

Pharmacotherapy for Cocaine Use Disorder—a Systematic Review and Meta-analysis



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BACKGROUND: Currently, there are no accepted FDA-approved pharmacotherapies for cocaine use disorder, though numerous medications have been tested in clinical trials. We conducted a systematic review and meta-analysis to better understand the effectiveness of pharmacotherapy for cocaine use disorder.

METHODS: We searched multiple data sources (MEDLINE, PsycINFO, and Cochrane Library) through November 2017 for systematic reviews and randomized controlled trials (RCTs) of pharmacological interventions in adults with cocaine use disorder. When possible, we combined the findings of trials with comparable interventions and outcome measures in random-effects meta-analyses. We assessed the risk of bias of individual trials and the strength of evidence for each outcome using standardized criteria. Outcomes included continuous abstinence (3+ consecutive weeks); cocaine use; harms; and study retention. For relapse prevention studies (participants abstinent at baseline), we examined lapse (first cocaine positive or missing UDS) and relapse (two consecutive cocaine positive or missed UDS).

RESULTS: Sixty-six different drugs or drug combinations were studied in seven systematic reviews and 48 RCTs that met inclusion criteria. Antidepressants were the most widely studied drug class (38 RCTs) but appear to have no effect on cocaine use or treatment retention. Increased abstinence was found with bupropion (2 RCTs: RR 1.63, 95% CI 1.02 to 2.59), topiramate (2 RCTs: RR 2.56, 95% CI 1.39 to 4.73), and psychostimulants (14 RCTs: RR 1.36, 95% CI 1.05 to 1.77), though the strength of evidence for these findings was low. We found moderate strength of evidence that antipsychotics improved treatment retention (8 RCTs: RR 1.33, 95% CI 1.03 to 1.75).

DISCUSSION: Most of the pharmacotherapies studied were not effective for treating cocaine use disorder.

Bupropion, psychostimulants, and topiramate may improve abstinence, and antipsychotics may improve retention. Contingency management and behavioral interventions along with pharmacotherapy should continue to be explored.

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KEY WORDS: substance use; pharmacotherapy; systematic review; cocaine.

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INTRODUCTION

Cocaine use disorder remains a serious problem in the USA and worldwide. In the USA, 900,000 adults met criteria for cocaine use disorder in 2014 and 40% of visits to emergency departments for drug misuse or abuse involved cocaine.¹ Cocaine use is associated with cardiovascular and neurologic effects, and chronic repeated exposure leads to tolerance, adverse psychological and behavioral effects, and complications including infections, stroke, and seizure.^{2,3}

Psychosocial and behavioral therapies, including cognitive behavioral therapy (CBT) and contingency management (CM) interventions, are the primary treatments for cocaine use disorder. However, they are time-consuming, not universally accessible, and suffer from low treatment retention. Currently, there are no Food and Drug Administration (FDA)-approved medications to treat cocaine use disorder. One challenge in establishing the evidence base for pharmacotherapy of cocaine use disorder is the sheer number of drug classes that have been studied. Prior systematic reviews (SRs) have largely focused on single drugs⁴ or drug classes (anticonvulsants/carbamazepine,⁵ dopamine agonists,⁶ psychostimulants,⁷ and antipsychotics⁸). To our knowledge, none have examined the treatment of cocaine use disorder across drug classes. This SR examines the benefits and harms of pharmacological interventions for cocaine use disorder, and was part of a larger report of stimulant use disorders commissioned by the Veterans Health Administration (VHA).

Prior Presentations

This paper was accepted, but not presented at the annual meeting of the Society of Behavioral Medicine (March 2019). It has also been accepted to the annual meeting of the Society of General Internal Medicine (Poster; May 2019), College on Problems of Drug Dependence (Poster; June 2019), and the American Psychological Association's annual convention (Poster and "Rapid Response"; August 2019).

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METHODS

Data Sources and Search Strategies

We searched MEDLINE, PsycINFO, and EBM Reviews Cochrane Database of Systematic Reviews through November 2017 (Online Appendix Table 1). 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 PROSPERO before we initiated the study (CRD42018085667). Our methods and reporting follow PRISMA guidelines.⁹

Study Selection

Study selection was guided by an analytic framework (Online Appendix Figure 1). We included randomized controlled trials (RCTs) of adults with cocaine use disorder that compared pharmacotherapies (head to head), to placebo, usual care, or psychotherapy. We also included RCTs that had been included in existing good quality SRs. We excluded studies examining patients with comorbid psychotic spectrum or bipolar disorders. We excluded studies that did not perform urine drug screens (UDS) at least once per week. PICOTS and study selection criteria are specified in Online Appendix Tables 2 and 3.

We dual reviewed and evaluated titles and abstracts for 18.6% of the 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, and a second investigator confirmed details related to study design, setting, population, intervention and follow-up, co-interventions, outcomes, and harms. Two reviewers independently assessed the quality of each RCT using a tool developed by the Cochrane Collaboration¹⁰ (Online Appendix Table 8). We directly report the findings from previous SRs as well as their assessments of study quality.

Our outcomes of interest were sustained abstinence (three or more weeks of negative UDS'),¹¹ cocaine use, treatment retention, serious adverse events (SAEs), and treatment dropouts due to adverse events (AEs). For relapse prevention studies of participants abstinent at baseline, we examined lapse (first cocaine positive or missed UDS) and relapse (two consecutive cocaine positive or missed UDS'). For outcomes related to abstinence and use, we excluded studies relying on self-reported drug use, with the exception of findings from previous SRs.

Data Synthesis and Analysis

We qualitatively synthesized the evidence and separately examined the findings in patients with comorbid opioid use disorder. When possible, we combined data from trials as they were reported in previous SRs with data we abstracted directly from newer RCTs identified in our search in random-effects meta-analyses.¹² We used RevMan 5.3¹³ to calculate the overall relative risk (RR) and 95% CI of each outcome in the active treatment group compared with placebo. We assessed statistical heterogeneity among the pooled studies using the I^2 statistic.^{14, 15}

We assessed the overall strength of evidence (SOE) for each outcome using an established method, and classified SOE as high, moderate, low, or insufficient.¹⁶

RESULTS

Our larger search for stimulant use disorders yielded 5564 citations. After reviewing the full text of 354 studies, we included seven systematic reviews and 48 RCTs specific to cocaine use disorder (Fig. 1). The included SRs and RCTs examined 66 different drugs including antidepressants, anti-psychotics, anxiolytics, cognitive enhancing drugs, dopamine agonists, muscle relaxants, anticonvulsants, medications approved by the FDA for other substance use disorders, and a wide range of other pharmacotherapies (Online Appendix Table 4).

Table 1 presents a brief summary of findings for all drug classes. Table 2 provides a more detailed summary of the evidence on all pharmacotherapies for cocaine use disorder, stratified by drug class. The characteristics and findings of individual studies are provided in Online Appendix Tables 5 and 6.

Psychopharmacotherapies

Antidepressants: Bupropion, Desipramine, Fluoxetine, Mirtazapine, Nefazodone, Paroxetine, Sertraline, Venlafaxine. Antidepressants were the most widely studied among the drug classes. We found 34 trials from two previous systematic reviews^{7, 17} and four subsequent trials^{18–21} investigating antidepressants (including bupropion) for cocaine use disorder. The more recent trials examine sertraline,^{20, 21} venlafaxine,¹⁸ and mirtazapine.¹⁹ Overall, there were no differences on sustained abstinence, use, retention, or harms outcomes.

In a meta-analysis combining 10 RCTs^{7, 17, 18} across all antidepressants, abstinence occurred more frequently in the antidepressant groups than placebo (RR 1.27, 95% CI 0.99 to 1.63), but the difference did not reach statistical significance ($P=0.06$; Online Appendix Figure 2). We found moderate SOE of no difference on cocaine use between antidepressants as a class and placebo. Findings were consistent across four RCTs reported in a systematic review¹⁷ (RR 1.05, 95% CI 0.91 to 1.21) and two additional RCTs.^{18, 19} We found high

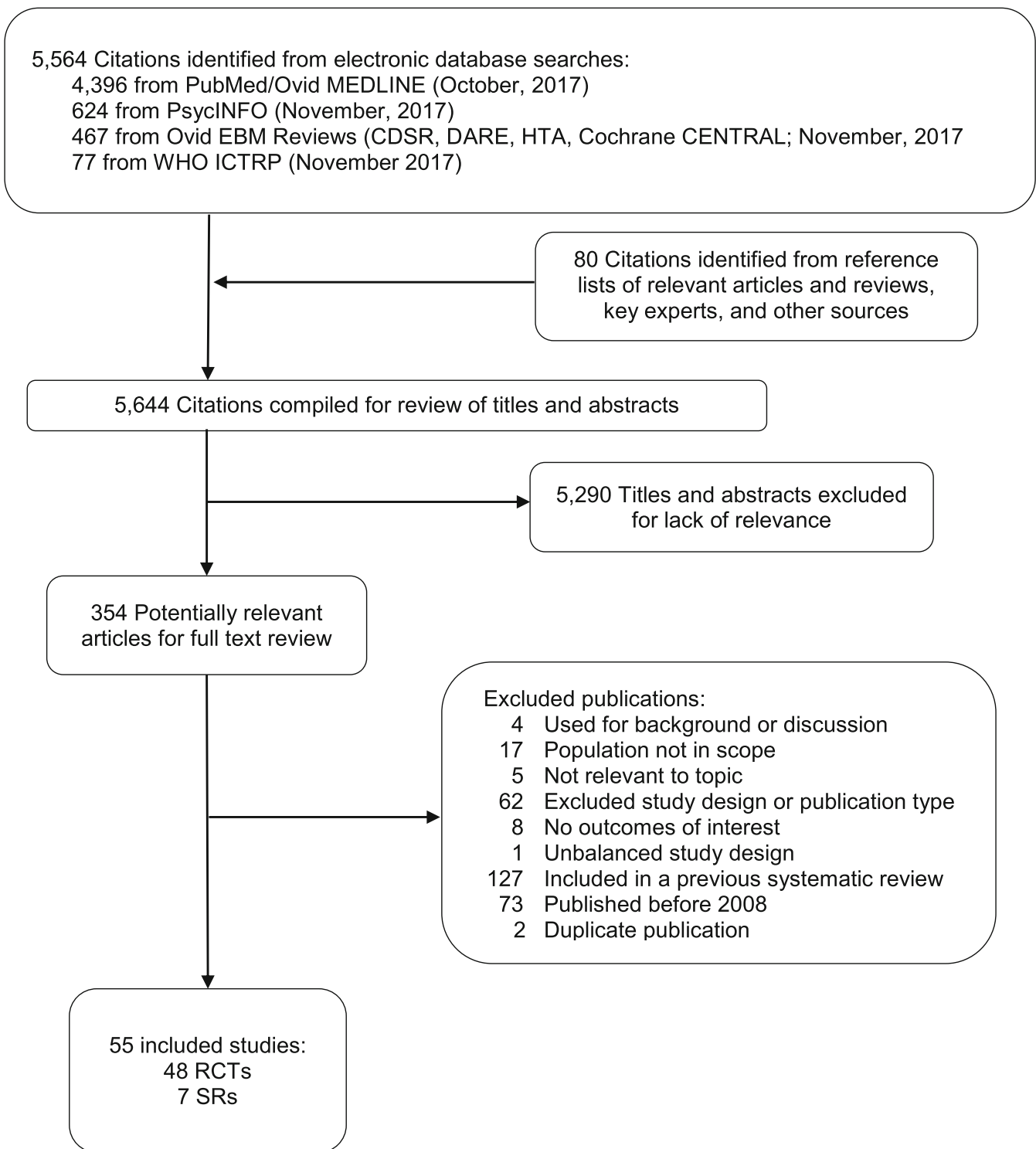


Figure 1 Literature flow diagram. RCT, randomized controlled trial; SR, systematic review.

SOE that antidepressants as a class are no better than placebo for study retention (33 RCTs; RR 0.95, 95% CI 0.87 to 1.03; Fig. 2). There were no differences in dropouts due to AEs (moderate SOE) or SAEs (low SOE).

Selective Serotonin Reuptake Inhibitors: Fluoxetine, Paroxetine, and Sertraline. We found two low risk of bias (ROB) RCTs^{20, 21} and seven RCTs in the SR of

antidepressants¹⁷ that provide moderate SOE that selective serotonin reuptake inhibitors (SSRIs) do not improve study retention ($N=527$; RR 0.94, 95% CI 0.68 to 1.29; Fig. 2). However, three RCTs ($N=251$) in the SR¹⁷ provide low-strength evidence of a higher risk of dropout due to AEs with SSRIs compared with placebo (RR 3.55, 95% CI 1.11 to 11.34).

Table 1 Brief Summary of Findings

| | Abstinence | Use | Lapse | Relapse | Retention | Harms |
|---|------------|-----|-------|---------|-----------|-------|
| All Antidepressants: Bupropion, Desipramine, Fluoxetine, Mirtazapine, Nefazodone, Paroxetine, Sertraline, Venlafaxine | ★★ | ★★ | ★ | ★ | ★★★ | ★★ |
| Aminoketone: Bupropion | ★ | ★ | NA | NA | ★★ | ∅ |
| SSRIs: Fluoxetine, Paroxetine, and Sertraline | NA | NA | ∅ | ∅ | ★★ | ★ |
| SSRI in patients abstinent at Baseline: Sertraline | NA | NA | ★ | ★ | ★ | ∅ |
| All Antipsychotics: Aripiprazole, Haloperidol, Lamotrigine, Olanzapine, Quetiapine, Risperidone, Reserpine | ★ | ★ | ∅ | ∅ | ★★ | ∅ |
| Psychostimulants: Dexamphetamine, Lisdexamfetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Selegiline | ★ | ★ | NA | NA | ★★ | ★★ |
| Cognitive Enhancing Drugs: Memantine, Atomoxetine | ∅ | ∅ | NA | ∅ | ∅ | ∅ |
| Anxiolytic: Buspirone | ∅ | NA | ∅ | ∅ | ∅ | ∅ |
| Anticonvulsants/Muscle Relaxants: Baclofen, Carbamazepine, Gabapentin, Lamotrigine, Phenytoin, Tiagabine, Topiramate, Vigabatrin | NA | ★★ | NA | NA | ★★ | ∅ |
| Anticonvulsant: Topiramate | ★ | ∅ | NA | NA | ★★ | ∅ |
| Drugs for other substance use disorders: Acamprosate, Buprenorphine, Buprenorphine + Naloxone, Disulfiram, Naltrexone, Methadone, Varenicline | ★ | ∅ | ∅ | ∅ | ∅ | ∅ |
| Disulfiram | ★ | ★ | NA | NA | ★★ | ★ |
| Dopamine agonists: Amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline, hydroxyergine, and pramipexole | ★ | NA | NA | NA | ★★ | NA |

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 |
| ∅ | Insufficient |
| ★ | Low |
| ★★ | Moderate |
| ★★★ | High |

Relapse Prevention: Sertraline. We found two trials ($N = 116$) examining sertraline for relapse prevention among subjects who were cocaine-abstinent at baseline.^{20, 21} These RCTs provided a 2-week residential treatment program during which subjects were required to achieve abstinence in order to continue treatment in a 10-week outpatient program. Patients treated with sertraline were less likely to experience lapse (first cocaine positive or missing UDS samples [combined RR 0.80, 95% CI 0.63 to 1.02]) and relapse (two consecutive cocaine positive or missing UDS [combined RR 0.75, 95% CI 0.58 to 0.98; Online Appendix Figure 3]), although only the latter

finding was statistically significant. Retention was also higher versus placebo (combined RR 1.43, 95% CI 0.94 to 2.15; Online Appendix Figure 4), though the difference was not statistically significant ($P = 0.09$).

Bupropion. There were three trials reported in two existing SRs^{7, 17} that examined bupropion for cocaine use disorder. There was low SOE that bupropion improved abstinence versus placebo (2 RCTs; combined RR 1.63, 95% CI 1.03 to 2.59).⁷ Bupropion had no effect on cocaine use (low SOE) or retention (3 RCTs, combined RR 0.94, 95% CI 0.76 to 1.15;

Table 2 Summary of the Evidence on Pharmacotherapies for Cocaine Use Disorder, Stratified by Drug Class

| Outcomes | N studies per outcome; ROB (N = combined participants) | Summary of findings by outcome | Strength of evidence* | Comments and rationale for strength of evidence rating |
|---|--|--|--|---|
| Psychopharmacotherapies (antidepressants, antipsychotics, anxiolytics, cognitive enhancing drugs, and psychostimulants) | | | | |
| Antidepressants (all) | | | | |
| Abstinence | 1 SR of 8 RCTs ¹⁷ (N = 942) 1 low-ROB RCT ¹⁸ (N = 130) | No difference. Meta-analysis of 10 RCTs, N = 1226, RR 1.27 (95% CI 0.99 to 1.63) | Moderate | Inconsistent findings. Trend toward benefit disappeared when restricted to studies using strict criteria for cocaine dependence. |
| Use | 1 SR of 4 RCTs ¹⁷ (N = 251) 1 low-ROB RCT ¹⁸ (N = 130) 1 high-ROB RCT ¹⁹ (N = 24) | No difference. 1 SR reported a combined use of cocaine (self-reported or objective) RR of 1.05 (95% CI 0.91 to 1.21). Similar findings were reported in both more recent low-ROB and high-ROB RCTs. | Moderate | Indirectness (of outcome) |
| Lapse | 2 low-ROB RCTs ^{20, 21} (N = 116) | Favors antidepressants. Participants abstinent at baseline with 1 cocaine positive UDS, combined RR 0.79 (95% CI 0.62 to 1.00). | Low | Small body of evidence |
| Relapse | | Favors antidepressants. Participants abstinent at baseline with 2 consecutive cocaine positive UDS', combined RR 0.74 (95% CI 0.57 to 0.96). | Low | Indirectness (of results to general population—participants had achieved abstinence prior to the outpatient phase). Lapse is defined as the first cocaine positive or missing UDS; relapse is 2 consecutive cocaine positive or missing UDS'. |
| Retention | 1 SR of 27 RCTs ¹⁷ (N = 2417) 3 low-ROB RCTs ^{18, 20, 21} (N = 263) | No difference. Meta-analysis of 33 RCTs N = 2918, RR 0.95 (95% CI 0.87 to 1.03) | High | Findings were similar in analyses limited to RCTs specifying DSM cocaine dependence criteria for inclusion. |
| Harms | 1 SR of 13 RCTs ¹⁷ (N = 1396) 1 low-ROB RCT ¹⁸ (N = 130) 1 high-ROB RCT ¹⁹ (N = 24) | No difference. 1 SR reported a combined withdrawal due to an adverse event RR of 1.39 (95% CI 0.91 to 2.12). Two more recent RCTs (1 low-ROB, 1 high-ROB) reported consistent findings. No difference. Two RCTs found no difference in severe adverse events by group. | Withdrawal due to AEs: Moderate Severe AEs: low | Treatment withdrawal findings are from 1 low and 1 high RCT and a SR/meta-analysis of 37 RCTs. The SR included studies with any definition of cocaine dependence or abuse. Findings of SAEs are from a small body of evidence. |
| Antidepressants (tricyclics) | | | | |
| Abstinence | 1 SR of 5 RCTs ¹⁷ (N = 367) | No difference. 3+ week abstinence, combined RR 1.55 (95% CI 1.10 to 2.17). Limited to DSM criteria for cocaine dependence (3 studies, N = 234); combined RR 1.41, (95% CI 0.93 to 2.14). | Low | 4/5 studies are of desipramine. |
| Use | 1 SR of 2 RCTs ¹⁷ (N = 37) | No difference. Use of cocaine (self-reported or objective), combined RR 0.85 (95% CI 0.34 to 2.11) | Insufficient | Small body of evidence. Imprecise estimate. Indirectness (of outcome) |
| Retention | 1 SR of 15 RCTs ¹⁷ (N = 1141) | No difference. Number of participants who did not complete the trial, combined RR 1.00 (95% CI 0.85 to 1.18) | High | Findings were similar in an analysis limited to RCTs specifying DSM cocaine dependence criteria for inclusion and in an analysis excluding high-ROB trials. 13/15 studies are of desipramine. |
| Harms | 1 SR of 5 RCTs ¹⁷ (N = 381) | No difference. Withdrawal due to an adverse event, combined RR 1.24 (95% CI 0.64 to 2.43) SAE: NA | Moderate No evidence: SAE | Findings were similar in analyses limited to RCTs specifying DSM cocaine dependence criteria for inclusion. Imprecise estimate. 4/5 studies are of desipramine. |
| Antidepressants (SSRIs): fluoxetine and sertraline | | | | |
| Abstinence | NA | NA | No evidence | NA |
| Use | NA | NA | No evidence | NA |
| Relapse | 2 low-ROB RCTs ^{20, 21} (N = 133) | Favors sertraline. Participants abstinent at baseline with 2 consecutive cocaine positive UDS', combined RR 0.74 (95% CI 0.57 to 0.96). | Low | Small body of evidence |
| Lapse | | Favors sertraline. Abstinent at baseline participants with 1 cocaine positive UDS, combined RR 0.79 (95% CI 0.62 to 1.00). | Low | Indirectness (of results to general population—participants had achieved abstinence prior to the outpatient phase). Lapse is defined as the first cocaine positive UDS, relapse is 2 consecutive cocaine positive UDS'. |
| Retention | 1 SR of 7 RCTs ¹⁷ (N = 527) 2 low-ROB RCTs ^{20, 21} (N = 133) | No difference. The SR's combined RR for participants not completing the trial was 0.99 (95% CI 0.70 to 1.71). No difference in 2 more recent RCTs. | Moderate | Inconsistent results. Findings favored placebo when excluding 1 outlier, and no difference was found when further excluding 1 high-ROB RCT. Indirectness (of population)—2 more |

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Table 2. (continued)

| Outcomes | N studies per outcome; ROB (N = combined participants) | Summary of findings by outcome | Strength of evidence* | Comments and rationale for strength of evidence rating |
|---|---|---|-------------------------------------|---|
| Harms | 1 SR of 3 RCTs ¹⁷ (N = 251) | Favors placebo. Withdrawal due to an adverse event, combined RR 3.55 (95% CI 1.11 to 11.34). SAE: NA | Low No evidence: SAE | recent RCTs enrolled only patients who had achieved abstinence. Imprecise estimate, small body of evidence |
| Antidepressant (SNRI): venlafaxine | | | | |
| Abstinence | 1 low-ROB RCT ¹⁸ (N = 130) | No difference. 1 RCT found no difference in 3+ week abstinence between groups (P = 0.94). | Insufficient | 1 single site study. |
| Use | | No difference. 1 RCT found no difference in negative UDS' between groups (P = 0.74). | Insufficient | |
| Retention | | No difference. 1 RCT found no difference in retention between groups. | Insufficient | |
| Harms | | No difference. 1 RCT found no difference in withdrawals due to adverse events by group. | Insufficient | |
| | | No difference. 1 RCT found no difference in severe AEs between groups. | | |
| Antidepressant (Atypical): mirtazapine | | | | |
| Abstinence | NA | NA | No evidence | NA |
| Use | 1 high-ROB RCT ¹⁹ (N = 24) | No difference. 1 RCT found no difference in study period use between groups. | Insufficient | 1 very small underpowered study. Details regarding randomization and allocation concealment NR. |
| Retention | NA | NA | No evidence | NA |
| Harms | 1 high-ROB RCT ¹⁹ (N = 24) | No difference. 1 RCT found no difference in withdrawals due to AEs between groups (none). No difference. 1 RCT found no difference in severe AEs between groups (because there were none). | Insufficient | 1 very small underpowered study. Details regarding randomization and allocation concealment NR. |
| Antidepressant (aminoketone): bupropion | | | | |
| Abstinence | 1 SR of 2 RCTs ⁷ (N = 176) | Favors bupropion. 1 SR reported a combined 3+ week abstinence RR of 1.63 (95% CI 1.02 to 2.59). | Low | Small body of evidence Imprecise estimates |
| Use | | No difference. Use of cocaine, combined SMD 0.24 (95% CI -0.06 to 0.54). | Low | |
| Retention | 1 SR of 3 RCTs ¹⁷ (N = 325) | No difference. The SR's combined RR for participants not completing the trial was 0.99 (95% CI 0.79 to 1.25). | Moderate | Inconsistent results |
| Harms | 1 SR of 1 RCT ⁷ | No difference. Mean withdrawals due to AEs RD 0.00 (95% CI -0.05 to 0.05) SAE: NA | Insufficient No evidence: SAE | Small body of evidence |
| Antipsychotics (all) | | | | |
| Abstinence | 1 SR of 3 RCTs ⁸ (N = 139) | No difference. 1 SR reported a combined 3+ week abstinence RR of 1.30 (95% CI 0.73 to 2.32). | Low | Small body of evidence Imprecise estimate |
| Use | 1 SR of 2 RCTs ⁸ (N = 150) 1 high-ROB RCT ²² (N = 18 opioid randomized, 41 enrolled opioid-dependent participants) | No difference. | Low | Small body of evidence Methodological limitations of studies. Indirectness of population. |
| Relapse Lapse | 1 high-ROB RCT ²² (N = 18 opioid randomized, 41 enrolled opioid-dependent participants) | No difference. No difference. | Insufficient Insufficient | Small, methodologically limited single trial. Indirectness (of results to general population—participants had achieved abstinence prior to the outpatient phase). Lapse is defined as the first cocaine positive UDS, relapse is 2 consecutive cocaine positive UDS'. |
| Retention | 1 SR of 8 RCTs ⁸ (N = 397) 1 high-ROB RCT ²² (N = 18 randomized, 41 enrolled opioid-dependent participants) | Favors any antipsychotic. 1 SR reported dropouts RR 0.75 (95% CI 0.57 to 0.97). 1 high-ROB RCT of comorbid cocaine and opioid-dependent methadone-maintained participants found no difference in retention between groups. | Moderate | Newer trial found no difference (indirectness of population). |

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Table 2. (continued)

| Outcomes | N studies per outcome; ROB (N = combined participants) | Summary of findings by outcome | Strength of evidence* | Comments and rationale for strength of evidence rating |
|---|---|--|-------------------------------------|---|
| Harms | 1 high-ROB RCT ²² (N = 18 randomized, 41 enrolled opioid-dependent participants) | Withdrawals: no difference. SAE: NA | Insufficient No evidence: SAE | Small, methodologically limited single trial. Indirectness (of population) |
| Antipsychotics (first generation): haloperidol | | | | |
| Abstinence | NA | NA | No evidence | NA |
| Use | NA | NA | No evidence | NA |
| Retention | 1 SR of 1 RCT ⁸ (N = 31) | No difference. 1 SR reported a RR for participants not completing the trial of 1.50 (95% CI 0.63 to 3.57). 1 head to head trial found no difference between haloperidol and olanzapine (N = 31; RR 1.50, 95% CI 0.63 to 3.57). | Insufficient | Findings are from a single study in a SR/meta-analysis of 14 RCTs. |
| Harms | NA | NA | No evidence | NA |
| Antipsychotics (second generation): aripiprazole, olanzapine, risperidone, quetiapine | | | | |
| Abstinence | 1 SR of 3 RCTs ⁸ (N = 139) | No difference. Three studies in a SR found no difference between an atypical antipsychotic and placebo on sustained abstinence. | Low | Small body of evidence Imprecise estimate |
| Use | 1 SR of 1 RCT ⁸ (N = 31) 1 high-ROB RCT ²² (N = 18 randomized, 41 enrolled opioid-dependent participants) | No difference. 1 RCT from 1 SR and 1 high-ROB RCT of opioid-dependent participants found no difference between groups. | Insufficient | Small body of evidence Methodological limitations of studies. Indirectness of population. |
| Relapse | 1 high-ROB RCT ²² (N = 18 randomized, 41 enrolled opioid-dependent participants) | No difference. 1 high-ROB found no difference in relapse by group. | Insufficient | Small, methodologically limited single trial. Indirectness (of results to general population—participants had achieved abstinence prior to the outpatient phase). Lapse is defined as the first cocaine positive UDS, relapse is 2 consecutive cocaine positive UDS'. |
| Lapse | | No difference. 1 high-ROB found no difference in lapse by group. | Insufficient | Newer trial found no difference (indirectness of population). |
| Retention | 1 SR of 7 RCT ⁸ (N = 365) 1 high-ROB RCT ²² (N = 18 randomized, 41 enrolled opioid-dependent participants) | No difference. Seven studies in 1 SR and 1 high-ROB RCT of comorbid cocaine and opioid-dependent methadone-maintained participants found no benefit of atypical antipsychotics on study retention | Moderate | |
| Harms | 1 high-ROB RCT ²² (N = 18 randomized, 41 enrolled opioid-dependent participants) | No difference. 1 high-ROB RCT of comorbid cocaine and opioid-dependent methadone-maintained participants found no difference in withdrawals due to AEs by group. SAE: NA | Insufficient No evidence: SAE | Small, methodologically limited single trial. Indirectness (of results to general population—participants had achieved abstinence prior to the outpatient phase). |
| Antipsychotics (other): reserpine | | | | |
| Abstinence | NA | NA | No evidence | NA |
| Use | 1 SR of 1 RCT ⁸ (N = 119) | No difference. 1 study in the SR found a no difference in use between groups. | Insufficient | Small body of evidence. Imprecise estimate. |
| Retention | NA | NA | No evidence | NA |
| Harms | NA | NA | No evidence | NA |
| Anxiolytics: buspirone | | | | |
| Abstinence | 1 High-ROB RCT ²⁶ (N = 62) | No difference. 1 RCT found no difference between groups in the mean number of days of (post-discharge) abstinence. | Insufficient | Small, methodologically limited single trial. Indirectness (of results to general population—participants had achieved abstinence prior to the outpatient phase). Lapse is defined as the first cocaine positive UDS, relapse is 2 consecutive cocaine positive UDS'. |
| Use | | NA | No evidence | |
| Lapse | | No difference. 1 RCT found no difference between groups in number of days to lapse. | Insufficient | |
| Retention | | No difference. 1 RCT reported high rates of retention (94% buspirone vs 93% placebo), but no difference between groups. | Insufficient | |
| Withdrawal due to AE | | No difference. In 1 RCT there were no withdrawals due to AEs. | Insufficient | |
| Severe AE | | Favors placebo. In 1 RCT there were 3 SAEs in participants receiving buspirone vs 0 receiving placebo. | Insufficient | |
| Cognitive enhancing drugs: memantine, atomoxetine | | | | |
| Abstinence | 1 low-ROB RCT ²⁴ (N = 81) | | Insufficient | |

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Table 2. (continued)

| Outcomes | N studies per outcome; ROB (N = combined participants) | Summary of findings by outcome | Strength of evidence* | Comments and rationale for strength of evidence rating |
|---|---|---|-----------------------|---|
| Use | 1 low-ROB RCT ²⁴ (N = 81) 1 unclear-ROB RCT ²⁵ (N = 50) | No difference. Participants who did not achieve abstinence at baseline (N = 45), there was no difference between groups in the achievement of sustained abstinence (3+ weeks). No difference. There was no difference in cocaine negative UDS' between groups. | Insufficient | Single small RCT with a 2-week placebo lead-in to encourage abstinence after randomization. Small body of evidence. Methodological limitations of studies. |
| Relapse | 1 low-ROB RCT ²⁴ (N = 81) | No difference. Among participants who achieved abstinence at baseline (N = 36), there was no difference between groups in relapse or time to relapse. | Insufficient | Small body of evidence. Indirectness (of results to general population—participants had achieved abstinence prior to the outpatient phase). Relapse is defined as 2 consecutive cocaine positive UDS'. |
| Retention | 1 low-ROB RCT ²⁴ (N = 81) | No difference. There was no difference in retention by group. | Insufficient | Small body of evidence. Methodological limitations of studies. |
| Harms | 1 unclear-ROB RCT ²⁵ (N = 50) | No difference. There was no difference in retention by group. No difference. 0 participants receiving memantine experienced a SAE compared with 2 who received placebo. | Insufficient | Methodological limitations of studies. |
| Psychostimulants: dexamphetamine, mazindol, methamphetamine, methylphenidate, mixed amphetamine salts, modafinil, lisdexamphetamine, selegiline | | | | |
| Abstinence | 1 SR of 14 studies ⁷ (N = 1549) | Favors psychostimulants. 1 SR reported a combined 3+ week abstinence RR of 1.36 (95% CI 1.05 to 1.77). | Low | Large body of evidence and consistent results even after removing bupropion studies, but many trials were methodologically flawed. Findings from individual drugs favor dexamphetamine (small body of evidence) and mixed amphetamine salts (single study). |
| Use | 1 SR of 8 RCTs ⁷ (N = 526) | No difference. Use of cocaine, combined SMD 0.16 (95% CI -0.02 to 0.33). | Low | Trend toward small benefit, inconsistent results |
| Retention | 1 SR of 24 studies ⁷ (N = 2205) | No difference. Number of participants who did not complete the trial, combined RR 1.00 (95% CI 0.93 to 1.06) | Moderate | Methodological limitations of many included studies. Heterogeneous population. |
| Harms | Withdrawal: 1 SR of 19 RCTs ⁷ (N = 1601) Serious AEs: 1 SR of 6 RCTs ⁷ (N = 444) | No difference. Number of participants who withdrew due to AEs, combined mean RD 0.00 (95% CI -0.01 to 0.01). No difference. Number of participants who reported severe AEs, combined mean RD -0.02 (95% CI -0.06 to 0.01). | Moderate | No bupropion studies are included in findings of SAEs. |
| Anticonvulsants and muscle relaxants | | | | |
| Baclofen | | | | |
| Abstinence | 2 unclear-ROB RCTs ^{27, 28} (N = 230) | No difference. | Low | |
| Use | 2 unclear-ROB RCTs ^{27, 28} (N = 230) | No difference. | Low | |
| Retention | 2 unclear-ROB RCTs ^{27, 28} (N = 230) | No difference. | Low | |
| Withdrawal due to AE | 1 unclear-ROB RCT ²⁷ (N = 70) | No difference. | Insufficient | |
| Severe AE | 2 unclear-ROB RCTs ^{27, 28} (N = 230) | No difference. | Low | |
| Carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and vigabatrin (drugs combined in analysis) | | | | |
| Abstinence | 1 SR ⁵ | NR | No evidence | These represent the combined results for all drug classes included in the SR. ⁵ |
| Use | 1 SR of 9 RCTs ⁵ (N = 867) | No difference. Use of cocaine (self-reported or objective), combined RR 0.92 (95% CI 0.84 to 1.02) ⁵ | Moderate ⁵ | SOE was determined by the SR authors |
| Retention | 1 SR that included 17 RCTs ⁵ (N = 1695) | No difference. RR 0.95 (95% CI 0.86 to 1.05) ⁵ | Moderate ⁵ | |
| Topiramate | | | | |
| Abstinence | 1 low-ROB RCT ²⁹ (N = 60) 2 unclear-ROB RCTs ^{31, 32} | Favors topiramate (3 RCTs). Relapse prevention RCTs: combined findings from 2 unclear-ROB RCTs ^{31, 32} (RR 2.56 [95% CI 1.39 to 4.73]) for 3 or more weeks of continuous abstinence | Low | |

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Table 2. (continued)

| Outcomes | N studies per outcome; ROB (N = combined participants) | Summary of findings by outcome | Strength of evidence* | Comments and rationale for strength of evidence rating |
|--|--|--|-----------------------|---|
| Use | 1 low-ROB RCT ²⁹ (N = 60) | Favors topiramate. | Insufficient | Only 1 small trial |
| Retention | 5 RCTs: 1 high-ROB ³³ ; 2 unclear-ROB ^{30, 32} ; 2 low-ROB ^{29, 34} (N = 617) | No difference. Combined RR 1.01 (95% CI: 0.93 to 1.10). | Moderate | Methodological limitations of several trials. |
| Harms | 1 low-ROB RCT ²⁹ (N = 60) | No withdrawals occurred due to AE. No severe AEs occurred. | Insufficient | Only 1 small RCT |
| Vigabatrin | | | | |
| Abstinence | 1 high-ROB RCT ⁸³ (N = 103) | Favors vigabatrin. Full 3-week end-of-trial abstinence 28% vs 7.5% $P \leq 0.01$ | Insufficient | Incomplete data was reported for the full trial period. |
| Use | 1 unclear-ROB RCT ⁸⁴ (N = 186) 1 high-ROB RCT ⁸³ (N = 103) | No difference. Total events: 76 (treatment), 86 (placebo). RR 0.88; 95% CI 0.69 to 1.13 | Low | Analysis from SR ⁵ |
| Retention | 1 unclear-ROB RCT ⁸⁴ (N = 186) 1 high-ROB RCT ⁸³ (N = 103) | No difference. Total events: 98 (treatment), 108 (placebo). RR 0.74; 95% CI 0.53 to 1.02. | Low | |
| Harms | 1 unclear-ROB RCT ⁸⁴ (N = 186) | No difference. RR 0.97; 95% CI 0.88 to 1.08 | Insufficient | |
| Medications FDA-approved for other substance use disorders | | | | |
| Acamprosate | | | | |
| Abstinence | – | No evidence | – | |
| Use | 1 low-ROB RCT ⁵⁰ (N = 60) | No difference. % UDS(-): 22% vs 23%, $P = 0.44$ | Insufficient | Only 1 small RCT |
| Retention | 1 low-ROB RCT ⁵⁰ (N = 60) | No difference. 18/34 (53%) vs 18/26 (69%), $P = NS$ | Insufficient | Only 1 small RCT |
| Harms | – | No evidence | – | |
| Buprenorphine plus naloxone, 2 doses | | | | |
| Abstinence | 1 low-ROB RCT ⁴⁹ (N = 302) | No difference. Rates of abstinence during weeks 5–8 similar between placebo group (16%) and Bup 4 mg 17.9%, ($P = 0.36$) and Bup 16 mg 18.6%, ($P = 0.32$) | Insufficient | Only 1 trial |
| Use | 1 low-ROB RCT ⁴⁹ (N = 302) | Mixed findings. Significantly less use with Bup 16 mg + naloxone 4 mg vs placebo. No difference with lower dose | Insufficient | |
| Retention | 1 low-ROB RCT ⁴⁹ (N = 302) | No difference. Rates of retention similar between placebo (87.3%) vs Bup 4 mg (86.0%) vs Bup 16 mg (88.0%) | Insufficient | |
| Harms | – | No evidence | – | |
| Buprenorphine vs methadone | | | | |
| Abstinence | 2 low-ROB RCTs ^{35, 36} (N = 278) | Mixed findings. Longer abstinence with methadone in 1 RCT; no difference in 1 RCT | Insufficient | Mixed findings |
| Use | 1 low-ROB RCT ³⁵ (N = 116) | Favors Methadone. Lower use with methadone vs buprenorphine ($P < 0.05$) | Insufficient | |
| Retention | 2 low-ROB RCTs ^{35, 36} (N = 278) | Mixed findings. Better retention with methadone in 1 RCT; no difference in 1 RCT | Insufficient | Mixed findings |
| Harms | 1 low-ROB RCT ³⁶ (N = 162) | Elevated LFT in 1 subject | Insufficient | |
| Disulfiram | | | | |
| Abstinence | 3 RCTs ^{37, 41, 85} (N = 296) | No difference. Continuous abstinence disulfiram vs placebo, combined RR from 3 RCTs $N = 296$, RR 0.96 (95% CI 0.63 to 1.45) | Low | ROB unclear overall |
| Use | 4 RCTs ^{37–40} (N = 440) | No difference. Combined RR from 4 RCTs: 0.95 (95% CI 0.64 to 1.39). The effect varied among studies, and statistical heterogeneity was highly significant ($P < 0.001$). | Low | Heterogeneous findings among studies |
| Retention | 1 SR ⁴ that included 2 RCTs (N = 87): 1 unclear-ROB (N = 20), ⁸⁵ 1 high-ROB ⁸⁶ (N = 67) 5 low-ROB RCTs ^{37–41} (N = 617) | Favors placebo. Treatment retention was lower with disulfiram: Meta-analysis of 7 RCTs, $N = 704$, RR 0.90 (95% CI 0.83 to 0.99). | Moderate | The combination of findings from all 7 studies (N = 704) was statistically homogeneous ($P = 0.90$) |
| Harms | 4 RCTs ^{38–41} (N = 548) | Withdrawals due to AE ranged from 0 to 5.9%, and included elevated liver enzymes and rash. Severe AEs not otherwise reported. | Low | – |

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Table 2. (continued)

| Outcomes | N studies per outcome; ROB (N = combined participants) | Summary of findings by outcome | Strength of evidence* | Comments and rationale for strength of evidence rating |
|--|---|--|--------------------------|---|
| Naltrexone | | | | |
| Abstinence | 2 low-ROB RCT ^{43, 47} 1 unclear-ROB RCT ⁴⁶ (N = 416) | No difference. 2 studies found no differences in N weeks to relapse. 1 study found no differences in abstinence (17.9% vs 17.1%, P = 0.918) | Low | Imprecision due to small number of studies; 1 study rated unclear ROB |
| Use | 1 low-ROB RCT ⁴⁵ (N = 80) | No difference. 1 study compared % (+) UDS at weeks 1–4; 5–8; and 9–12 and found no differences between T vs C. | Insufficient | Only 1 small RCT |
| Retention | 3 low RCTs ^{44, 45, 48} 1 unclear-ROB RCT ⁴⁶ (N = 416) | No difference. All 4 studies reported no differences in treatment retention | Low | Imprecision due small number of trials; indirectness due to behavioral co-interventions |
| Harms | 1 low RCT ⁴⁷ (N = 64) | No difference. In 1 trial of 64 pts., 2 in treatment arm and 11 in placebo arm experienced AE, non-significant. | Insufficient | Only 1 small RCT |
| Varenicline | | | | |
| Abstinence | – | No evidence | – | |
| Use | 2 unclear-ROB RCTs ^{51, 52} (N = 68) | No evidence. 1 study found trend toward lower use with varenicline (OR = 0.49, P = 0.08); 1 study found no difference (P = 0.84) | Insufficient | Few trials included; inconsistency of findings |
| Retention | 2 unclear-ROB RCTs ^{51, 52} (N = 68) | No difference. 1 study reported 77% total retention with no “significant difference in time to last visit” (P = 0.1); 1 study reported 5 drop out and no differences between groups (P = 0.26) | Insufficient | Unclear risk of bias, small number of studies. |
| Harms | 1 unclear-ROB RCT ⁵¹ (N = 31) | No difference. 1 trial reported no withdrawals due to AEs. | Insufficient | Unclear risk of bias, only 1 trial, few events |
| Dopamine agonists | | | | |
| Amantadine, bromocriptine, L-dopa/carbidopa, pergolide, cabergoline, hydroxyergine, and pramipexole (drugs combined in analysis) | | | | |
| Abstinence | 1 SR of 11 RCTs ⁶ (N = 731) | No difference. At 6 weeks: RR 1.12 (95% CI 0.85 to 1.47); at 4 months: RR 1.1 (95% CI 0.61 to 1.98) | Low ⁶ | Strength of evidence was determined by the SR authors ⁶ |
| Use | NR | NR | – | |
| Retention | 1 SR of 20 studies ⁶ (N = 1656) | No difference. RR 1.04 (95% CI 0.94 to 1.14) | Moderate ⁶ | |
| Harms | 1 SR of 7 studies ⁶ (N = 252) | SAEs and withdrawals due to AE NR. | No evidence ⁶ | |

AE, adverse event; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; MD, mean difference; NR, not reported; P, p value; RCT, randomized control trial; RD, risk difference; RR, relative risk; ROB, risk of bias; SAE, severe adverse event; SMD, standard mean difference; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SR, systematic review; UDS, urine drug screens

*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 follows¹⁶: 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; insufficient, any estimate of effect is very uncertain

moderate SOE; Fig. 2). We found insufficient evidence related to harms.

Antipsychotics: Aripiprazole, Haloperidol, Lamotrigine, Olanzapine, Quetiapine, Risperidone, Reserpine. Fourteen RCTs (N = 719) in an existing SR⁸ and one additional RCT²² examined antipsychotics as a class for the treatment of cocaine use disorder. The additional RCT²² of recently abstinent subjects found no difference between 15 mg of aripiprazole and placebo for any outcome of interest. Overall, we found low SOE that antipsychotics did not improve abstinence⁸ or reduce cocaine use,^{8, 22} and

insufficient evidence for lapse and relapse in participants abstinent at baseline.²² We found moderate SOE that antipsychotics improve study retention compared with placebo based on findings from eight RCTs in the SR (RR 0.75, 95% CI 0.57 to 0.97),⁸ and the additional RCT.²² We found insufficient evidence to form conclusions on harms.

Psychostimulants: Dexamphetamine, Lisdexamfetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Selegiline. A SR of 14 RCTs examined psychostimulants for treatment of cocaine use disorder. These trials reported low-strength evidence that

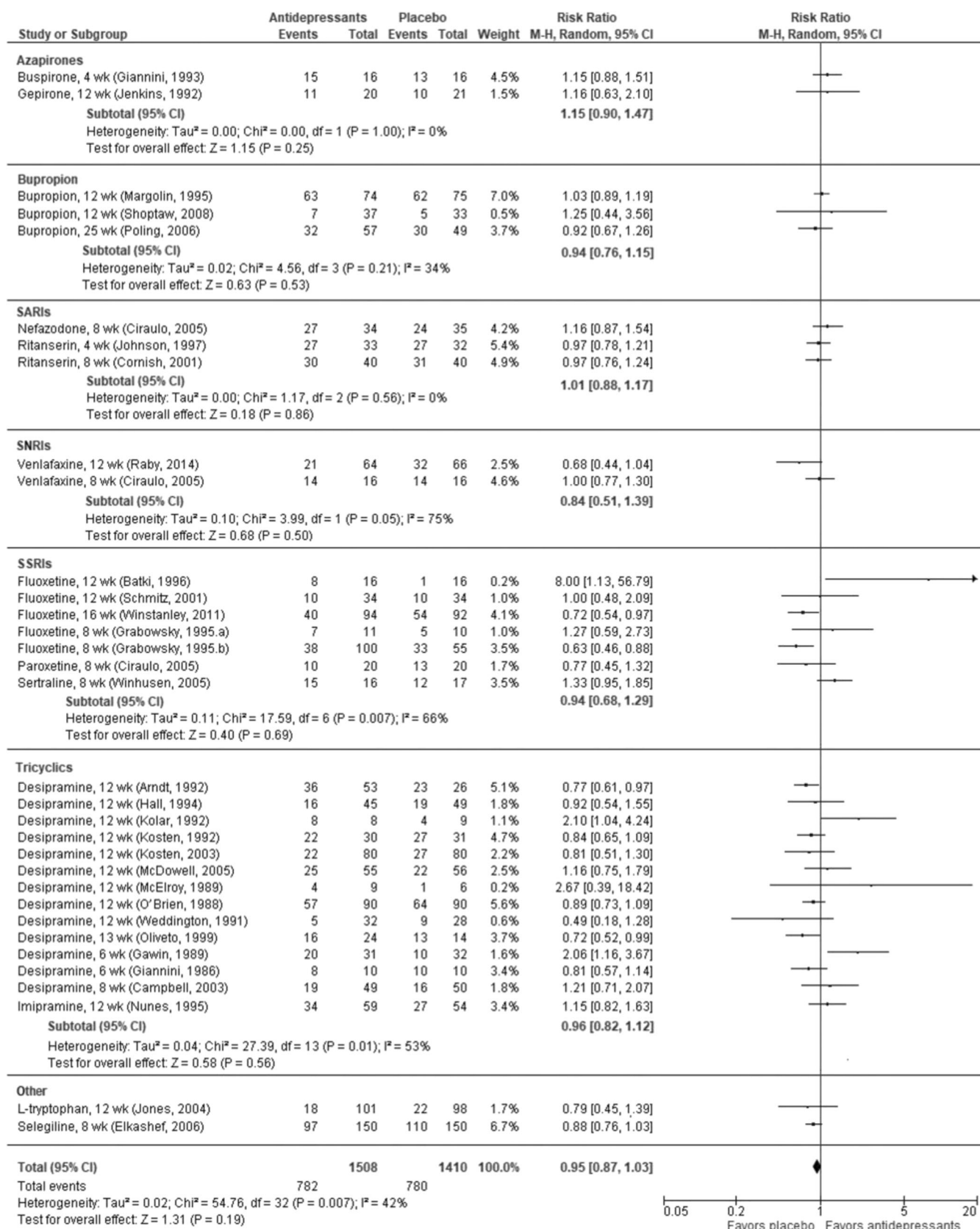


Figure 2 Treatment retention in RCTs of antidepressants vs placebo for cocaine use disorder.

psychostimulants improved abstinence versus placebo (RR 1.36, 95% CI 1.05 to 1.77).⁷ Although one study of bupropion

(which we classified as an antidepressant) was included in the combined estimate, its removal does not change the

conclusion.²³ There were no significant differences between groups for cocaine use during the trial period (SOE low), study retention (moderate SOE), or harms (moderate SOE).

Cognitive Enhancing Drugs: Atomoxetine, Memantine. We found two small RCTs, including one examining memantine (low ROB) and the other examining atomoxetine (unclear ROB), that provide insufficient evidence to draw conclusions about the effects of cognitive enhancing drugs on any outcome of interest.^{24, 25}

Anxiolytics: Buspirone. We identified only one small ($N=62$), multi-site, high-ROB RCT that compared 60 mg of buspirone to placebo, along with CM and once weekly optional individual or group psychosocial treatment and relapse prevention.²⁶ This provides insufficient evidence for the use of buspirone for cocaine use disorder.

Other Pharmacotherapies

Anticonvulsants and Muscle Relaxants: Baclofen, Carbamazepine, Gabapentin, Lamotrigine, Phenytoin, Tiagabine, Topiramate, Vigabatrin. We identified 20 RCTs in a prior SR,⁵ and three additional RCTs^{27–29} examining the effectiveness of anticonvulsants and muscle relaxants. The SR examined anticonvulsants and found moderate SOE that anticonvulsants as a class are no different than placebo for retention (17 RCTs, combined RR 0.95, 95% CI 0.86 to 1.05) or cocaine use (9 RCTs, RR 0.92, 95% CI 0.84 to 1.02). We identified one additional RCT ($N=60$) that found improved abstinence and a reduction in cocaine use associated with topiramate, and no difference in retention.²⁹ Two additional RCTs^{27, 28} compared baclofen (60 mg and 20 mg) to placebo. Neither study reported differences between groups on any of the outcomes of interest. Across all anticonvulsants and muscle relaxants as a class, there is insufficient evidence to form conclusions about the effects on abstinence, moderate SOE of no difference from placebo on cocaine use and study retention, and insufficient evidence on harms.

Topiramate. Five RCTs—four^{30–34} from an existing SR⁵ and one additional RCT²⁹—examined topiramate for cocaine use disorder. We found low SOE favoring topiramate over placebo for abstinence (2 RCTs, combined RR 2.56, 95% CI, 1.39 to 4.73; Fig. 3) and moderate SOE that topiramate was no different from placebo for study retention (5 RCTs, combined RR 1.01, 95% CI 0.93 to 1.10; Fig. 3). There was insufficient evidence to form conclusions on AEs.

Medications FDA-Approved for Other Substance Use Disorders: Acamprosate, Buprenorphine, Buprenorphine and Naloxone, Disulfiram, Methadone, Naltrexone, Varenicline. One SR⁴ and 18 RCTs^{35–52} examined FDA-approved pharmacotherapies for other substance use disorders. We found low SOE from six trials^{43–48} that naltrexone was no different than placebo for abstinence or retention. There was

insufficient evidence on use reduction and AEs. For studies of acamprosate,⁵⁰ varenicline,^{51, 52} buprenorphine plus naloxone,⁴⁹ and methadone compared directly with buprenorphine,^{35, 36} there was insufficient evidence to form conclusions on the outcomes of interest.

Disulfiram. Disulfiram for the treatment of cocaine use disorder was examined in a previous SR⁴ of seven RCTs and in five more recently published RCTs.^{37–41} There was low SOE that disulfiram does not increase abstinence (3 RCTs, combined RR 0.96, 95% CI 0.63 to 1.45; Figure 7) or increase harms versus placebo. We found moderate SOE that disulfiram worsened rates of retention versus placebo (7 RCTs, combined RR 0.90, 95% CI 0.83 to 0.99; Online Appendix Figure 5). The effects of disulfiram on cocaine use were significantly heterogeneous ($I^2=97\%$, $P<0.00001$) in a meta-analysis of four RCTs (Online Appendix Figure 5), and the evidence was therefore insufficient for drawing conclusions.

Dopamine Agonists: Amantadine, Bromocriptine, Cabergoline, Hydergine, L-Dopa/Carbidopa, Pergolide, Pramipexole. A 2015 SR of 24 trials found no difference between dopamine agonists and placebo on retention (moderate SOE), abstinence (low SOE), and a lack of evidence on AEs.⁶ We identified no additional trials of examining dopamine agonists for cocaine use disorder.

Other Pharmacotherapies. Nineteen trials^{53–71} examined the effects of other drugs or drug combinations for cocaine use disorder (Table 2). Although there is insufficient evidence to form conclusions due to limited power, positive findings on abstinence and use reduction were reported in studies of doxazosin,⁵⁹ ondansetron,⁶⁶ propranolol,⁷⁰ and topiramate combined with mixed amphetamine salts.⁶⁴ There were no positive or negative findings on the outcomes of interest for any of the other drugs or drug combinations.

Pharmacotherapies for Comorbid Opioid Use Disorder. Data from 6 SRs^{4, 5, 7, 8, 17, 72} and 14 additional RCTs^{22, 35–41, 49, 51, 54, 61, 62, 69} contribute to the evidence on pharmacotherapy for the treatment of cocaine use disorder in adults with comorbid opioid use disorder. Table 5 summarizes the findings of pharmacotherapies studied in patients with comorbid opioid use disorder, and additional details are provided in an online data supplement (Online Appendix Table 7).

We found low SOE that antidepressants are more effective than placebo for cocaine abstinence,^{7, 17, 72} and that psychostimulants are more effective than placebo for reducing cocaine use in patients with comorbid opioid use disorder.^{8, 22} However, we also found moderate SOE that both retention and dropouts due to AEs were higher in subjects receiving antidepressants versus placebo, and moderate SOE of poorer retention associated with disulfiram. There was no difference between placebo and antipsychotics or psychostimulants on

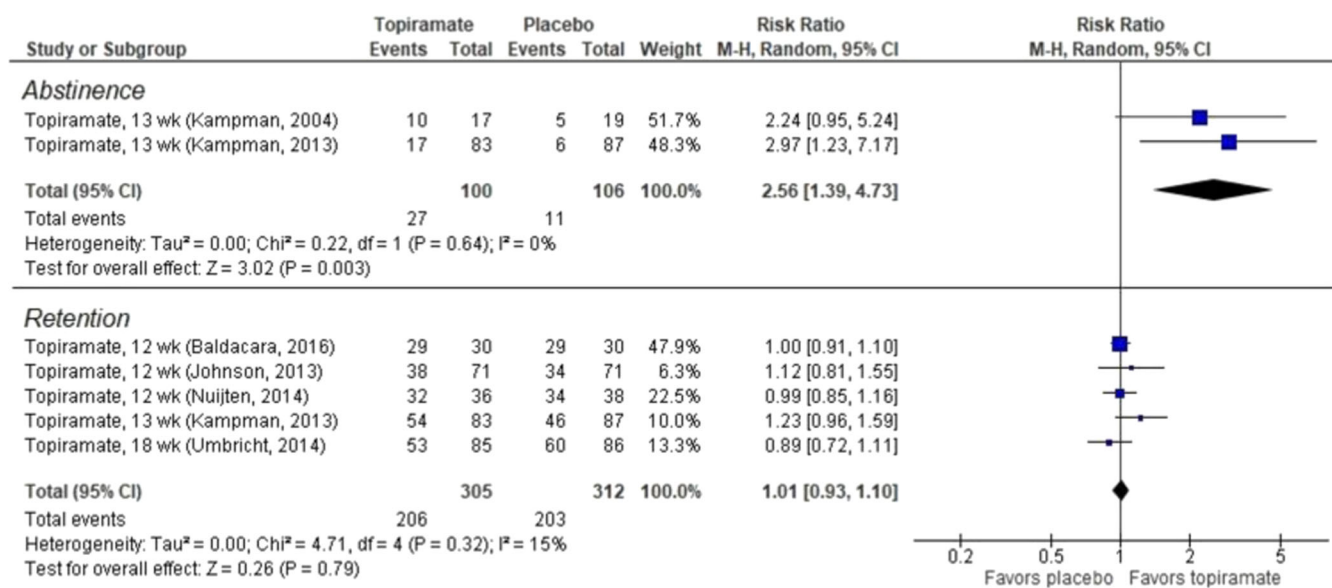


Figure 3 Abstinence and retention in RCTs of topiramate vs placebo for cocaine use disorder.

retention (low SOE). All other medication/outcomes were insufficient to form conclusions.

DISCUSSION

In this review, we identified seven SRs and 48 RCTs examining a variety of pharmacotherapies for cocaine use disorder. We found no strong evidence that any drug class was effective in increasing abstinence, reducing use, or improving retention rates for cocaine use disorder. However, we found low SOE that bupropion, psychostimulants, and topiramate may improve abstinence, and low SOE that sertraline may reduce relapse rates in abstinent patients. There was moderate SOE that antipsychotics may improve treatment retention. We also found moderate SOE that disulfiram may actually worsen treatment retention, and low SOE that SSRIs were associated with higher dropouts due to AEs (Table 4).

To our knowledge, this is the first report to summarize multiple classes of medications used in treatment of cocaine use disorder, which continues to be a global public health problem with increasing morbidity and mortality.⁷³ One motivation for this review was to find potentially promising treatments and targets for future research for a devastating condition that has been historically difficult to treat with pharmacotherapy. Indeed, we did identify several promising treatments that may be good areas in which to prioritize future research (Table 3). Post hoc analyses in RCTs of bupropion suggest that it may be effective for patients with comorbid depression and in conjunction with CM. We also found that psychostimulants—which serve as a form of agonist replacement therapy—may improve abstinence outcomes. Finally, we found that topiramate, thought to work via GABAergic pathways to regulate dopamine release, was potentially effective for abstinence and warrants continued exploration.⁷⁴

Our review complements and extends the findings of prior SRs by examining and summarizing data across all drug classes. We defined abstinence as 2 or more weeks of negative UDS—which meant excluding studies using other measures of abstinence. We summarized retention as an outcome, recognizing that improving retention in treatment increases the chances for successful recovery of stimulant use disorders; therefore, we did not consider study retention in our SOE assessment. We were limited in our ability to compare and meta-analyze results across studies because many studies did not report these data, or used different measures, and future research should look to standardize outcome reporting such as 3 or more-week abstinence to compare efficacy across trials and drug classes. It is also possible that the lack of significant findings was due to insufficient power to detect differences.

A lack of engagement in treatment on the part of some study participants who are actively using stimulants may affect the efficacy of pharmacotherapies; retention rates varied widely across studies (24–97%), and overall low rates of retention may have affected the assessment of treatment effectiveness in the majority of studies (attrition was greater than 20% in more than a third of the trials reporting retention rates). Unfortunately, pharmacotherapy alone (aside from antipsychotics) does not appear to be effective in improving treatment retention rates. Two areas of promise that are notable include those in which patients have already demonstrated engagement in treatment, or may have another rationale for ongoing engagement, as is the case for some patients with comorbid opiate use disorder. Indeed, we found low SOE that antidepressants and psychostimulants improved cocaine use outcomes in patients with comorbid opioid use disorder (Table 5). Given that the prevalence of cocaine use among heroin users is between 30 and 80%,⁷⁵ and concurrent opioid use increases risk of death due to cocaine,⁷⁶ further investigation on treatments for comorbid opioid use disorder is warranted.

Furthermore, more trials of medications that integrate evidence-based psychosocial and behavioral interventions are necessary to move the field forward. Given the largely disappointing pharmacotherapy results, these interventions (e.g., CM, CBT), alone or in combination, continue to be mainstays of treatment and management of stimulant use disorders.^{77, 78} A systematic review by Minozzi et al. found that any psychosocial treatment likely reduces dropout rates and may increase the period of abstinence (most of the studies reviewed included CM in addition to treatment as usual).⁷⁸ The combination of pharmacotherapy with CM is an important area for future research as we do not know how medication may enhance the effectiveness of these interventions.^{79, 80} When we compared studies with a CM co-intervention to those without, we found that pharmacotherapeutic effects were similar in both.⁸¹

Our SR has several limitations. Our scope 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 SRs with newer trials from our search. Our definition of abstinence (3 or more 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.⁸²

CONCLUSIONS

We found no strong or consistent evidence that any drug class was effective in increasing abstinence, reducing use, or improving treatment retention for people with cocaine use disorder. There are several promising classes deserving of further research including psychostimulants, bupropion, topiramate, and treatment of patients with comorbid opioid use disorder.

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Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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