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A Review of Treatment Options for Co-Occurring Methamphetamine Use Disorders and Depression

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Abstract

Co-occurring methamphetamine use and depression interferes with treatment outcomes. Female methamphetamine users are known to have higher rates of depression than male methamphetamine users, although this is also true for the general population. There are limited treatment options for the management of depression among methamphetamine users. In this integrative review, we summarize data on treatment strategies for co-occurring depression and methamphetamine use disorders. English-language articles were identified from PsychINFO, CINAHL, PubMed, and Medline as well as from reference lists of key articles. Search terms included “methamphetamine,” “depression,” and “treatment.” Research articles describing psychological ($n=3$), pharmacological ($n=6$), nutritional supplement ($n=1$), and psychological combined with pharmacological ($n=3$) approaches for the treatment of methamphetamine use or withdrawal and/or depression are included in this review. Psychological and combination of psychological with pharmacological approaches have not been shown to be effective in treating these co-occurring conditions. Antidepressants have been determined to be ineffective and/or to introduce side effects. Gender differences with response to treatment were examined in only one of the published studies. There is a large gap in knowledge regarding treatment of co-occurring methamphetamine use disorders and depression. Considering that female methamphetamine users experience higher rates of depression than men, a focus on gender-specific treatment approaches is warranted.

Keywords

co-occurring disorders; depression; gender-specific; methamphetamine use disorder; treatment options

Methamphetamine (MA), a derivative of amphetamine, is a potent stimulant that affects the brain and central nervous system. MA use results in increased dopamine release in the brain

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as well as reduction of dopamine uptake, causing feelings of pleasure, increased energy, and greater alertness, and as a result, MA has high abuse potential. The current MA use trend in the United States is decreasing with approximately 493,000 Americans aged 12 years or older reporting being current MA users versus 2.4 million in 2005 and 2006 (U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2012). Although rates of MA use are declining nationally, the consequences of MA abuse are still a public health concern. Both acute and chronic MA abuses have serious medical, psychiatric, and dental repercussions. Short- and long-term health effects of MA abuse include stroke (Perez, Arsur, & Strategos, 1999), cardiac arrhythmia (Haning & Goebert, 2007), depression (McKetin, Lubman, Lee, Ross, & Slade, 2011; Thomas, Angoa Perez, Francescutti-Verbeem, Shah, & Kuhn, 2010), anxiety (Glasner-Edwards et al., 2010), insomnia, paranoia (McGregor et al., 2005), and structural and chemical changes to the brain (Sekine et al., 2003; Yoon et al., 2010). Depression, in particular, is a public health concern because cost-of-illness research has indicated that depression is associated with considerable economic burden, with most of the burden deriving from lost work productivity (Wang, Simon, & Kessler, 2003). Along those same lines, depression also impacts our healthcare system as nearly 70% of patients seen in a primary care setting present with symptoms consistent with depression (Robinson, Geske, Prest, & Barnacle, 2005), but accurate depression diagnoses are often delayed by comorbid medical conditions (Katon, 2004). Finally, with respect to MA dependency and co-occurring depression, research shows that this dual diagnosis worsens the overall prognosis and confounds treatment outcomes (Glasner-Edwards et al., 2010).

It is not uncommon for depression and substance use to co-occur (McKetin et al., 2011; Thomas et al., 2010). The association between the two conditions is likely bidirectional, with short- and long-term substance use resulting in mood changes and substance use being a compensatory behavior to alleviate symptoms of depression (Koob et al., 2014). MA has unique effects as its chronic use is known to reduce brain concentrations of dopamine and serotonin, which predisposes MA users to depression (Sekine et al., 2003; Thomas et al., 2010). Moreover, MA directly influences brain monoamine regulation resulting in a state that includes several of the features of major depression, including mood, sleep, and appetite disturbances (London et al., 2004). However, symptoms of depression are not exclusive to MA use. Studies of other substances of abuse, such as cocaine, heroin, alcohol, and nicotine, have documented increased rates of depression that exceed general population estimates. Similarly, a pattern of elevated co-occurring substance use disorders and depression generally involves more women than men. For example, in a study of adults seeking treatment for cocaine abuse, 34.8% of women versus 28.6% of men also met criteria for lifetime major depression (McCance-Katz, Carroll, & Rouansaville, 1999). Findings from large survey studies are similar for both opioid use disorders and major depression as well as alcohol dependence and major depression. Rates have been documented as 63.5% of women compared with 45.7% of men (Grella, Karno, Warda, Niv, & Moore, 2009) and 48.5% of women compared with 24.3% of men, respectively, meeting criteria for co-occurring depression and an opioid use disorder or alcohol dependence (Kessler et al., 1997). The prevalence of daily nicotine use and co-occurring depression, on the other hand, appears to

be higher in men (36.8%) compared with women (33.6%) (Husky, Mazure, Paliwal, & McKee, 2008).

Several studies have shown that depression rates are higher in MA-using women compared with men (Glasner-Edwards et al., 2008a, 2008b; Semple, Zians, Strathdee, & Patterson, 2007; Zweben et al., 2004). With that said, it is unclear if this is a result of an existing gender difference, a type of self-medication, or a consequence of MA use; however, the prevalence of premorbid depressive disorders in MA users has been documented to be high, with most reporting a significant lifetime history of depression (Hall, Andrus, Oostveen, Althaus, & VonVoigtlander, 1996; Darke, Kaye, McKetin, & Duflou, 2008; Zweben et al., 2004). For example, in one study, MA users had a 62% rate of depression and a 23% rate of suicidality before initiating MA use, and after MA use was initiated, depression rates increased by nearly 20% (Hall et al., 1996). Furthermore, using the Beck Depression Inventory, Semple and colleagues (2007) noted that 60% of MA-using women in their study met criteria for moderate-to-severe depression, and these women were three times more likely to have used MA “to cope with mood” compared with women with lower levels of depressive symptoms. Moreover, in a longitudinal study of MA-dependent adults participating in the Methamphetamine Treatment Project, 70% of the women who met criteria for major depressive disorder at study initiation still met criteria for depression at a 3-year follow-up visit (Glasner-Edwards et al., 2008a). In contrast, in one study of MA-dependent adults, rates of depression were noted as higher in men (31%) than women (28%), but as the authors noted, the instrument used, the Psychiatric Diagnostic Screening Questionnaire, does not indeed detect *Diagnostic and Statistical Manual of Mental Disorders (DSM)* criteria but, rather, serves as a screening tool (Polcin, Buscemi, Nayak, Korcha, & Galloway, 2012). Nonetheless, most of these findings highlight that women in general are more likely than men to have depression, and with substance use disorders, gender differences are underscored in ways that suggest greater rates of co-occurring depression in women relative to men.

The diagnosis and treatment of depression among MA users is problematic because intoxication and withdrawal symptoms mirror symptoms of depression. There are at least three distinct syndromes to consider when assessing MA users: (a) expected effects from MA use and symptoms of withdrawal when MA use is discontinued, (b) depressive symptoms that develop during periods of active MA use, and (c) a depressive disorder that is independent from MA use. *The DSM Fifth Edition (DSM-5)* offers guidelines for discerning independent depressive disorders and substance-induced disorders. According to the *DSM-5*, if depressive symptoms develop before substance use was initiated or if symptoms occur and persist for 4 weeks or longer after substance use is terminated, criteria are met for an independent depressive disorder (American Psychiatric Association [APA], 2013). In addition, based on *DSM-5* criteria, depressive symptoms that manifest during a period of substance use that is insufficient to attain intoxication or withdrawal effects would be a diagnosis of an independent depressive disorder (APA, 2013). Conversely, criteria for substance-induced depression are met when depressive symptoms occur during or soon after intoxication or withdrawal from a substance that is capable of producing the symptoms (APA, 2013). Yet, to our knowledge, there are no published studies that have addressed the reliability of *DSM-5* criteria for differentiating between substance intoxication and

withdrawal symptoms versus an independent depressive disorder. There is some evidence, though, of acceptable reliability ($\kappa = 0.75$) for a current independent diagnosis of depression among substance users as well as reliability ($\kappa = 0.66$) for current substance-induced depression in a study evaluating the Psychiatric Research Interview for Substance and Mental Disorders for *DSM Fourth Edition* (Hasin et al., 2006), although these measures of reliability are limited to one report and it is not well documented if the Psychiatric Research Interview for Substance and Mental Disorders is widely used. It is also noteworthy that time constraints in a clinical setting may not permit for rigorous patient interviewing to separate substance-induced symptoms from more enduring symptoms. In the face of these challenges with distinguishing between an independent depressive disorder and a substance-induced depressive disorder, the significance of these differential diagnoses is centered on treatment planning and improving outcomes.

Despite the evidence regarding depression rates in MA users, little is known about treatment options for depression among MA users. Treatment approaches for MA dependence have been recently reviewed (Ciketic, Hayatbakhsh, Doran, Naiman, & McKetin, 2012; Lee & Rawson, 2008), but the issue of managing co-occurring conditions has not been examined closely. Therefore, the purpose of this article is to summarize published reports on treating depression in MA users with a particular focus on treatment response differences by gender. Evaluating treatment response by gender is important because rates of MA use among men and women approach nearly equal proportions (Durell, Kroutil, Crits-Christoph, Barchha, & Van Brunt, 2008). This use rate pattern is unlike that observed with many other drugs of abuse, which typically show men using more than women (Cohen, Greenberg, Uri, Halpin, & Zweben, 2007; Durell et al., 2008). Given the paucity of information with regard to treating co-occurring MA use disorders and depression, the current article will help provide a review of treatment approaches and their outcomes.

METHODS

Following Whittemore and Knafl's (2005) guidelines, an integrative review was conducted with a specific focus on treatment approaches for depression in MA use disorders. Methods were used to identify relevant literature included searching electronic databases and searching the reference lists of key articles. The electronic databases searched included PsychINFO, CINAHL, PubMed, and Medline. The key search terms included in the search were "methamphetamine," "depression," and "treatment." Next, data were evaluated for inclusion. Articles were selected for their relevance to the research focus. Publications reporting findings from preclinical or animal studies were excluded. Finally, the data were extracted from primary sources and organized by treatment approach.

RESULTS

There is very little documentation available regarding the treatment of co-occurring MA use and depression. The peer-reviewed publications selected for this integrative review included empirical research reports that described findings from randomized controlled trials (RCTs) and nonrandomized trials. Publications emerged beginning in the early to mid-1990s. The search yielded three articles reporting psychological approaches for managing co-occurring

depression and MA dependence. There were six articles found reporting findings from studies evaluating pharmacological approaches to treating MA dependence or withdrawal, and although the primary outcome of these studies was not to treat co-occurring depression and MA dependence, they were included in this review because depression was a secondary outcome measure. There was one article reporting the results of a nutritional supplement trial of cooccurring unipolar or bipolar depression and MA dependence identified in the search. Finally, three articles were found reporting findings from a study investigating the combination of a pharmacological and psychological approach for the treatment of MA dependence.

Psychological Approaches

All of the studies evaluating psychological approaches to treating co-occurring depression and MA use investigated cognitive behavioral therapy (CBT) as an intervention (see Table 1). During the last 3 decades, CBT has been considered one of the most effective types of therapy for treatment of alcohol and drug dependencies (Anton et al., 2005; DeRubeis & Crits-Christoph, 1998; Mattick & Heather, 1993), but little evidence exists regarding the use of CBT for treating co-occurring depression and MA use. In fact, Peck and colleagues (2005) compared 16 weeks of CBT, contingency management, CBT plus contingency management, and gay-specific CBT and noted a 75% decrease in MA use across all groups randomized to the four difference conditions, but no statistically significant changes in depression were detected. In another study, subjects assigned to CBT reported nearly 50% less amphetamine use over 6 months, but CBT had only a short-term effect on depression rating scores (Baker et al., 2004). Baker and colleagues (2004) did not separate the findings by type of amphetamine so changes specific to MA use are unknown. Collectively, these findings suggest that CBT is useful for reducing MA use but not for the treatment of co-occurring MA use and depression.

Stepped care, which is a healthcare model that supports starting with a less intensive approach to treatment and transitioning to more intensive therapy if indicated (Murphy, Lynch, Oslin, McKay, & TenHave, 2007), has also been evaluated for treatment of alcohol and drug use disorders. As with CBT, there are limited reports of stepped care being effective for co-occurring depression and MA use. In a feasibility study, a stepped-care approach was shown to be effective in reducing depressive symptoms (Kay-Lambkin et al., 2010); however, these findings warrant further exploration and replication in a larger sample of MA users.

Two of the studies evaluating psychological approaches to the treatment of MA included subjects of both genders (Baker et al., 2004; Kay-Lambkin et al., 2010), whereas one of the studies included male homosexual subjects only (Peck et al., 2005). Of the two studies that included both men and women, treatment response results were not separated by gender. However, although there was a gender bias favoring the enrollment of men, 62.6% (Baker et al., 2004) and 56% (Kay-Lambkin et al., 2010), more women (83.3%) were likely to complete treatment compared with men (60.5%; Baker et al., 2004).

Pharmacological Approaches

There is one published study on the use of an antidepressant for the management of MA withdrawal, four published studies on the utilization of antidepressants in treating MA dependence, one published study evaluating a stimulant for the treatment of MA dependence, and one published study on the utility of a nutritional supplement in treating co-occurring depression and MA use (see Table 1). In the studies evaluating the use of antidepressants, the authors also compared differences in depressive symptoms between the groups randomized to an antidepressant or placebo. The findings consistently showed no significant changes in depressive symptoms (Cruickshank et al., 2008; Elkashef et al., 2008; Galloway et al., 1994, 1996; Shoptaw et al., 2008). Elkashef et al., 2008; Galloway et al., 1994, 1996; Shoptaw et al., 2008).

Brown and Gabrielson (2012) reported findings from an RCT of the nutritional supplement citicoline or placebo for bipolar or unipolar depression among MA-dependent adults. Their study results showed a 33% improvement in depression rating scores measured by the Inventory of Depressive Symptomatology-Clinician Rated in the citicoline group, whereas the placebo group showed a 13% improvement in the Inventory of Depressive Symptomatology-Clinician Rated scores (Brown & Gabrielson, 2012). It is worth noting that citicoline (generic name for CDP-choline when used as a supplement) is a complementary and alternative medicine approach for the treatment of depression. In the United States, citicoline, which is a natural-occurring compound, is sold as a nutritional supplement over the counter (Adibhatla & Hatcher, 2005). Apart from the mood finding, self-report MA use and urine drug screen findings indicated no significant differences in MA use from study entry to study completion (Brown & Gabrielson, 2012). Finally, there were no significant differences noted with regard to frequency and amount of MA use for the duration of the study between groups (Brown & Gabrielson, 2012). These findings suggest that citicoline is not effective in the treatment management of co-occurring MA dependence and depression, although the study needs to be replicated in a larger sample focused solely on either unipolar or bipolar depressed subjects.

In an open-label study evaluating a nonamphetamine stimulant, modafinil, for the treatment of MA dependence, the authors reported a statistically significant decrease in Hamilton Depression Rating Scores from beginning of the study to completion (McGaugh et al., 2009). However, there was no change in the number of positive urine drug screens during the course of the 6-week trial (McGaugh et al., 2009). These findings should be interpreted with caution considering that the sample size at study initiation was eight and only four subjects remained at study completion. Furthermore, the choice of a parametric statistical method may not have been appropriate based on the small sample size.

Only one of the published findings of pharmacological approaches to treating either MA dependence or depression among MA users separated results by gender (Elkashef et al., 2008). All of the studies enrolled more men than women with the exception of the open-label modafinil study, which enrolled four women and three men (McGaugh et al., 2009).

Pharmacological and Psychological Approaches

There are three published studies regarding the combination of pharmacological and psychological approaches for the treatment of MA dependence (see Table 1). Most of the studies suggest that pharmacological and psychological studies are not effective for treatment of MA dependence (Heinzerling et al., 2010; Shoptaw et al., 2006) and/or the subjects experienced undesirable side effects (Shoptaw et al., 2006). Indeed, in the placebo-controlled trial of the selective serotonin reuptake inhibitor sertraline, the researchers found that subjects randomized to the selective serotonin reuptake inhibitor experienced sustained craving and had an increased rate of relapse (Shoptaw et al., 2006). On the other hand, in a sample of HIV-positive MA-abusing men, in a single-blind study of modafinil combined with CBT, medication responders experienced a decrease in depressive symptoms over 12 weeks, with medication response being defined as greater than 50% reduction in the number of days of self-report MA use (McElhiney et al., 2009). Because 55% of the men were on antiretroviral therapy (McElhiney et al., 2009), it is possible that there was an interaction between the antiretroviral medication and modafinil resulting in changes in mood. Nonetheless, the results of this study are not generalizable when taking into account the small homogenous sample ($n=10$ completers).

Of the three studies evaluating the combination of pharmacological and psychological interventions for the treatment of MA dependence, one of them included only men (McElhiney et al., 2009). The other two studies did not separate the findings by gender, and both studies enrolled more men than women (Heinzerling et al., 2010; Shoptaw et al., 2006).

DISCUSSION

This review explored treatment approaches for the management of co-occurring depression and MA use. The results yielded 13 publications. Studies evaluating psychological approaches, such as CBT, are limited, and results suggest that psychological interventions may be useful in treating MA dependence but not depression among MA users. In studies of antidepressants for treatment of MA withdrawal, dependence, and co-occurring mood disorders, findings have suggested that antidepressants are ineffective. However, results from a randomized control trial of the nutritional supplement citicoline indicate that citicoline may be effective in reducing depressive symptoms in a sample of unipolar and bipolar depressed MA-using adults but not effective in reducing MA dependence. Citicoline is an endogenous intermediate in the biosynthetic pathways of structural membrane phospholipids. Of relevance, citicoline increases brain dopamine and norepinephrine levels, presumably by increasing the activity of tyrosine hydroxylase (Secades & Lorenzo, 2006). Considering that chronic MA use results in disturbances in the dopaminergic systems, perhaps, citicoline administration helps correct these disturbances, and in turn, mood is improved. In a small open-label study of a nonamphetamine stimulant, modafinil, for the treatment of MA dependence, depressive symptoms improved over the course of the study, but concerns of a small sample size ($n=4$ completers) need to be examined when evaluating these results. Moreover, in a small ($n=10$ completers) study of modafinil combined with CBT in HIVpositive men, depressive symptoms improved, and self-report MA use was reduced over the 12-week treatment period. Modafinil has stimulant-like effects, which may

explain lower depression rating scores while taking it (Price & Taylor, 2005). Finally, studies investigating a nonamphetamine stimulant or antidepressant in addition to psychological approaches in treating MA dependence have shown to be ineffective, have undesirable side effect profiles, or enrolled a small homogenous sample, which limits generalizability of the study results. Only one of the published reports separated treatment response results by gender. Overall, there were a higher percentage of men enrolled in each study, which is not too surprising considering that several of the studies enrolled HIV-positive men only.

The main finding from this review that treatment options are scarce for co-occurring depression and MA use disorders was anticipated given that there is little evidence-based research guiding the management of co-occurring mood and substance use disorders. Findings from RCTs of pharmacotherapy for a co-occurring substance use disorder, with alcohol being the primary substance evaluated, and bipolar disorder consistently reveal that there are no changes in either depressive or manic symptoms (Brown et al., 2009; Salloum et al., 2005; Stedman et al., 2010; Tolliver, Desantis, Brown, Prisciandaro, & Brady, 2012) or reductions in alcohol use (Brown et al., 2009; Stedman et al., 2010; Tolliver et al., 2012). Results, however, are inconsistent from RCT studies of pharmacotherapy management of co-occurring substance use disorders, with opiates, alcohol, or cocaine largely investigated, and unipolar depression. Studies show either a reduction in cocaine or alcohol use but no changes in depressive symptoms (Ciraulo et al., 2005; Hernandez-Avila, Modesto-Lowe, Feinn, & Kranzler, 2004; Pettinati et al., 2010), reduced alcohol use, and depressive symptoms (Moak et al., 2003) or no changes in opiate, alcohol, or cocaine use and/or depressive symptoms (Carpenter, Brooks, Vosburg, & Nunes, 2004; Petrakis et al., 1998; Pettinati et al., 2001; Schmitz et al., 2001). Moreover, experimental and nonexperimental studies evaluating psychological approaches for the treatment of co-occurring mood disorders and substance use disorders show varying results but overall show that motivational interviewing combined with CBT may result in short-term reduced substance use and improvements in mental status (Cleary, Hunt, Matheson, & Walter, 2008).

One of the goals of this review was to investigate if treatment response differs by gender. However, reporting results by gender was not common, and more men compared with women were enrolled in most of the studies. Because rates of substance use overall generally favor men (Durell et al., 2008), we expected this finding. Nonetheless, barriers to seeking substance abuse treatment and treatment retention that are specific to women are worth considering. For instance, substance-abusing women worry about losing custody of their children if they seek services for substance-related issues (Brady & Ashley, 2005). Furthermore, limited access to and lack of financial support for childcare services in addition to responsibilities as a mother are frequently reported as obstacles to women seeking substance abuse treatment (Brady & Ashley, 2005; van Olphen & Freudenberg, 2004). Finally, reports suggest that women experience greater social stigma and guilt than men do, which may serve as an additional impediment to women seeking substance abuse treatment (Booth & McLaughlin, 2000; Brady & Ashley, 2005).

Studies of co-occurring depression and substance use disorders are faced with particular challenges. Notably, attrition rates are remarkably high (Gelkopf, Weizman, Melamed, Adelson, & Bleich, 2006; Sayre et al., 2002), and teasing apart symptoms of depression as a

primary diagnosis from substance withdrawal symptoms can be difficult. Along those same lines, measuring the severity depression in substance-abusing and substance-dependent populations is not easy. The oscillation between intoxication with and withdrawal from substances may artificially drive depression rating scores up or down. Although depression is common with abuse or dependence in all classes of substances, the distinct pharmacological effects of MA are unique. During periods of intoxication, by way of increased synaptic dopamine concentrations, MA may exert mood-elevating effects; however, once MA use is stopped, the “crash” or “come down” results in symptoms of depression.

RECOMMENDATIONS

The findings of this review show the limitations of treatment options for the management of co-occurring depression and MA use disorders. Although investigations of modafinil should be interpreted cautiously because of small, heterogeneous samples sizes, clinicians might consider prescribing it for patients with depression and MA use disorders. In addition, detailed psychiatric and substance use histories should be collected for making a distinction between a primary diagnosis of depression versus substance-induced depression.

Until there is a broader evidence-based foundation for the treatment of co-occurring depression and MA use disorders, attention should be focused on designing and conducting high-quality clinical trials. Future studies should include larger sample sizes in addition to standardized outcome measures. In addition, standardized treatment and follow-up periods would be advantageous for understanding treatment effects. Finally, as clinicians and clinical investigators investigate new strategies for treating co-occurring depression and MA use disorders, more gender-specific attention is warranted.

CONCLUSION

No clear treatment model exists to suggest how to optimally manage co-occurring depression and MA use disorders. Several studies have shown that female MA users experience depression at rates higher than male MA users, although this is also true in the general population. Investigating treatment options for MA users that have greater efficacy and/or safer side effect profiles is an important next step. In addition, standardizing measurement and reporting for future studies in this area (e.g., using the same depression rating scale and reporting outcomes by gender) would be useful for interpreting results and understanding additional gaps in our knowledge of co-occurring MA use and depression. High-quality studies of co-occurring depression and MA use disorders are required for building a more expansive foundation of evidence-based practice to guide clinical and research recommendations.

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Table 1
Results of Literature Review of Treatment Options for Methamphetamine (MA) Use and Depression

Author	Sample	Study Design	Intervention	Depression as Primary or Secondary Outcome	Tool for Measuring Depression	Length of Time in Treatment	Results
Psychological approaches for the treatment of comorbid depression and MA use							
Baker et al. (2004)	214 amphetamine users (62.6% men)	Randomized control trial	Motivational interviewing (MI), cognitive-behavioral therapy (CBT)	Secondary	Beck Depression Inventory II	Not specified, but participants randomized to two or four sessions of CBT + self-help booklet or self-help booklet alone	There was a statistically significant improvement in depression rating scores between pretreatment and posttreatment ($F_{1,148} = 48.61, p < .001$) and between pretreatment and 6-month follow-up ($F_{1,146} = 51.77, p < .001$), and no differences in scores between posttreatment and 6 months.
Kay-Lambkin, Baker, McKetin, and Lee (2010)	18 current MA users (56% men)	Nonrandomized trial	One-session integrated brief integrated CBT/MI stepped-care intervention	Primary	Beck Depression Inventory II	20 weeks	Participants receiving stepped-care intervention reported a 53% decrease in depression rating scores compared with a 48% decrease in the control group.
Peck, Reback, Yang, Rotheram-Fuller, and Shoptaw (2005)	162 gay and bisexual male MA users	Nonrandomized trial	CBT, contingency management (CM), CBT + CM, gay-specific CBT	Primary	Beck Depression Inventory	16 weeks	No statistically significant differences in depression were noted.
Pharmacological approach for the treatment of MA withdrawal							
Cruikshank et al. (2008)	31 amphetamine- or MA-dependent adults (63% men)	Double-blind, placebo-controlled randomized trial	Mirtazapine or placebo	Secondary	Depression-Anxiety-Stress Scale	2 weeks	No significant changes in depression in either condition.

Author	Sample	Study Design	Intervention	Depression as Primary or Secondary Outcome	Tool for Measuring Depression	Length of Time in Treatment	Results
Pharmacological approaches for the treatment of MA dependence							
Galloway, Newmeyer, Knaapp, Stalcup, and Smith (1994)	151 cocaine-dependent adults, 32 MA-dependent adults (71% men)	Double-blind, randomized trial	Imipramine 10, 50, 100, or 150 mg	Secondary	Beck Depression Inventory	26 weeks	No significant intergroup differences in depressive symptoms were observed.
Galloway, Newmeyer, Knaapp, Stalcup, and Smith (1996)	32 MA-dependent adults (91% men)	Double-blind, randomized trial	Imipramine 10 or 150 mg	Secondary	Beck Depression Inventory	26 weeks	No significant intergroup differences in depressive symptoms were observed.
Elkashaf et al. (2008)	151 MA-dependent adults (67% men)	Double-blind, placebo controlled randomized trial	Bupropion or placebo	Secondary	Hamilton Depression Rating Scale	12 weeks	No statistically significant changes in depression in either condition.
Shoptaw et al. (2008)	73 MA-dependent adults (64% men)	Double-blind, placebo controlled randomized trial	Bupropion or placebo	Primary	Beck Depression Inventory	12 weeks	No statistically significant differences in depression rating scores between the two conditions.
McGaugh et al. (2009)	8 MA-dependent adults (39% men)	Nonrandomized Feasibility trial	Modafinil	Primary	Hamilton Depression Rating Scale	6 weeks	Statistically significant decrease in depression ratings ($t = -2.50$, $df = 29$, $p = .03$).
Nutritional supplement approach for the treatment of depression among MA users							
Brown and Gabrielson (2012)	48 MA-dependent adults with unipolar or bipolar depression (54% men)	Double-blind, placebo controlled randomized trial	Citicoline or placebo	Primary	Inventory of Depressive Symptomatology-Clinician Version	12 weeks	Citicoline group experienced a 33% improvement in depression rating scores compared with a 13% improvement in the placebo group.
Pharmacological plus psychological approaches for the treatment of MA dependence							
Shoptaw et al. (2006)	229 MA-abusing or MA-dependent adults (61% men)	Double-blind, placebo controlled randomized trial	Sertraline or placebo + CM, sertraline, or placebo only	Secondary	Beck Depression Inventory	12 weeks	No significant differences for sertraline, contingency management, or

Author	Sample	Study Design	Intervention	Depression as Primary or Secondary Outcome	Tool for Measuring Depression	Length of Time in Treatment	Results
McElhiney, Rabkin, and Vunes (2009)	13 MA-abusing or MA-dependent HIV + men	Single-blind, nonrandomized feasibility trial	Modafinil + CBT	Secondary	Beck Depression Inventory	16 weeks	MA craving and depression ratings decreased in medication responders (defined as >50% reduction in reported days used per week at the end of the study compared with beginning of the study).