ADDICTION

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REVIEW

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Pharmacotherapy for methamphetamine/amphetamine use disorder—a systematic review and meta-analysis

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ABSTRACT

Aims Addiction to methamphetamine/amphetamine (MA/A) is a major public health problem. Currently there are no pharmacotherapies for MA/A use disorder that have been approved for use by the US Food and Drug Administration or the European Medicines Agency. We reviewed the effectiveness of pharmacotherapy for MA/A use disorder to assess the quality, publication bias and overall strength of the evidence. **Methods** Systematic review and meta-analysis. We searched multiple data sources (MEDLINE, PsycINFO and Cochrane Library) to April 2019 for systematic reviews (SRs) and randomized controlled trials (RCTs). Included studies recruited adults who had MA/A use disorder; sample sizes ranged from 19 to 229 participants. Outcomes of interest were abstinence, defined as 3 or more consecutive weeks with negative urine drug screens (UDS); overall use, analyzed as the proportion of MA/A negative UDS specimens; and treatment retention. One SR of pharmacotherapies for MA/A use disorder and 17 additional RCTs met our inclusion criteria encompassing 17 different drugs (antidepressants, antipsychotics, psychostimulants, anticonvulsants and opioid antagonists). We combined the findings of trials with comparable interventions and outcome measures in random-effects meta-analyses. We assessed quality, publication bias and the strength of evidence for each outcome using standardized criteria. **Results** There was low-strength evidence from two RCTs that methylphenidate may reduce MA/A use: 6.5 versus 2.8% MA/A-negative UDS in one study (n = 34, P = 0.008) and 23 versus 16% in another study (n = 54, P = 0.047). Antidepressants as a class had no statistically significant effect on abstinence or retention on the basis of moderate strength evidence. Studies of anticonvulsants, antipsychotics (aripiprazole), opioid antagonists (naltrexone), varenicline and atomoxetine provided either low-strength or insufficient evidence of no effect on the outcomes of interest. Many of the studies had high or unclear risk of bias. **Conclusions** On the basis of low- to moderate-strength evidence, most medications evaluated for methamphetamine/amphetamine use disorder have not shown a statistically significant benefit. However, there is low-strength evidence that methylphenidate may reduce use.

Keywords Amphetamine, methamphetamine, pharmacotherapy, stimulant use disorder, substance use disorder, systematic review.

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INTRODUCTION

Amphetamine and methamphetamine (MA/A) use disorder is an emerging problem in world-wide. with major medical, psychiatric, cognitive and social consequences [1]. According to the United Nations Office on Drugs and Crime's (UNODC), 2017 report, MA/A is the second most common drug used world-wide (approximately 35 million past year users), and methamphetamine use is increasing in North America, Oceania and Asia [2].

Adverse effects of MA/A include restlessness, insomnia, hyperthermia and possibly convulsions. Long-term use can lead to addiction, paranoia, mood disturbances, agitation, psychosis and cognitive impairment [3,4].

In the United States, according to the Centers for Disease Control and Prevention (CDC), among all overdose-related deaths in 2017, 14.7% were attributed to psychostimulants including MA/A, an increase over prior years [5]. MA/A accounted for 51.3 emergency department (ED) visits per 100 000 population in 2011, and ED

visits involving stimulants increased 68% between 2009 and 2011 [6]. MA/A use is also associated with behavioral consequences, including aggression and criminality, that indirectly lead to morbidity and mortality [7,8].

Considering the personal and societal costs of MA/A use disorder, the need for effective treatment strategies is imperative. Currently there are no medications for treatment of MA/A use disorder that have been approved for use by the US Food and Drug Administration or European Medicines Agency. Behavioral therapies, including cognitive behavioral therapy (CBT) and contingency management (CM) are currently the primary interventions for MA/A use disorder. However, it is unclear whether these interventions have durable effect long term, and access to these therapies may be limited for some patients [9].

This article is part of a larger report [10] commissioned by the Veterans Health Administration (VHA) and presents the results of a systematic review examining the benefits and harms of pharmacological treatments for MA/a use disorder in adults; we also examine the benefits and harms of treatment in special populations including patients with co-occurring opioid use disorder (OUD), and 2) subpopulations for whom specific pharmacological treatments may be more or less beneficial. We conducted assessments of the methodological quality of individual trials, the likelihood of publication bias, and the overall strength of the evidence.

METHODS

Data sources and strategies

We searched Ovid MEDLINE, OvidPsycINFO and Ovid EBM Reviews Cochrane Database of Systematic Reviews, and gray literature sources to 12 April 2019 (Supporting information, Appendix A). We reviewed the bibliographies of relevant articles and contacted experts to identify additional studies. To identify in-progress or unpublished studies, we searched ClinicalTrials.gov, OpenTrials, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). The review protocol was registered to the International Prospective Register of Systematic Reviews (PROSPERO) before we initiated the study (CRD42018085667) [11]. Our methods and reporting follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Study selection

We included randomized controlled trials (RCTs) of adults with MA/A use disorder that compared pharmacotherapies (head-to-head) or to placebo or psychotherapy. We excluded studies and comparisons examining patients with comorbid psychotic spectrum or bipolar disorders. We excluded studies that did not perform drug urinalysis (UDS) at least once per week. Detailed study selection criteria are specified in Supporting information, Appendix B. For outcomes related to abstinence and use, we excluded studies that relied on self-reported drug use, with the exception of studies in previous systematic reviews (Table 1).

Each title and abstract in the search was screened for inclusion by at least one reviewer using pre-specified selection criteria (Supporting information, Appendix B). We dual-reviewed an enriched batch of high-relevance abstracts (18.6% of the total search yield) to ensure reliability. Two investigators independently reviewed the full text of all potentially relevant articles for inclusion. All discordant results were resolved through consensus or consultation with a third reviewer.

Data abstraction and quality assessment

One investigator abstracted details related to study design; setting; population; intervention and follow-up; co-interventions; outcomes; and harms. A second investigator confirmed the abstraction. Our outcomes of interest were sustained abstinence, defined as 3 or more consecutive weeks of negative urine drug screens (UDS); overall use, which we analyzed as the proportion of UDS samples that were MA/A-negative; and treatment retention, defined as the proportion of randomized patients who completed treatment; and adverse effects.

Two reviewers independently assessed the risk of bias (ROB) of each RCT using criteria developed by the Cochrane Collaboration [13] (Supporting information, Appendix C). We report the findings from previous systematic reviews as well as their assessments of study quality at face value.

Data synthesis and analysis

We qualitatively synthesized the evidence and conducted random-effects meta-analyses [14] to combine the findings of trials with comparable interventions and outcome measures. We used RevMan version 5.3 [15] to calculate the overall relative risk (RR) and 95% confidence interval (CI) for each outcome in the active treatment group compared with placebo. We assessed statistical heterogeneity among the pooled studies using the I^2 statistic [16,17]. For studies in which an outcome of interest was collected but not completely reported, we contacted the authors to request additional data. We classified the overall strength of the body of evidence (SOE) examining each outcome as high, moderate, low or insufficient using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPCs) [18]. The SOE ratings are based on consideration of the quality (internal validity) of included studies, directness (of the outcomes measured and population studied to those of

Table 1 Key questions and scope parameters.

Key question	What are the benefits and harms of pharmacotherapy for MA/A use disorder (alone, or as an adjunct or follow-up to psychosocial treatment)?	Are there subpopulations for whom different forms of pharmacotherapy are most/least effective for MA/A use disorder?
Population	Included: non-pregnant adults with MA/A use disorder Excluded: subjects with psychotic spectrum disorder, bipolar disorder	Subpopulations may include: Demographic factors Housing status Severity Comorbid mental and substance use disorders (e.g. HIV, mood and anxiety disorders, ADHD, alcohol use, opioid use/methadone maintained) Other clinical conditions
Intervention	Included: pharmacotherapies identified as a potential treatment for MA/A use disorder (common adjuncts may be med management; interpersonal therapy; contingency management (or motivational incentives); CBT (including matrix therapy, relapse prevention) Excluded: treatment for temporary psychosis associated with stimulant overdose	
Comparators	Usual care, placebo, or other interventions (control groups should receive the same adjunctive treatments)	
Outcomes	• Intermediate/behavioral outcomes Abstinence (UDS only. Self-report only in addition to UDS) Also of interest when available: longest duration of abstinence (LDA), and whether patients reach at least 3 consecutive weeks (21 or more days) of abstinence. MA/A use (quantitative urine levels) Retention in treatment • Health and other outcomes Morbidity/mortality Quality of life Legal/employment outcomes • Harms Study withdrawal due to AE, and severe AE (as reported in the trials)	
Timing	Minimum study duration (including follow-up) 4 weeks	
Settings	• Out-patient • In-patient • Incarceration/detention centers, correctional facilities	
Study design	• Randomized controlled trials • Systematic reviews	

ADHD = attention deficit hyperactivity disorder; AE = adverse event; LDA = longest duration of abstinence; CBT = cognitive behavioral therapy; HIV = human immunodeficiency virus; MA/A = methamphetamine/amphetamine; UDS = urinalysis.

interest to this review), consistency of evidence across trials, precision of summary estimates and reporting or publication bias [19].

Although the small number of trials for each medication precluded quantitative analysis for publication bias, we assessed publication bias qualitatively by considering whether or not it was likely that negative studies were selectively withheld from publication [20]. We considered factors such as number of positive studies included, review of study sponsorship and searching clinicaltrials.gov to ensure no studies that should have been reported but had remained unpublished.

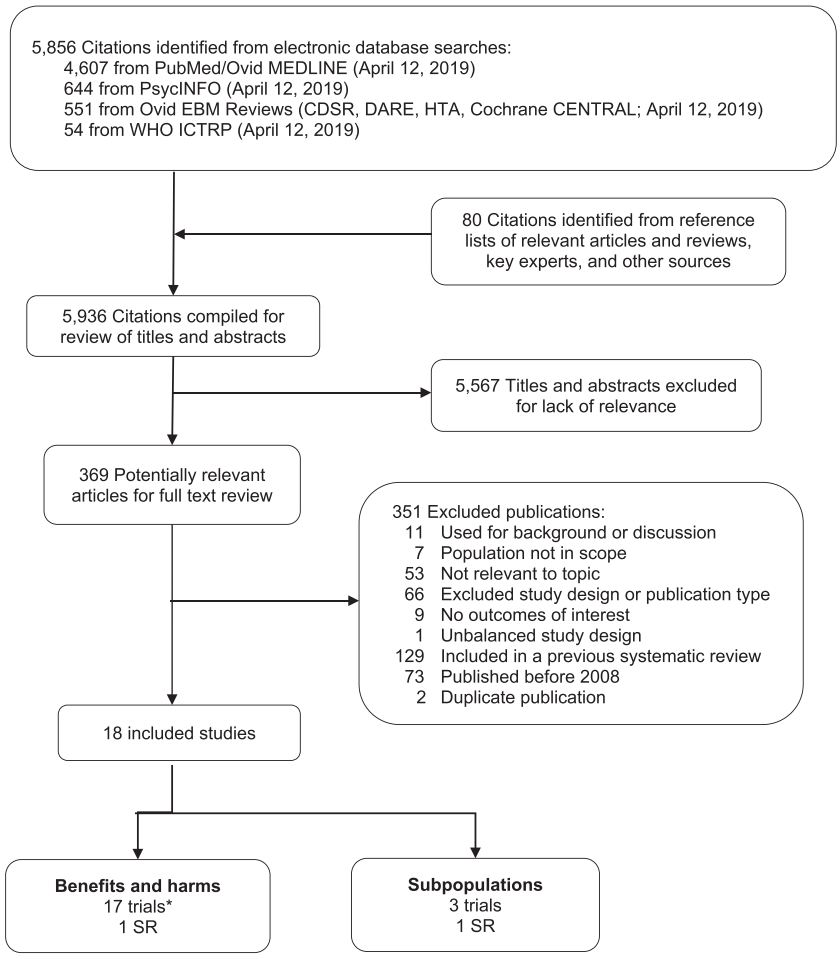
We separately examined the evidence in subpopulations including patients with comorbid OUD, alcohol use disorder, attention deficit hyperactivity disorder (ADHD) and depression. We also examined whether treatment effects differed by baseline characteristics such as gender, HIV status, severity of MA/A use and MA/A-negative UDS at randomization.

RESULTS

We reviewed a total of 5936 citations and selected 369 for full text review. One existing systematic review of 17 studies and 17 additional RCTs that were not included in the previous systematic review met inclusion criteria (Fig. 1). Sample sizes among the 34 RCTs ranged from 19 to 229 patients, with mean enrollment of 90 (SD = 53). Seventeen different drugs were studied, including antidepressants, antipsychotics, psychostimulants, anticonvulsants and opioid antagonists (Table 2).

Table 3 presents a brief summary of findings, and Table 4 provides a more detailed summary of the evidence for each drug or drug class. The characteristics, quality assessment, and findings of primary studies are provided in the Supporting information, Appendices C and D.

Only three of the 17 studies we identified had a low risk of bias quality assessments. Many of the included studies had methodological flaws, including poor outcome



*Several studies addressed more than one key question.

Figure 1 Literature flow diagram

Table 2 Number of systematic reviews and primary trials by drug and drug class.

SRs	*RCTs not in previous SRs*	*Drug category*	*Drug*
1[21]	3 [22–24]	Antidepressants	Bupropion, mirtazapine, sertraline
–	2 [25,26]	Antipsychotics	Aripiprazole
–	2 [29,30]	Muscle relaxants/anticonvulsants	Topiramate, baclofen, gabapentin
–	4 [31–34]	Medications for other substance use disorders; opioid antagonists	Naltrexone
	1 [35]	Medications for other substance use disorders; smoking cessation	Varenicline
	1 [27]	Non-stimulant medications for ADHD	Atomoxetine
–	4 [36–39]	Other pharmacotherapies	Citicoline, ondansetron, PROMETA, riluzole
1[21]	–	Psychostimulants	Dexamphetamine, methylphenidate, modafinil

ADHD = attention deficit hyperactivity disorder; RC = randomized controlled trial; SR = systematic review.

reporting, incomplete allocation methods description and small sample sizes. In addition, we found high attrition rates in the majority of studies we reviewed. There was marked variation across trials in outcome and treatment adherence reporting (e.g. self-report, biochemical confirmation or not reported). This precluded our ability to conduct meta-analyses in many cases because reported outcomes used various definitions and time-points, preventing comparison to one another.

There were too few trials for any given drug to conduct quantitative estimates of publication bias. However, we felt that there was a low likelihood of publication bias because:

Table 3 Brief summary of findings.

	Abstinence	Use	Retention	Harms
All Antidepressants	★★	Ø	★★	★
Aminoketone: Bupropion	★	★	★★	Ø
Atypical Antidepressant: Mirtazapine	NA	Ø	Ø	Ø
SSRI: Sertraline	Ø	NA	Ø	NA
Atypical Antipsychotics: Aripiprazole	Ø	★	Ø	Ø
Psychostimulants and Other Medications for ADHD				
All Psychostimulants: Modafinil, Dexamphetamine, Methylphenidate	★	Ø	★	NA
Methylphenidate	NA	★	★	NA
Atomoxetine	NA	Ø	Ø	Ø
All Anticonvulsant and Muscle Relaxants: Baclofen, Gabapentin, Topiramate	Ø	Ø	Ø	Ø
Topiramate	NA	★	★	★
Medications used for other substance use disorders				
Naltrexone	Ø	★	★	★★
Varenicline	NA	Ø	Ø	Ø

Shading represents the direction of effect:

(No color)	Unclear
Grey	No difference
Green	Evidence of benefit
Red	Favors placebo

Symbols represent the strength of the evidence:

NA	No evidence or not applicable
Ø	Insufficient
★	Low
★★	Moderate
★★★	High

(1) the body of evidence is largely negative—we did not find a disproportionate number of positive studies; (2) most of the published studies were not industry-sponsored; and (3) we searched clinicaltrials.gov and did not find additional studies that should have been reported [20].

Antidepressants: bupropion, mirtazapine and sertraline

A previous systematic review [21] and three additional trials [22–24] provided evidence on the use of antidepressants for MA/A use disorder. The systematic review [21] focused on psychostimulants for MA/A use disorder, but included six RCTs of bupropion, an aminoketone, which we classified as an antidepressant. Our literature search identified placebo-controlled trials of three antidepressants: bupropion (n = 151) [22], mirtazapine (n = 60) [24] and sertraline (n = 229) [23].

We found moderate-strength evidence that antidepressants as a class had no statistically significant effect on the achievement of sustained abstinence (three RCTs in the systematic review [21] and one additional RCT [23], combined RR = 0.92, 95% CI = 0.63–1.34; Fig. 2) or study retention (four RCTs in the systematic review [21] and three additional RCTs [22–24], combined RR = 0.98, 95% CI = 0.89–1.07; Fig. 3). We found low-strength evidence of no statistically significant difference in severe adverse events from two unclear-ROB RCTs [22,24].

We found insufficient evidence for the effectiveness of antidepressants on reducing MA/A use. Findings across trials were mixed, with no benefit reported by the systematic review [21] (three RCTs, n = 122), a modest but statistically non-significant decrease in use with bupropion reported by a more recent RCT (n = 151) [22] and a statistically significant reduction with mirtazapine in a small RCT (n = 60) [24]

Antipsychotics: aripiprazole

Our search identified two RCTs of aripiprazole for MA/A use disorder. In one 12-week, unclear-ROB RCT (n = 90), participants received either 20 mg of aripiprazole or placebo; all participants received once-weekly individual relapse prevention therapy [25]. The second trial, a 20-week, high-ROB RCT (n = 53), compared 15 mg of aripiprazole to placebo, with no concurrent interventions [26]. Both studies contribute to low-strength evidence that aripiprazole does not reduce MA/A use. The evidence for all other outcomes of interest is insufficient; however, it suggests no benefit of aripiprazole and the possibility of increased harm.

Psychostimulants and other medications used for ADHD (dexamphetamine, methylphenidate, modafinil and atomoxetine)

There were 11 RCTs included in the systematic review [21] of psychostimulants for the treatment of MA/A use

Table 4 Summary of the evidence on pharmacotherapies for MA/A use disorder, stratified by drug or drug class.

Outcome	*N studies per outcome; ROB (n = combined participants)*	*Summary of findings*	*Strength of evidence*[a]	*Comments*
Antidepressants (all combined)				
Abstinence	1 SR of 3 RCTs [21] (*n* = 361) 1 Unclear-ROB RCT [23] (*n* = 229)	No difference. One SR reported and one additional unclear-ROB RCT reported similar findings	Moderate	Body of evidence with methodological flaws. Consistent findings across studies
Use	1 SR of 3 RCTs [21] (*n* = 122) 1 Unclear-ROB RCT [22] (*n* = 151) 1 High-ROB RCT [24] (*n* = 60)	Mixed findings. One SR included 2 RCTs that found no difference in negative UAs, and one small trial (*n* = 19) that favored placebo. One additional RCT found no differences in week 12 negative UAs and rate of reduction, but a modest trend towards improvement favoring bupropion (*P* = 0.09). One small trial of MSM found that participants receiving mirtazapine had more negative UAs, with a larger increase in the number negative UA participants	Insufficient	Body of evidence with methodological flaws. Indirectness of population
Retention	1 SR of 4 RCTs [21] (*n* = 391) 2 Unclear-ROB RCTs [22,23] (*n* = 380) 1 High-ROB RCT [24] (*n* = 60)	No difference. One SR reported a combined number of participants not completing the trial OR of 1.10 (95% CI = 0.73–1.67). Two additional RCTs also found no difference in retention, and one RCT reported findings favoring placebo	Moderate	Body of evidence with methodological flaws. Indirectness of population. Consistent findings across studies
Harms	1 Unclear-ROB RCT [22] (*n* = 151) 1 High-ROB RCT [24] (*n* = 60)	Withdrawal due to AEs: NANo difference. Two RCTs found no difference between groups in reported severe AEs	No evidence: withdrawal due to AEsLow: SAEs	Small body of evidence with methodological flaws
Antidepressants (aminoketone): bupropion				
Abstinence	1 SR of 3 RCTs [21] (*n* = 361)	No difference. One SR reported combined abstinence OR of 1.12 (95% CI = 0.54–2.33)	Low	Small body of evidence with methodological flaws. Imprecision
Use	1 SR of 3 RCTs [21] (*n* = 122) 1 Unclear-ROB RCT [22] (*n* = 151)	No difference. One SR included 2 RCTs that found no difference in negative UAs, and one small trial (*n* = 19) that favored placebo. In addition, one RCT found no differences in week 12 negative UAs and rate of reduction, but a modest trend towards improvement favoring bupropion (*P* = 0.09)	Low	Body of evidence with methodological flaws
Retention	1 SR of 4 RCTs [21] (*n* = 391) 1 Unclear-ROB RCT [22] (*n* = 151)	No difference. One SR reported a combined number of participants not completing the trial OR of 1.10 (95% CI = 0.73–1.67). One additional RCT also found no difference in retention	Moderate	

(*Continues*)

Table 4. (Continued)

Outcome	N studies per outcome; ROB (n = combined participants)	Summary of findings	Strength of evidence[a]	Comments
Harms	1 Unclear-ROB RCT [22] (n = 151)	No difference. There was no difference between groups in reported severe AEs.Withdrawal due to AEs: NA	No evidence: withdrawal due to AEsInsufficient: SAEs	Single multi-site study with methodological flaws. Imprecision
Antidepressants (atypical): mirtazapine				
Abstinence	NA	NA	No evidence	NA
Use	1 High-ROB RCT [24] (n = 60)	Favors mirtazapine. At the end of the study participants receiving mirtazapine had more negative UAs, with a larger increase in the number negative UA participants	Insufficient	Single study with methodological flaws. Indirectness of study population. Imprecision
Retention	All participants: men who have sex with men	No difference. There was no difference between study groups	Insufficient	
Harms		No difference. There was no difference in SAEs between study groupsWithdrawal due to AEs: NA	No evidence: withdrawal due to AEsInsufficient: SAEs	
Antidepressants (SSRI): sertraline				
Abstinence	1 Unclear-ROB RCT [23] (n = 229)	No difference. For participants receiving sertraline with or without CM versus placebo with or without CM, there was a strong trend favoring placebo (P = 0.052)	Insufficient	Single multi-site study with methodological flaws. Imprecision
Use	NA	NA	No evidence	NA
Retention	1 Unclear-ROB RCT [23] (n = 229)	Favors placebo. Participants receiving sertraline were retained for significantly less time than those receiving placebo. When collapsed, fewer participants receiving sertraline with or without CM were retained	Insufficient	Single multi-site study with methodological flaws. Imprecision
Harms	NA	NA	No evidence	NA
Atypical antipsychotics: aripiprazole				
Abstinence	1 Unclear-ROB RCT [25] (n = 90)	No difference. One study found no difference in 2+ week abstinence	Insufficient	Single study with methodological flaws. Imprecision
Use	1 Unclear-ROB RCT [25] (n = 90) 1 High-ROB RCT [26] (n = 53)	No difference. Neither study found a positive effect of aripiprazole on reducing MA/A use (one study significantly favored placebo)	Low	Small body of evidence with methodological flaws. Imprecision
Retention	1 High-ROB RCT [26] (n = 53)	No difference. No difference in the number of participants who did not complete the trial	Insufficient	Single study with methodological flaws that was ended early due to unfavorable interim results. Imprecision

(*Continues*)

Table 4. (Continued)

Outcome	*N studies per outcome; ROB (n = combined participants)*	*Summary of findings*	*Strength of evidence*[a]	*Comments*
Harms	Withdrawal due to AEs: 1 Unclear-ROB RCT [25] (n = 90) 1 High-ROB RCT [26] (n = 53) Severe AEs: 1 High-ROB RCT [26] (n = 53)	Favors placebo. One unclear-ROB study found significantly more withdrawals due to AEs than placebo A second small high-ROB study found no differenceNo difference. One high-ROB found no difference in severe AEs	Insufficient	Small body of evidence with methodological flaws
Anticonvulsants and muscle relaxants: topiramate, baclofen, gabapentin				
Abstinence	1 Low-ROB RCT [30] (n = 88)	No difference. One study of baclofen versus gabapentin versus placebo reported % 3+ weeks abstinence (44 versus 34.6 versus 40.5%; P = NS)	Insufficient	Small body of evidence, imprecision
Use	1 Low-ROB RCT [29] (n = 140) 1 Low-ROB RCT [30] (n = 88)	Mixed, favors topiramate. Use was significantly lower in topiramate versus placebo; no difference in UA neg samples in baclofen versus gabapentin versus placebo (50.3 versus 37.1 versus 37.7%; P = 0.58	Insufficient	Small body of evidence, imprecision; indirectness due to topiramate outcome reported
Retention	1 Low-ROB RCT [29] (n = 140) 1 low-ROB RCT [30] (N = 88)	No difference. Both studies reported non-sig differences in treatment retention	Insufficient	Small body of evidence, imprecision
Harms	1 Low-ROB RCT [29] (n = 140) 1 low-ROB RCT [30] (n = 88)	No difference. Both studies reported no differences in harms	Insufficient	Small body of evidence, few outcomes reported
Medications for other substance use disorders (opioid antagonist): naltrexone				
Abstinence	1 unclear-ROB RCT [33] (n = 100)	No difference	Insufficient	1 RCT in MSM participants; limited applicability to general population
Use	1 low-ROB RCTs [31] (n = 80) 3 unclear-ROB RCTs [32–34] (n = 300)	Mixed findings. No consistent evidence of effect	Insufficient	Inconsistent results and methodological limitations. Higher rate of negative UA in 1 low-ROB study, but no difference in 3 unclear-ROB studies
Retention	1 low-ROB RCTs [31] and 3 unclear-ROB RCTs were included in MA [32–34] (n = 380)	No difference. Treatment retention naltrexone versus placebo: RR =1.11, 95% CI = 0.88–1.41, I^2 = 61%	Low	Studies reported inconsistent results and risk of bias
Harms	1 low-ROB RCTs [31] (n = 80) 3 unclear-ROB RCTs [32–34] (n = 300)	No difference. WD due to AEOnly 1 of the 4 studies reported severe AEs (3) [33]	Moderate	Studies had low and unclear-ROB
Medications for other substance use disorders (smoking cessation aid): varenicline				
Abstinence	NA	NA	No evidence	NA

(*Continues*)

Table 4. (Continued)

Outcome	*N studies per outcome; ROB (n = combined participants)*	*Summary of findings*	*Strength of evidence*[a]	*Comments*
Use	1 Unclear-ROB RCT [35] $n = 52$	No difference. % free UA(−), mean (SD): 8.6 (10.1) versus 8.1 (8.2)	Insufficient	Small body of evidence with small number of participants and unclear-ROB due to procedures altered mid-trial
Retention	1 Unclear-ROB RCT [35] $n = 52$	No difference. 14/27 (52%) versus 12/25 (48%), $P = 0.78$	Insufficient	
Harms	1 Unclear-ROB RCT [35] $n = 52$	No difference. Severe AEs: none. Withdrawals due to AEs: 1/27 versus 1/25, $P = 0.96$	Insufficient	
Psychostimulants: modafinil, dexamphetamine, methylphenidate				
Abstinence	1 SR [21]: 2 RCTs of modafinil ($n = 281$)	No difference. In one SR, 2 RCTs of modafinil reported abstinence, with combined OR 0.86 (95% CI = 0.46–1.61)	Low	Small body of evidence with methodological flaws
Use	1 SR [21]: 8 RCTs of modafinil, dexamphetamine, and methylphenidate ($n = 611$)	Mixed findings. Six of 8 RCTs in a SR reported no difference in negative UAs.For methylphenidate: 2 high-ROB RCTs reported a positive effect on use, while 2 other high-ROB RCTs found no difference; 2 RCTs provided incomplete data	Class: insufficient. Methylphenidate: low	Body of evidence with methodological flaws. Findings in favor of methylphenidate (low SOE), but not modafinil and dexamphetamine
Retention	1 SR of 11 RCTs [21] ($n = 1027$)	No difference Number of participants who did not complete the trial, combined OR = 1.11 (95% CI = 0.86–1.44)	Low	Body of evidence with methodological flaws. Participants receiving bupropion are included in the combined OR. Findings were similar for bupropion
Harms	NA	NA	No evidence	NA
Non-stimulant medication for ADHD: atomoxetine				
Abstinence	NA	NA	No evidence	NA
Use	1 Unclear-ROB RCT [27] ($n = 69$)	No difference. Proportion (95% CI) of UA(−) samples:77% (63–91%) versus 67% (53–81%), $P = 0.41$	Insufficient	Small body of evidence with unclear-ROB. Inadequate dosing adherence noted for atomoxetine
Retention	1 Unclear-ROB RCT [27] ($n = 69$)	No difference. 91 versus 97%, $P = 0.317$	Insufficient	
Harms	1 Unclear-ROB RCT [27] ($n = 69$)	No difference. Severe AEs: noneWithdrawals due to AE: none	Insufficient	

ADHD = attention deficit hyperactive disorder; AE = adverse event; CI = confidence interval; MD = mean difference; NR = not reported; OR = odds ratio; RCT = randomized control trial; RD = risk difference; ROB = risk of bias; RR = risk ratio; SAE = severe adverse event; SMD = standard mean difference; SR = systematic review; SOE = strength of evidence. [a]The overall quality of evidence for each outcome is based on the consistency, coherence and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows [18]: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

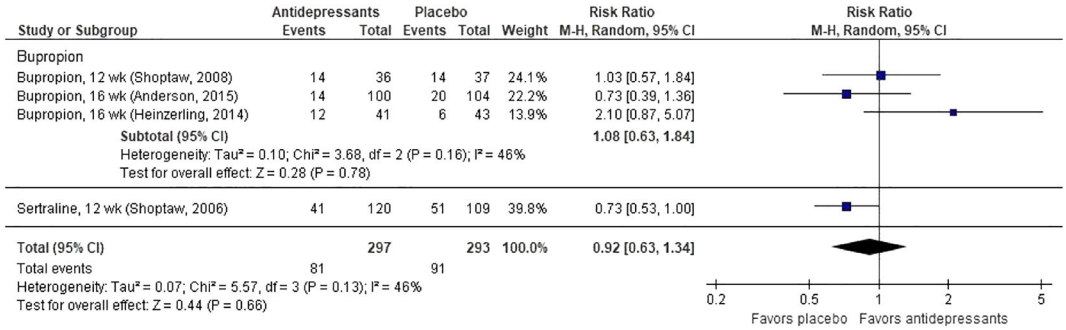


Figure 2 Abstinence in randomized controlled trials (RCTs) of antidepressants versus placebo for methamphetamine/amphetamine (MA/A) use disorder [Colour figure can be viewed at wileyonlinelibrary.com]

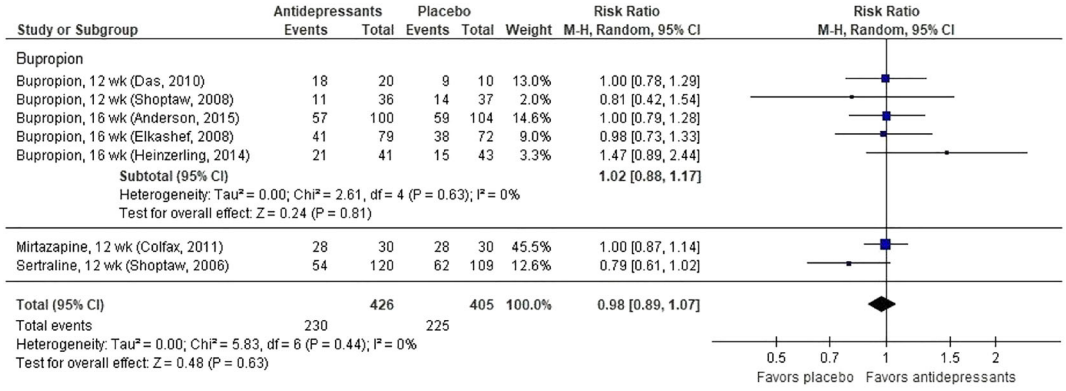


Figure 3 Retention in randomized controlled trials (RCTs) of antidepressants versus placebo for methamphetamine/amphetamine (MA/A) use disorder [Colour figure can be viewed at wileyonlinelibrary.com]

disorder [21]. Six of these RCTs (one low, one unclear, four high-ROB) examined methylphenidate, three RCTs (one unclear, two high-ROB) examined modafinil and two RCTs (one low, one unclear-ROB) examined dexamphetamine. In addition, we identified one unclear-ROB RCT of atomoxetine, a non-stimulant medication for ADHD that was evaluated for MA/A use disorder [27].

Overall, there was low-strength evidence that psychostimulants as a class have no statistically significant effect on sustained abstinence, retention or harms. There was insufficient evidence for effects on MA/A use due to mixed findings.

Methylphenidate

The systematic review of psychostimulants [21] included five RCTs (n = 323) that examined methylphenidate and found no statistically significant effect on treatment retention (combined OR = 1.29, 95% CI = 0.67–2.48; low-strength evidence) [21]. However, two of the five RCTs reported statistically significant reductions in MA/A use among subjects receiving methylphenidate (low-strength evidence). In ine trial (n = 34) [26], the mean proportion of amphetamine-negative urine samples at 20 weeks in the methylphenidate group was 32.7% compared to 18.0% in the placebo group. When analyzed in an intent-to-treat fashion (where all missing urine samples were considered positive), the mean proportion of amphetamine-negative urine samples was 6.5% in the methylphenidate group and 2.8% in the placebo group (adjusted odds of positive urine sample = 0.46, 95% CI = = 0.26–0.81, P = 0.008). In a separate trial of patients who began treatment while in prison (n = 54), the group treated with methylphenidate had a higher proportion of amphetamine-negative urines (23 versus 16%, P = 0.047) after release from prison (weeks 3–24) [28]. This trial was also rated high risk of bias, owing to incomplete outcome data and other sources of potential bias [21].

Atomoxetine

We identified one recently published trial of atomoxetine in 69 patients with co-morbid OUD on buprenorphine/naloxone that found no difference in use, retention, or harms outcomes compared to placebo [27]. The risk of bias in this study was unclear, therefore the findings provide insufficient evidence to form conclusions.

Anticonvulsants and muscle relaxants: baclofen, gabapentin, topiramate

Our search identified two RCTs that examined anticonvulsants and muscle relaxants for treatment of MA/A use

disorder. One RCT (17 weeks; low ROB; $n = 140$) compared 200 mg of topiramate to placebo, along with once-weekly behavioral compliance enhancement treatment (BCET) [29]. The second RCT (16 weeks; low ROB; $n = 88$) was a three-arm trial, comparing 200 mg baclofen, 800 mg gabapentin and placebo, along with concurrent thrice-weekly group relapse prevention therapy [30].

Findings from one study of topiramate indicate no statistically significant effect on MA/A use, although more patients on topiramate had a 25%+ reduction in UDS-methamphetamine quantity in weeks 6–12 compared with baseline (low-strength evidence) [29]. There were no statistically significant differences between baclofen, gabapentin and placebo on any outcome of interest [30]. The evidence for anticonvulsants and muscle relaxants is insufficient to form conclusions on any outcome of interest.

Medications used for other substance use disorders: naltrexone and varenicline

Opioid antagonists: naltrexone

Our search identified four RCTs examining naltrexone [a drug approved by the Food and Drug Administration (FDA) for treating opioid and alcohol use disorders] for the treatment of MA/A use disorder at formulations of 50 mg [31], 380 mg extended-release [32,3] and 1000 mg implant [34]. We found low-strength evidence that naltrexone has no statistically significant effect on study retention (four RCTs [31–34]; RR = 1.11, 95% CI = 0.88–3.12; Fig. 4) [31–34] or overall use (three RCTs [31–33], combined RR for amphetamine-negative UDS = 1.05, 95% CI = 0.92–1.18; Fig. 4), and moderate evidence of no statistically significant difference in harms (four RCTs; $n = 380$) [31–34]. Evidence related to abstinence is insufficient to form conclusions.

Comorbid OUD

We identified only one RCT that examined naltrexone for MA/A use disorder in patients with comorbid OUD [34]. The study was a multi-site trial conducted in Russia that randomized 100 patients to receive naltrexone implant (Prodetoxon 1000-mg implant) and found no statistically significant effect on MA/A use (40 versus 24%, $P = 0.09$), but better retention compared to placebo (52 versus 28%, $P = 0.01$). In addition, more subjects with the naltrexone implant had heroin-negative UAs at 10 weeks (52 versus 20%, $P < 0.001$) [34]. These findings provide insufficient evidence to form conclusions, but suggest potential benefit.

Smoking cessation aid: varenicline

We identified one recently published study ($n = 52$) of varenicline for MA/A use disorder that found no statistically significant effect on abstinence, use or retention (Table 4). The risk of bias for this study was unclear, thus providing insufficient evidence to form conclusions [35].

Other pharmacotherapies: citicoline, ondansetron, PROMETA and riluzole

We found four additional studies that examined other drugs or drug combinations in patients with for MA/A use disorder No effects were reported in studies of citicoline [36], ondansetron [37] or PROMETA (a combination of flumazenil, gabapentin and hydroxyzine) [38]. A high risk of bias trial of riluzole found statistically significant reductions in use, a statistically non-significant increase in retention and an increased risk of harms in the treatment arm; together, these studies provide insufficient evidence to draw conclusions [39].

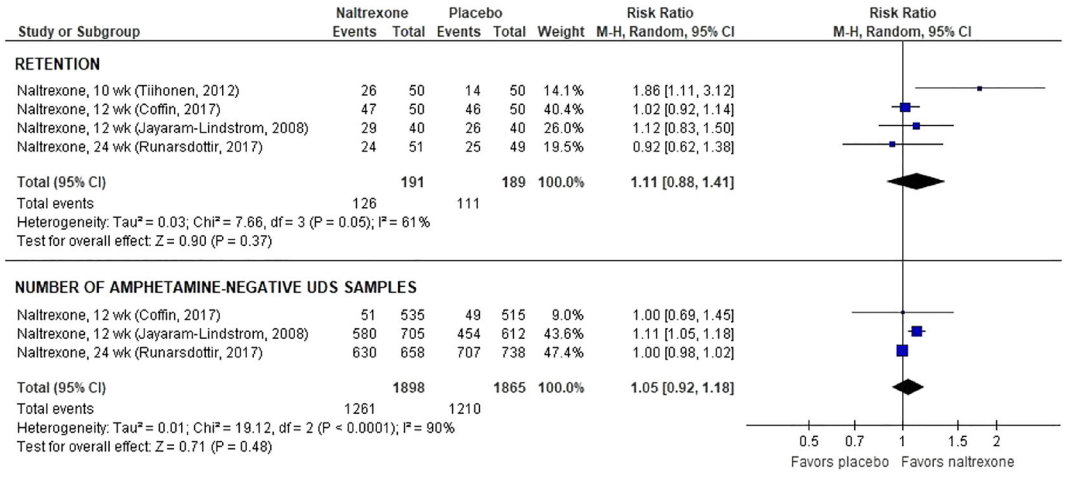


Figure 4 Retention and overall use in randomized controlled trials (RCTs) of naltrexone versus placebo for methamphetamine/amphetamine (MA/A) use disorder [Colour figure can be viewed at wileyonlinelibrary.com]

Subpopulations

The systematic review of psychostimulants [21] and three additional RCTs [22,25,29] (not included in the systematic review) examined subgroup differences in adults with MA/A use disorder: MA/A severity at baseline [21,22,25], methamphetamine-negative UDS at randomization [29], gender [22], comorbid or life-time alcohol use disorder [29], comorbid ADHD [22], comorbid depression [22] and HIV status [25].

Overall, findings are inconclusive due to methodological issues and a limited number of studies examining each subpopulation. However, it is possible that bupropion [22], but not aripiprazole [25] or psychostimulants [21], may be more effective in reducing MA/A use in individuals who are less severely addicted at baseline [22], and topiramate may be more effective in individuals who produce a negative urine screen at randomization [29]. In addition, bupropion may be more effective for males with MA/A use disorder than for females, and there is a possibility that some individuals with comorbid depression may experience more benefit than placebo [22]. No statistically significant differences were found according to ADHD diagnosis [22], life-time alcohol use disorder [29] or HIV status [25] (Table S5 in Supporting information, Appendix D).

DISCUSSION

We identified one systematic review and 17 additional RCTs (not included in the systematic review) of pharmacotherapies for treatment of MA/A use disorder. In general, the research examining pharmacotherapies for MA/A use disorder is limited, and with the exception of studies examining anticonvulsants/muscle relaxants, the risk of bias in trials are largely high or unclear.

There was marked variation across trials in outcome and treatment adherence reporting (e.g. self-report, biochemical confirmation or not reported). This precluded our ability to conduct meta-analyses in many cases because reported outcomes used various definitions and time-points, preventing comparison to one another. Many of the included studies had methodological flaws, including poor outcome reporting, incomplete allocation methods description and small sample sizes. We also found a wide range of medication dosages used in the trials, leading to concern that the lack of effects seen could be due in part to under-dosing of medications. In addition, we found high attrition rates in the majority of studies.

Many of our findings were insufficient to form strong conclusions. However, we found moderate-strength evidence that antidepressants as a class have no statistically significant effect on abstinence or retention, and low-strength evidence of no statistically significant effect on harms. We found low-strength evidence that psychostimulants have no statistically significant effect on abstinence and retention, although methylphenidate may more effective than placebo in reducing use. Similarly, although the evidence for anticonvulsants/muscle relaxants was insufficient, we found low-strength evidence that topiramate is more effective than placebo for reducing MA/A use. In addition, there was low-strength evidence that naltrexone did not improve treatment retention. There was low-strength evidence that the antipsychotic aripiprazole has no statistically significant effect on MA/A use. All findings related to subpopulation differences were insufficient.

To date, this is the first report, to our knowledge, summarizing the effectiveness of pharmacotherapies for MA/A use disorder across drug classes. Because there are currently no FDA-approved medications for this increasingly clinically relevant condition, the primary goal of our review is to aid clinicians in treatment decisions for this high-risk population. In addition, given the limited existing research, we hope that our findings will provide guidance to health services researchers in identifying potential signals both for further investigation, as well as drugs or classes that should no longer be pursued. Although our results largely echo those of the prior systematic reviews examining psychostimulants (including bupropion) [21], our review includes a broad perspective across all classes of pharmacotherapies, and provides clinicians and researchers with a more holistic view of how to help patients struggling with this condition.

Our findings have several implications. First, against the background of the opioid epidemic, the number of deaths involving MA/A and other stimulants is increasing [5]. This review highlights the urgent need for increased research into medications to treat this emerging epidemic. Many of the pharmacotherapies reviewed were initially targeted for other indications, reflecting the National Institute of Drug Abuse's 'repurposing' strategy to accelerate development of medications for addictions [40]. Secondly, our review highlights the challenge of pharmacotherapies for stimulant use disorder and the chronic disease of addiction [41] and the need for novel medications specifically targeted toward the neurobiology of MA/A use disorder. A multi-pronged strategy of medications and behavioral therapies may be necessary to see lasting effects on abstinence and use. While individual pharmacotherapies we reviewed were not effective, combinations of medications may yield different results; we are aware of at least one ongoing trial of combination bupropion and extended-release naltrexone for MA/A use disorder that may change conclusions [42]. Thirdly, we identified only one study examining MA/A use disorder in subjects with comorbid OUD. Given the increasing overlap in patients using both substances [43], research guiding the treatment of these co-occurring substance use disorders is vital. Finally, our review

highlights research gap in defining and reporting of meaningful outcomes. In the era of harm reduction, perhaps abstinence should not be the primary outcome for pharmacotherapy—we looked at use reduction and treatment retention, but often these were incompletely reported in journals, and trials may not have been powered with these outcomes in mind, increasing the risk of bias and limiting the ability to detect differences. Coming to a consensus concerning what treatment and recovery for MA/A use disorder 'looks like' from a psychosocial or behavioral perspective (i.e. standardized definitions of engagement in treatment, adherence to medications and behavioral therapies) and identifying more clinically important outcomes would allow for a better evaluation of the effectiveness of pharmacotherapies in the next generation of trials.

Limitations

Our systematic review has several limitations. The scope of our review was broad, and we relied on existing SRs when available. We sought to minimize the disadvantages of using existing SRs by only including those that met key quality criteria; conducting updated searches to identify more recent trials; and combining data in meta-analysis from trials in previous systematic reviews with newer trials from our search. Our definition of abstinence (three or more consecutive weeks) served as a proxy for sustained abstinence, and the effects of treatment on long-term abstinence cannot be directly interpolated. Our search was limited to English-language studies; however, the likelihood is low that the exclusion of non-English language studies would alter conclusions [44].

CONCLUSIONS

None of the drug classes studied in patients with MA/A use disorder had strong or consistent evidence of benefit on MA/A use, abstinence or treatment retention. Methylphenidate and topiramate are promising drugs deserving of further study. Methodological flaws and inconsistent outcome reporting temper these conclusions. We found variation in treatment dosing and outcomes reporting across trials that can be addressed in future studies. Continued research on subpopulations, including patients with co-occurring OUD, is necessary to build the knowledge base.

SR registration

PROSPERO CRD42018085667.

Declaration of interests

No investigators have any affiliations or financial involvement (e.g. employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix A Search Strategy.
Appendix B Study Selection Criteria.
Appendix C Quality Assessment.
Appendix D Data Supplement.