. They concluded that the program may serve as a means to engage some segments of a difficult-to-reach population but that significant proportions remained disengaged.

Motivational Interviewing

Engaging the disengaged is a key aim of MI, and a number of studies have examined different forms of MI for MA use disorders. In a study using a pre-post design (N = 80, mean age = 29), a one-session intervention, called the Psychostimulant Check-Up, was associated with a reduction in self-reported MA use and related consequences 3 months after the intervention.[33] A two-session brief MI-based intervention was associated with fewer days of self-reported MA use in Thai adolescents (N = 48, mean age = 17) at 8 weeks compared to a psychoeducation control condition.[34] Moreover a three-session motivational enhancement therapy (MET) intervention using the principles of MI was associated with increased readiness to change MA and MDMA use among Taiwanese adolescents (N = 94, mean age = 17) compared to a psychoeducation control condition.[35]

Polcin et al.[36] developed a nine session individually delivered MET manual for a treatment of MA dependence that came to be known as intensive motivational interviewing (IMI). The first session focused on problem identification and feedback. Session two focused on ambivalence, reasons for using, and desires for change. The third session focused on developing a change plan and identifying possible obstacles. Patterned after the "booster sessions" in the Project MATCH MET manual, sessions four through eight reviewed events of the past week, relapses, and other concerns raised by the client; focused on progress made on the change plan, ambivalence towards the change plan, revision of goals, and desired changes in strategies for achieving goals.

In a preliminary study using a pre-post design (N = 30, 73% White/non-minority), Galloway et al.[37] found that retention of treatment-seeking MA-dependent individuals through the end of treatment was good (73%), participants attended 78% of the IMI sessions, and the proportion of urine drug screens positive for MA declined from 64% to 44%.

Polcin et al.[38] conducted a RCT of the 9-session IMI compared to a single session of MI plus 8 nutrition-education sessions among MA-dependent individuals (N = 217, 67% White/non-minority) delivered weekly to individuals

over 2 months. All study participants also received standard outpatient group treatment three times per week. Both groups showed significant decreases in MA use and Addiction Severity Index drug scores from baseline through the 6-month follow-up, but there were no significant differences between the two groups. Thus, the single MI session appeared to be as effective as the 9-session IMI intervention with respect to MA use. With regard to psychiatric severity scores, the IMI intervention evidenced better results than the single MI session.

Korcha et al.[39] examined the effectiveness of the 9-session IMI treatment for persons with MA dependence, a substantial majority of whom (75%) had a concurrent alcohol use disorder. Participants (N = 163, 67% White/non-minority) were randomly assigned to either a single 90-minute session of MI plus 8 nutrition-education sessions or nine 50-minute sessions of IMI provided weekly. Individuals in both conditions took part in outpatient CBT group sessions focusing on craving identification and management. The study did not report MA-related outcomes as there appeared to be some overlap with the Polcin et al.[38] study. The researchers reported an unexpected finding that women with co-occurring alcohol problems in the IMI condition reduced the severity of their alcohol problems significantly more than women in the Standard MI condition at the 6-month follow-up.

Contingency Management

CM is behavioral technique that seeks to encourage positive behavior change (e.g., abstinence) by providing positive reinforcement (i.e., desirable consequences) when clients meet treatment goals and by withholding reinforcement or providing punishment when patients engage in an undesired behavior (e.g., drug use). For example, consequences for abstinence may include positive reinforcement in the form of vouchers exchangeable for money or prizes while consequences for drug use may include non-reinforcement by withholding vouchers or punishment by making an unfavorable report to a parole officer. Reinforcing or punishing consequences may be contingent on objective evidence of drug use (e.g., urine screens) or on another important behavior, such as compliance with a medication regimen or regular clinic attendance. CM procedures are frequently implemented with written contracts that detail the desired behavior change, duration of intervention, frequency of monitoring, and potential consequences of the persons success or failure in making the agreed upon behavior changes.[40]

From their review of the literature, Minozzi et al.[17] concluded that CM was the most studied and probably the most promising psychosocial approach to be added to TAU. While there are no systematic literature reviews of CM for MA use disorders, Schierenberg et al.[41] reviewed the literature regarding the effectiveness of CM for cocaine dependence in 2012. They found 19 articles that met inclusion criteria with a total of 1,664 participants. The investigators concluded that, although CM as a standalone treatment needs further study, when combined with other group-based or individual behavioral or psychosocial treatments such as CBT, CM increased cocaine abstinence and improved treatment retention. When incorporated into pharmacotherapy trials, CM provided provided an added benefit. A similar review by Farronato et al.[42] in 2013 sought to compare the effectiveness of CBT and CM in cocaine dependence and to analyze potential benefits when combining these psychosocial interventions. They found 8 articles that met their inclusion criteria with 989 participants. The researchers concluded that in all 5 trials in which CM alone was tested against CBT alone or the combination of both, CM reduced cocaine use during treatment and was superior to CBT alone, which did not reduce cocaine use during treatment. In 3 of 5 studies, the groups including CM showed sustained effects on cocaine use during the follow-up period. Unfortunately, however, the researchers noted that implementation of CM procedures in treatment clinics was costly (even at $200 per person using a low-cost CM procedure implemented by Petry et al.[43]), time consuming, and resource intensive, and questions remained about who should cover the costs.

Studies examining CM in the context of MA use disorders specifically have drawn similar conclusions. Shoptaw et al.[44] compared the effects of a 12-week trial of sertraline or placebo to 12 weeks of CM + sertraline or placebo for MA dependence. All participants (N=229, 74% White/non-minority) received standard MM treatment. No statistically significant main or interaction effects for sertraline or CM in reducing MA use were observed.

However, a significantly higher proportion of participants in CM conditions achieved three consecutive weeks of MA abstinence than those in non-CM conditions (47% vs 33%, p=.036). With regard to sertraline, the sertraline-only condition had significantly poorer retention than the other conditions, and the sertraline conditions had significantly more adverse events than placebo conditions.

A different study by Shoptaw et al.[45] compared 16 weeks of MM+CM to the same length of MM alone and CM alone for treatment-seeking gay and bisexual men who were dependent on MA (N = 162, 80% White/non-minority). The investigators found that participants in CM conditions were retained at a higher rate than those in MM alone. Across all conditions, participants reduced their drug use from baseline through 16-weeks (48.4% urine samples positive for metabolite at baseline, 16.5% positive at 16 weeks) and drug use, psychiatric severity, and sexual risk from baseline through follow-up. Compared to MM alone, the CM conditions evidenced significantly longer periods with MA-free urine tests; however, the difference was not observed at follow-up.

Rawson et al.[46] conducted a similar study comparing 16 weeks of MM+CM to MM alone and CM alone for treatment-seeking, stimulant-dependent individuals (N = 177, 55% White/non-minority). MM in this study consisted of 48 group CBT sessions. The researchers found that participants in the CM and CM+MM groups remained in treatment significantly longer (12.0-12.6 weeks) than those in the MM group (9.0 weeks) and gave more stimulant-free urine samples (Ms=27.6 and 28.6, respectively) during treatment than the MM only group (M=15.5). Fewer participants in MM only group (34.5%) achieved abstinence for 3 or more consecutive weeks compared to CM (60.0%) or MM+CM (69.5%). Those in MM+CM attended more CBT sessions (M=26.5) than those in MM (M=19.0). Those in CM and MM+CM earned comparable amounts from vouchers ($572 and $601, respectively, p=ns). All groups showed significant reductions in self-reported MA use, problems related to employment, alcohol, drugs, family/social, and psychiatric domains. At the 17-, 26- and 52-week follow-ups, the urinalysis results no longer showed significant differences between conditions, with groups having between 67% and 79% stimulant-free samples across time-points.

Roll et al.[47] conducted a secondary analysis of a large, multisite clinical trial of CM for stimulant abusers[48] focusing on outcomes in the subsample of participants whose drug of choice was MA (N = 113, 69% White/non-minority). The study compared 12 weeks of TAU to TAU + CM. MA users had been enrolled at 4 sites. At clinic at which largest number of MA using participants was enrolled, TAU was MM. The other sites generally employed other forms of CBT. The researchers found that, while retention and attendance did not differ between groups, CM participants submitted more stimulant- and alcohol-negative samples (p = .01) and had a longer mean period of continuous abstinence (approximately 4.6 weeks) than TAU participants (approximately 2.8 weeks) with 17.6% of CM participants remaining abstinent throughout the entire trial compared to 6.5% of TAU participants. There were no differences between groups at the 3- and 6-month follow-up assessments.

Hall et al.[49] conducted a study with offenders participating in a diversion drug treatment program, whose drug of choice was primarily MA (N = 139, 55% White/non-minority), comparing 26-weeks of TAU (MM) to TAU+CM. CM was tested in three formats with CM participants being randomized to one of the following conditions: vouchers for negative drug tests (max $20/week), vouchers for treatment adherence (max $20/week), and vouchers for both clean testing and adherence (max $40/week). All clients were provided with three sessions per week for 17 weeks, then one session per week for 11 weeks, and then voluntary aftercare. The researchers found that only 30-43% of participants in each group completed the intervention. The mean number of weeks in the intervention was 17-19. There were no significant differences between groups in time to treatment dropout. Each of the groups eligible to earn vouchers earned less than half of the maximum possible with the drug testing group earning a mean of $227, the treatment plan group earning a mean of $103, and the combined group earning a mean of $266. There were no significant differences between groups in measures of drug use. The combined reinforcement group showed a trend toward more rapid return to drug use. The researchers concluded that the drug court context may have overridden the CM treatment effect.

A study conducted in Seattle by Menza et al.[50] examined the effectiveness of a standalone voucher-based 12-week CM intervention compared to a control condition consisting of a referral to community resources for MSM who reported use of MA and sexual risk behavior (N = 127, 60% White/non-minority). Participants were assessed for MA use and sexual risk behaviors at baseline and every 6 weeks thereafter for 24 weeks. The investigators found retention to be 84% at 24 weeks. During the intervention sexual risk behavior declined in both groups, which were equally likely to provide an MA-positive urine sample. However, during the follow-up period, those in the CM group tended to be more likely than those in the control group to submit an MA-positive urine sample. During the intervention and follow-up periods, CM participants reported heavier and more frequent MA use compared to control participants. The investigators concluded that their 12-week CM intervention was associated with a potential increase in MA use and decreases in sexual risk that were not statistically significant. Thus, they felt their findings suggested that CM would be unlikely to produce large, sustained reductions in MA use among MSM.

Also in Seattle, McDonell et al.[51] compared the effects of 12 weeks of TAU + a CM add-on with contingent reinforcement to a control add-on with non-contingent reinforcement. Participants (N = 176, 54% White/non-minority) were individuals with serious mental illness and stimulant dependence. TAU was mental health, chemical dependency, housing, and vocational services. Most saw a case manager weekly, had access to psychiatric medication management, and could participate in various group treatments. A subset of participants in the CM group (46%) and the noncontingent control group (54%) received intensive outpatient group or individual substance abuse treatment during the study. The researchers found that the CM group retained participants for fewer weeks and had fewer participants retained throughout treatment compared with the control group. Those in CM group were 2.4 times as likely to submit a stimulant-negative urine sample during treatment and 1.4 times as likely during the 12-week follow-up period compared to the control group. Those in the CM group reported fewer days of stimulant use during treatment ($p<.05$) and follow-up ($p<.05$) compared to controls. Those in the CM group were less than one-third as likely to report IVDU during treatment compared to controls but groups did not differ during follow-up. There were no other differences in drug use or sexual risk behavior between groups.

In summary, while studies and findings from CM trials among persons with MA use disorders are complex, the treatment appears to be as effective for MA-dependent individuals as for cocaine-dependent individuals.[18] As noted by Shearer in a 2007 review of the literature[52], studies suggest that the efficacy of CM programs tends to be greatest during the treatment period when contingent rewards are provided and deteriorates after rewards are withdrawn, which further underscores Vocci and Montoya[18] that stimulant dependence may be best approached from a chronic disease perspective with treatments such as CM being provided over the long term. Cost effectiveness and sustainability of this resource-intensive intervention remains in question.

Mindfulness-Based Approaches

Mindfulness-based approaches are considered among the "third wave" of cognitive and behavioral therapies, where behavior therapy and traditional CBT represent the first and second waves. Unlike traditional CBT, mindfulness-based cognitive therapy does not seek to directly engage with and change thoughts but rather encourages its adherents simply to notice thoughts without engaging with or judging them and striving to be present fully in the moment.

ACT for substance use disorders emphasizes observation of the thinking process rather than disputation and modification of thought content, reducing experiential avoidance through increasing distress tolerance and acceptance skills, and values clarification to direct alternative activities to substance use.[28] As mentioned above, Smout et al.[28] compared a 12-session individual CBT intervention to a 12-session ACT intervention for MA users who primarily inject and found that ACT and CBT showed comparable attendance and reductions in self-reported MA use, consequences, and dependence symptoms. However, only the CBT group showed a significant

improvement in objectively assessed MA use. The investigators concluded that two broad directions seemed worth pursuing in developing ACT interventions. Given low the low attendance observed in their study, the researchers suggest it might be promising to combine ACT with CM to enhance attendance as CM has been found to enhance CBT. The researchers also suggested that because injection-MA users may only be willing to commit to brief therapy (4 sessions or less), shorter ACT protocols should be examined.

Glasner et al.[53] conducted a pilot RCT of a mindfulness-based relapse prevention (MBRP) intervention for individuals with stimulant dependence compared to a health education control condition. All participants (N = 63, 30% White/non-minority) received 12 weeks of twice-weekly prize-based CM. After a 4-week lead-in period of CM only, in addition to CM, participants received 8 weeks of weekly group-delivered MBRP or health education, according to random assignment. Goals of MBRP were to increase awareness of relapse triggers, interrupt automatic behavior sequences to promote mindful responses to triggers and cravings, and practice nonjudgmental awareness of one's moment-to-moment experience. Participants were given meditation exercise CDs for between-session practice and a log to record time spent practicing. MBRP sessions began with a guided meditation followed by homework review and were guided by a manual by Bowen et al.[54] The investigators found no between group differences in the number of MA-free urine samples; however, MBRP was associated with lower depression, anxiety, and psychiatric severity over time compared to health education.

Exercise

Because MA dependence is associated with comorbid depression and anxiety, and cessation of MA use produces an abstinence syndrome characterized by anhedonia, dysphoria, irritability, poor concentration, hypersomnia, low energy, and possible suicidality coupled with drug cravings and exercise has been shown to ameliorate negative mood states and improve cognition, physical exercise has been proposed as a potential treatment for MA dependence.[55] Morais et al.[56] reviewed the extant literature on exercise and MA dependence and concluded that MA users who engaged in a physical exercise program showed less depression and anxiety symptoms, lower relapse rates, and sustained abstinence when compared to nonexercised individuals. Relatively few studies examined MA use outcomes.

Haglund et al.[57] randomly assigned 135 individuals newly enrolled in residential treatment (41% White/non-minority) to a structured 8-week, 60-minute, 3 times per week exercise intervention or health education control group and examined outcomes during the 8-week treatment. The investigators found that, compared to the control condition, exercise was associated with a greater reduction in depression from baseline to the 8-week treatment discharge. Rawson et al.[58] examined follow-up outcomes of these participants after they were discharged to the community and assessed at 1-, 3-, and 6-months post-residential care. The investigators found that the exercise intervention was associated with a trend towards lower relapse rates at 1-, 3-, and 6-months post discharge. Results were not significant except among lower baseline severity users.

Trivedi et al.[59] conducted a RCT in 9 residential treatment programs across the US in which individuals with stimulant use disorders (N =302, 45% White/non-minority) were randomly assigned to either a thrice weekly dosed exercise intervention or a health education control intervention in addition to TAU over the course of 12 weeks. The researchers found that exercise modestly improved drug use outcomes only for those who were adherent to the prescribed exercise dose.

Summary

With no available approved medications for the treatment of MA dependence, behavioral and psychosocial interventions are the only demonstrated effective treatments available to those with MA use disorders. The treatments with supporting evidence include MM, CBT, MI, mindfulness-based approaches, and exercise. While effects have generally been modest, treatment response among those with MA use disorders have been found

to be are as good as the response among those with other substance use disorders.[19] Manning et al.[60] opined that evidence that the outcomes following engagement in treatment are at least as good among those with MA use disorders as they are among those with heroin or alcohol-related problems, both in terms of reduced substance use and improved wellbeing, is a critical message for professionals and the public alike and asserted that future priorities include stronger communication to the general population of the potential for positive outcomes for MA users following treatment as well as increased promotion of strategies to encourage treatment-seeking and facilitate access to diverse evidence-based treatment options.

References

1. http://adai.washington.edu/wadata/methamphetamine.htm
2. Hando J, Topp L, Hall W. Amphetamine-related harms and treatment preferences of regular amphetamine users in Sydney, Australia. Drug & Alcohol Dependence. 1997 Jun 6;46(1):105-13.
3. McKetin R, Mcketin R, Kelly E, Mcketin R, Kelly E. Socio-demographic factors associated with methamphetamine treatment contact among dependent methamphetamine users in Sydney, Australia. Drug and Alcohol Review. 2007 Jan 1;26(2):161-8.
4. Treatment Outcomes and Performance Pilot Studies Enhancement (TOPPS II) Inter-State Study, funded by the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration in September 1998 with 19 states
5. Ahmed KA, Yusuf C. Socio-demographic profiles and treatment outcomes of methamphetamine abusers in rural and urban areas. In The National Rural Alcohol and Drug Abuse Network Awards for Excellence 2004, Submitted and Award-Winning Papers. Technical Assistance Publication (TAP) number 28. DHHS Publication No. (SMA) 06-4183. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, 2006.
6. Walker SC, Lyon AR, Aos S, Trupin EW. The consistencies and vagaries of the Washington State Inventory of Evidence-Based Practice: the definition of "evidence-based" in a policy context. Administration and Policy in Mental Health and Mental Health Services Research. 2017 Jan 1;44(1):42-54.
7. Panenka WJ, Procyshyn RM, Lecomte T, MacEwan GW, Flynn SW, Honer WG, Barr AM. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug & Alcohol Dependence. 2013 May 1;129(3):167-79.
8. Morley KC, Cornish JL, Faingold A, Wood K, Haber PS. Pharmacotherapeutic agents in the treatment of methamphetamine dependence. Expert Opinion on Investigational Drugs. 2017 May 4;26(5):563-78.
9. Colfax GN, Santos GM, Das M, Santos DM, Matheson T, Gasper J, Shoptaw S, Vittinghoff E. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. Archives of General Psychiatry. 2011 Nov 7;68(11):1168-75.
10. Heinzerling KG, Swanson AN, Hall TM, Yi Y, Wu Y, Shoptaw SJ. Randomized, placebo-controlled trial of bupropion in methamphetamine-dependent participants with less than daily methamphetamine use. Addiction. 2014 Nov 1;109(11):1878-86.
11. Stoops WW, Rush CR. Combination pharmacotherapies for stimulant use disorder: a review of clinical findings and recommendations for future research. Expert Review of Clinical Pharmacology. 2014 May 1;7(3):363-74.
12. Pérez-Mañá C, Castells X, Torrens M, Capellà D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD009695. DOI: 10.1002/14651858.CD009695.pub2.
13. Longo M, Wickes W, Smout M, Harrison S, Cahill S, White JM. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. Addiction. 2010 Jan 1;105(1):146-54.
14. Shearer J, Darke S, Rodgers C, Slade T, Van Beek I, Lewis J, Brady D, McKetin R, Mattick RP, Wodak A. A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. Addiction. 2009 Feb 1;104(2):224-33.
15. Knopf A. MAT for methamphetamine or cocaine addiction: The case for Rx stimulants. Alcoholism & Drug Abuse

Weekly. 2015 Sep 21;27(36):1-4.
16. Ciketic S, Hayatbakhsh MR, Doran CM, Najman JM, McKetin R. A review of psychological and pharmacological treatment options for methamphetamine dependence. Journal of Substance Use. 2012 Aug 1;17(4):363-83.
17. Minozzi S, De Crescenzo F, Saulle R, Amato L. Psychosocial interventions for psychostimulant misuse. Cochrane Database of Systematic Reviews. 2016, Issue 9. Art. No.: CD011866. DOI: 10.1002/14651858.CD011866.pub2.
18. Vocci FJ, Montoya ID. Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. Current Opinion in Psychiatry. 2009 May;22(3):263.
19. Luchansky B, Krupski A, Stark K. Treatment response by primary drug of abuse: Does methamphetamine make a difference?. Journal of Substance Abuse Treatment. 2007 Jan 1;32(1):89-96.
20 ..Obert JL, McCann MJ, Marinelli-Casey P, Weiner A, Minsky S, Brethen P, Rawson R. The matrix model of outpatient stimulant abuse treatment: history and description. Journal of Psychoactive Drugs. 2000 Jun 1;32(2):157-64.
21. Obert J, McCann M, Rawson RA. Development and Dissemination of the Matrix Model of Intensive Outpatient Treatment. In: el-Guebaly N., Carrà G., Galanter M. (eds) Textbook of Addiction Treatment: International Perspectives. Springer, Milan. 2015.
22. Rawson RA, Marinelli-Casey P, Anglin MD, Dickow A, Frazier Y, Gallagher C, Galloway GP, Herrell J, Huber A, McCann MJ, Obert J. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. Addiction. 2004 Jun 1;99(6):708-17.
23. Rawson RA, Huber A, Brethen P, Obert J, Gulati V, Shoptaw S, Ling W. Status of methamphetamine users 2–5 years after outpatient treatment. Journal of Addictive Diseases. 2001 Dec 17;21(1):107-19.
24. Hillhouse MP, Marinelli-Casey P, Gonzales R, Ang A, Rawson RA. Predicting in-treatment performance and post-treatment outcomes in methamphetamine users. Addiction. 2007 Apr 1;102(s1):84-95.
25. Lee NK, Rawson RA. A systematic review of cognitive and behavioural therapies for methamphetamine dependence. Drug and Alcohol Review. 2008 May 1;27(3):309-17.
26. Baker A, Boggs TG, Lewin TJ. Randomized controlled trial of brief cognitive-behavioural interventions among regular users of amphetamine. Addiction. 2001 Sep 1;96(9):1279-87.
27. Baker A, Lee NK, Claire M, Lewin TJ, Grant T, Pohlman S, Saunders JB, Kay-Lambkin F, Constable P, Jenner L, Carr VJ. Brief cognitive behavioural interventions for regular amphetamine users: a step in the right direction. Addiction. 2005 Mar 1;100(3):367-78.
28. Smout MF, Longo M, Harrison S, Minniti R, Wickes W, White JM. Psychosocial treatment for methamphetamine use disorders: a preliminary randomized controlled trial of cognitive behavior therapy and Acceptance and Commitment Therapy. Substance Abuse. 2010 Apr 20;31(2):98-107.
29. Reback CJ, Shoptaw S. Development of an evidence-based, gay-specific cognitive behavioral therapy intervention for methamphetamine-abusing gay and bisexual men. Addictive Behaviors. 2014 Aug 1;39(8):1286-91.
30. Shoptaw S, Reback CJ, Peck JA, Yang X, Rotheram-Fuller E, Larkins S, Veniegas RC, Freese TE, Hucks-Ortiz C. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. Drug & Alcohol Dependence. 2005 May 9;78(2):125-34.
31. Tait RJ, McKetin R, Kay-Lambkin F, Carron-Arthur B, Bennett A, Bennett K, Christensen H, Griffiths KM. A web-based intervention for users of amphetamine-type stimulants: 3-month outcomes of a randomized controlled trial. JMIR Mental Health. 2014 Jul;1(1).
32. Tait RJ, McKetin R, Kay-Lambkin F, Carron-Arthur B, Bennett A, Bennett K, Christensen H, Griffiths KM. Six-month outcomes of a web-based intervention for users of amphetamine-type stimulants: randomized controlled trial. Journal of Medical Internet Research. 2015 Apr;17(4).
33. Smout MF, Longo M, Harrison S, Minniti R, Cahill S, Wickes W, White JM. The Psychostimulant Check-Up: A pilot study of a brief intervention to reduce illicit stimulant use. Drug and Alcohol Review. 2010 Mar 1;29(2):169-76.
34. Srisurapanont M, Sombatmai S, Boripuntakul T. Brief intervention for students with methamphetamine use disorders: a randomized controlled trial. The American Journal on Addictions. 2007 Mar 4;16(2):111-6.
35. Huang YS, Tang TC, Lin CH, Yen CF. Effects of motivational enhancement therapy on readiness to change MDMA

and methamphetamine use behaviors in Taiwanese adolescents. Substance Use & Misuse. 2011 Feb 8;46(4):411-6.
36. Polcin DL, Brown M, Galloway, GP. Higher dose motivational enhancement therapy manual. Addiction Pharmacology Research Laboratory, San Francisco. 2005.
37. Galloway GP, Polcin D, Kielstein A, Brown M, Mendelson J. A nine session manual of motivational enhancement therapy for methamphetamine dependence: adherence and efficacy. Journal of Psychoactive Drugs. 2007 Nov 1;39(sup4):393-400.
38. Polcin DL, Bond J, Korcha R, Nayak MB, Galloway GP, Evans K. Randomized trial of intensive motivational interviewing for methamphetamine dependence. Journal of Addictive Diseases. 2014 Jul 3;33(3):253-65.
39. Korcha RA, Polcin DL, Evans K, Bond JC, Galloway GP. Intensive motivational interviewing for women with concurrent alcohol problems and methamphetamine dependence. Journal of Substance Abuse Treatment. 2014 Feb 1;46(2):113-9.
40. Higgins ST, Petry, N. Contingency management: incentives for sobriety. Alcohol Research & Health. 1999;23(2):123-7.
41. Schierenberg A, van Amsterdam J, van den Brink W, E Goudriaan A. Efficacy of contingency management for cocaine dependence treatment: a review of the evidence. Current Drug Abuse Reviews. 2012 Dec 1;5(4):320-31.
42. Farronato NS, Dürsteler-MacFarland KM, Wiesbeck GA, Petitjean SA. A systematic review comparing cognitive-behavioral therapy and contingency management for cocaine dependence. Journal of Addictive Diseases. 2013 Jul 1;32(3):274-87.
43. Petry NM, Martin B, Cooney JL, Kranzler HR. Give them prizes, and they will come: contingency management for treatment of alcohol dependence. Journal of Consulting and Clinical Psychology 2000; 68:250–7
44. Shoptaw S, Huber A, Peck J, Yang X, Liu J, Dang J, Roll J, Shapiro B, Rotheram-Fuller E, Ling W. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. Drug & Alcohol Dependence. 2006 Oct 15;85(1):12-8.
45. Shoptaw S, Reback CJ, Peck JA, Yang X, Rotheram-Fuller E, Larkins S, Veniegas RC, Freese TE, Hucks-Ortiz C. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. Drug & Alcohol Dependence. 2005 May 9;78(2):125-34.
46. Rawson RA, McCann MJ, Flammino F, Shoptaw S, Miotto K, Reiber C, Ling W. A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. Addiction. 2006 Feb 1;101(2):267-74.
47. Roll JM, Petry NM, Stitzer ML, Brecht ML, Peirce JM, McCann MJ, Blaine J, MacDonald M, DiMaria J, Lucero L, Kellogg S. Contingency management for the treatment of methamphetamine use disorders. American Journal of Psychiatry. 2006 Nov;163(11):1993-9.
48. Peirce JM, Petry NM, Stitzer ML, Blaine J, Kellogg S, Satterfield F, Schwartz M, Krasnansky J, Pencer E, Silva-Vazquez L, Kirby KC. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: A National Drug Abuse Treatment Clinical Trials Network study. Archives of General Psychiatry. 2006 Feb 1;63(2):201-8.
49. Hall EA, Prendergast ML, Roll JM, Warda U. Reinforcing abstinence and treatment participation among offenders in a drug diversion program: Are vouchers effective?. Criminal justice and behavior. 2009 Sep;36(9):935-53.
50. Menza TW, Jameson DR, Hughes JP, Colfax GN, Shoptaw S, Golden MR. Contingency management to reduce methamphetamine use and sexual risk among men who have sex with men: a randomized controlled trial. BMC Public Health. 2010 Dec;10(1):774.
51. McDonell MG, Srebnik D, Angelo F, McPherson S, Lowe JM, Sugar A, Short RA, Roll JM, Ries RK. Randomized controlled trial of contingency management for stimulant use in community mental health patients with serious mental illness. American Journal of Psychiatry. 2013 Jan;170(1):94-101.
52. Shearer J. Psychosocial approaches to psychostimulant dependence: a systematic review. Journal of Substance Abuse Treatment. 2007 Jan 1;32(1):41-52.
53. Glasner S, Mooney LJ, Ang A, Garneau HC, Hartwell E, Brecht ML, Rawson RA. Mindfulness-based relapse prevention for stimulant dependent adults: a pilot randomized clinical trial. Mindfulness. 2017 Feb 1;8(1):126-35.

54. Bowen S, Chawla, N, Marlatt, GA. Mindfulness-based relapse prevention for addictive behaviors: a clinician's guide. Guilford Press, New York. 2011.
55. Mooney LJ, Cooper C, London ED, Chudzynski J, Dolezal B, Dickerson D, Brecht ML, Peñate J, Rawson RA. Exercise for methamphetamine dependence: rationale, design, and methodology. Contemporary Clinical Trials. 2014 Jan 1;37(1):139-47.
56. Morais AP, Pita IR, Fontes-Ribeiro CA, Pereira FC. The neurobiological mechanisms of physical exercise in methamphetamine addiction. CNS neuroscience & therapeutics. 2017 Dec 22;24:85-97.
57. Haglund M, Ang A, Mooney L, Gonzales R, Chudzynski J, Cooper CB, Dolezal BA, Gitlin M, Rawson RA. Predictors of depression outcomes among abstinent MA-dependent individuals exposed to an exercise intervention. American Journal on Addictions. 2015 Apr 1;24(3):246-51.
58. Rawson RA, Chudzynski J, Mooney L, Gonzales R, Ang A, Dickerson D, Penate J, Salem BA, Dolezal B, Cooper CB. Impact of an exercise intervention on methamphetamine use outcomes post-residential treatment care. Drug & Alcohol Dependence. 2015 Nov 1;156:21-8.
59. Trivedi MH, Greer TL, Rethorst CD, Carmody T, Grannemann BD, Walker R, Warden D, Shores-Wilson K, Stoutenberg M, Oden N, Silverstein M. Randomized controlled trial comparing exercise to health education for stimulant use disorder: results from the CTN-0037 stimulant reduction intervention using dosed exercise (STRIDE) Study. The Journal of Clinical Psychiatry. 2017;78(8):1075-82.
60. Manning V, Best D, Garfield JB, Allsop S, Berends L, Lubman DI. Money well-spent: Further evidence of improved outcomes for methamphetamine users following treatment. Drug and Alcohol Review. 2017 Mar 1;36(2).

Citation: Stoner SA. Effective Treatments for Methamphetamine Use Disorder: A Review. Seattle: Alcohol & Drug Abuse Institute, University of Washington, April 2018.
URL: http://adai.uw.edu/pubs/pdf/2018methtreatment.pdf.

This report was produced with support from the Washington State DSHS Division of Behavioral Health and Recovery (DBHR)

Table 1.

Mechanisms of Action of Medications Examined for Methamphetamine Use Disorders

	Mechanism	Current uses	Dopamine (DA)	Norepinephrine (NE)	Serotonin (S/5-HT)	Glutamate (GL/NMDA)	Epinephrine	Histamine (H)	Acetylcholine (ACH)	GABA	Calcium channels	Opioid system	Phosphodiesterase	Toll-like receptors	Angiotensin
Acamprosate	NMDA receptor antagonist, modulator of $GABA_A$	Alcohol use disorder								x					
Aripiprazole	Very complex effects on a variety of receptors, especially D and 5-HT	Antipsychotic	x		x										
Atomoxetine	Norepinephrine, dopamine reuptake inhibitor, NMDA receptor antagonist	Attention deficit disoder (ADHD)	x	x		x									
Baclofen	$GABA_B$ receptor agonist	Antispasmodic								x					
Bupropion	Reuptake inhibitor, blocks presynaptic DA transporter, targets NE transporter and nicotinic ACH receptors	Antidepressant, smoking cessation	x	x					x						
Buspirone	Decreases S, increases D/N, may affect oxytocin, does not affect GABA	Antianxiety	x	x	x										
Candesartan	Angiotensin II receptor antagonist	Hypertension													x
Cinnarizine	Antihistamine, calcium channel blocker	Motion sickness, vertigo, cerebral blood flow						x			x				
Citicoline	Possibly increases dopamine receptor densities	Memory disorders	x												
Creatine	Increases GABA	Building muscle mass								x					
Dextroamphetamine	Promotes release of DA, NE, & S	ADHD, narcolepsy	x	x	x	x	x	x			x				
Doxazosin, prazosin	Alpha blocker	Hypertension, diuretic, PTSD					x								
Entacapone	Inhibits COMT, increases catecholamines	Parkinson's disease	x	x											
Flumazenil + gabapentin	$GABA_A$ receptor agonist + ion channel effects of gabapentin	Benzodiazepine antagonist +antiepileptic								x	x				
Flumazenil + gabapentin + hydroxazine (Prometa)	$GABA_A$ receptor agonist + ion channel effects of gabapentin + histamine receptor antagonist	Benzodiazepine antagonist + antiepileptic + antihistamine						x		x	x				
Fluoxetine, sertraline, etc.	Selective serotonin reuptake inhibition	Antidepressant			x										
Flupentixol	Dopamine antagonist	Antipsychotic	x												
Gabapentin	Nonselective GABA agonist	Neuropathic pain, epilepsy, restless legs				x				x	x				
Ibudilast	Phosphodiesterase (PDE4) inhibitor	Asthma, stroke, MS, anti-inflammatory											x	x	
Imipramine, desipramine, etc.	Complex S/N reuptake inhibition; antagonists of 5-HT, α-adrenergic, NMDA, H, muscarinic ACH; agonists at sigma receptors; ion channel blockade; imipramine is TLR4 antagonist	Tricyclic antidepressant		x	x	x	x	x	x		x			x	
Isradipine, amlodipine	Calcium channel blockade	High blood pressure									x				
Lisdexamfetamine	Prodrug of d-amphetamine	ADHD, binge eating disorder	x	x	x	x	x	x			x				
Lobeline	Partial nicotinic ACH receptor agonist - act as MA antagonist	Smoking cessation							x						
Methylphenidate	Binds DA & NE transporters	ADHD	x	x											
Mirtazapine	Serotonin, histamine, and α_2–adrenergic antagonist	Antidepressant		x	x		x	x							
Modafinil	Complex, weak stimulant, binds DA transporter	Narcolepsy, sleep apnea, hypersomnia	x			x									
N-acetylcysteine	Complex-affects glutamate, glutathione, neurotrophins, apoptosis, mitochondria, inflammation	Acetaminophen overdose, various psych disorders, cocaine addiction				x									
Naltrexone	Opioid antagonist, TLR4 antagonist	Opioid and alcohol use disorders										x		x	
Ondansetron	$5\text{-}HT_3$ receptor antagonist	Antiemetic			x										
Oxazepam	Agonist of $GABA_A$	Antianxiety								x					
Perindopril	ACE inhibitor	Hypertension, CHF, CAD													x
Risperidone, paliperidone	$D_{1\text{-}5}$ and $5\text{-}HT_{2A/2C}$ receptor antagonist	Antipsychotic	x	x	x										
Rivastigmine	Inhibits cholinesterases	Alzheimer's and Parkinson's diseases							x						
Topiramate	Unclear, possibly $GABA_A$ receptor agonist + ion channel effects	Antiepileptic								x	x				
Tyrosine	Precursor to DA and N	Phenylketonuria	x	x											
Varenicline	high-affinity partial agonist for $\alpha_4\beta_2$ nicotinic ACH receptor→DA release in nucleus accumbens	Smoking cessation	x						x						
Vigabatrin, CPP-115	GABA transaminase inhibitor	Antiepileptic								x					