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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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 drugs[4] or drug classes (anticonvulsants/carbamazepine,[5] dopamine agonists,[6] psychostimulants,[7] and antipsychotics[8]). 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 Collaboration[10] (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 5.3[13] 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, antipsychotics, 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 review[17] (RR 1.05, 95% CI 0.91 to 1.21) and two additional RCTs.[18, 19] We found high

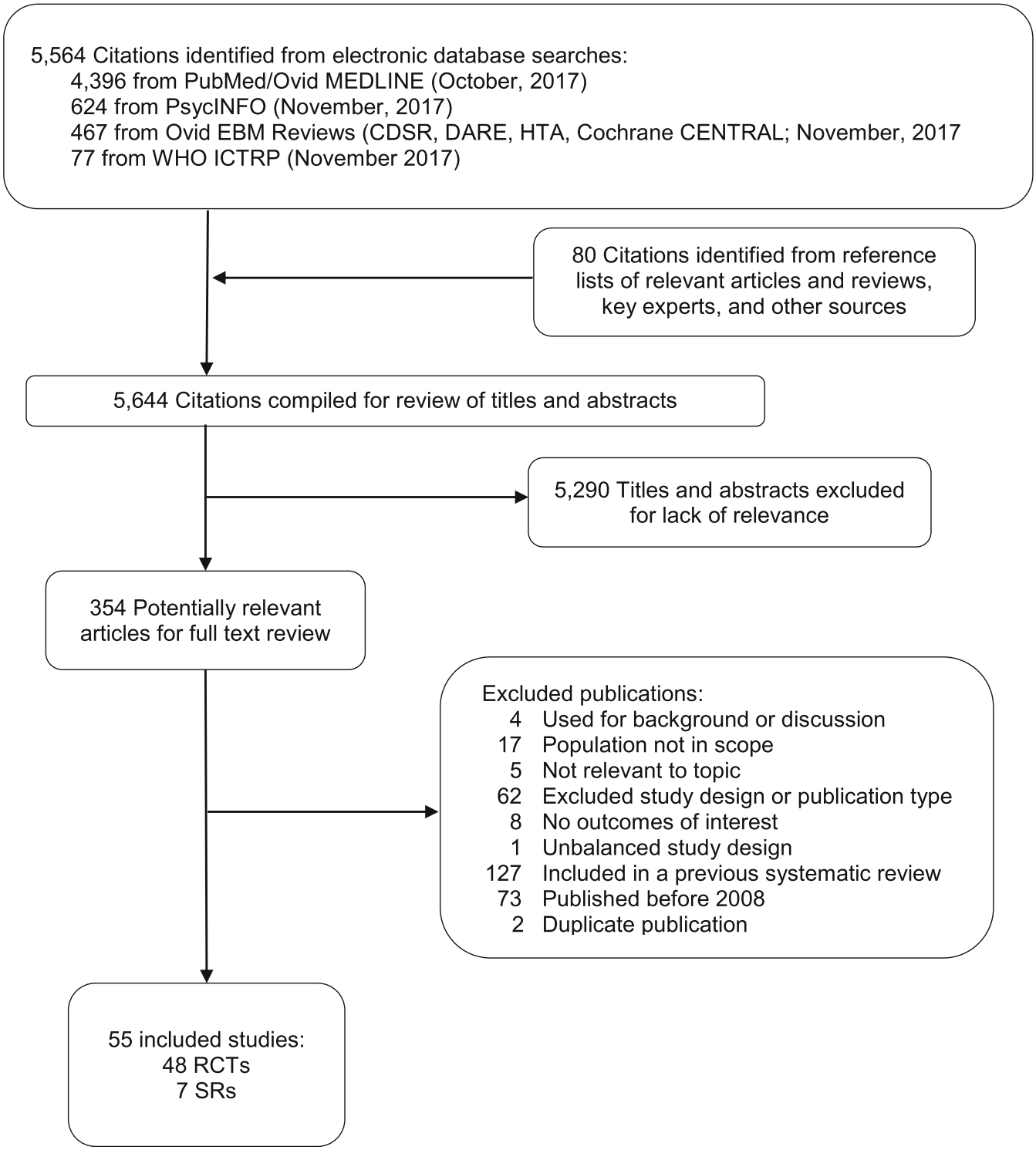

Figure 1 Literature flow diagram. RCT, randomized controlled trial; SR, systematic review.

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 antidepressants[17] 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 SR[17] 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	★★	Ø
SSRIs: Fluoxetine, Paroxetine, and Sertraline	NA	NA	Ø	Ø	★★	★
SSRI in patients abstinent at Baseline: Sertraline	NA	NA	★	★	★	Ø
All Antipsychotics: Aripiprazole, Haloperidol, Lamotrigine, Olanzapine, Quetiapine, Risperidone, Reserpine	★	★	Ø	Ø	★★	Ø
Psychostimulants: Dexamphetamine, Lisdexamfetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Selegiline	★	★	NA	NA	★★	★★
Cognitive Enhancing Drugs: Memantine, Atomoxetine	Ø	Ø	NA	Ø	Ø	Ø
Anxiolytic: Buspirone	Ø	NA	Ø	Ø	Ø	Ø
Anticonvulsants/Muscle Relaxants: Baclofen, Carbamazepine, Gabapentin, Lamotrigine, Phenytoin, Tiagabine, Topiramate, Vigabatrin	**NA**	★★	NA	NA	★★	**Ø**
Anticonvulsant: Topiramate	★	**Ø**	NA	NA	★★	**Ø**
Drugs for other substance use disorders: Acamprosate, Buprenorphine, Buprenorphine + Naloxone, Disulfiram, Naltrexone, Methadone, Varenicline	★	Ø	Ø	Ø	Ø	Ø
Disulfiram	★	★	NA	NA	★★	★
Dopamine agonists: Amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline hydergine, 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
Ø	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 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′.
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	
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 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		Favors sertraline. Abstinent at baseline participants with 1 cocaine positive UDS, combined RR 0.79 (95% CI 0.62 to 1.00).	Low	
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
				recent RCTs enrolled only patients who had achieved abstinence.
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	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. No difference. 1 RCT found no difference in severe AEs between groups.	Insufficient	
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	1 high-ROB RCT[22] (*N* = 18 opioid randomized, 41 enrolled opioid-dependent participants)	No difference.	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.	Insufficient	
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	No difference. 1 high-ROB found no difference in relapse by group.	Insufficient	Small, methodologically limited single trial. Indirectness (of results
Lapse	opioid-dependent participants)	No difference. 1 high-ROB found no difference in lapse by group.	Insufficient	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 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	Newer trial found no difference (indirectness of population).
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
		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).		Single small RCT with a 2-week placebo lead-in to encourage abstinence after randomization.
Use	1 low-ROB RCT[24] (*N* = 81) 1 unclear-ROB RCT[25] (*N* = 50)	No difference. There was no difference in cocaine negative UDS′ between groups.	Insufficient	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	
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] SOE was determined by the SR authors
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]	
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	

(continued on next page)

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 evens
Dopamine agonists				
Amantadine, bromocriptine, L-dopa/carbidopa, pergolide, cabergoline hydergine, 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 follows[16]: 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 SR[8] and one additional RCT[22] examined antipsychotics as a class for the treatment of cocaine use disorder. The additional RCT[22] 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 abstinence[8] 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

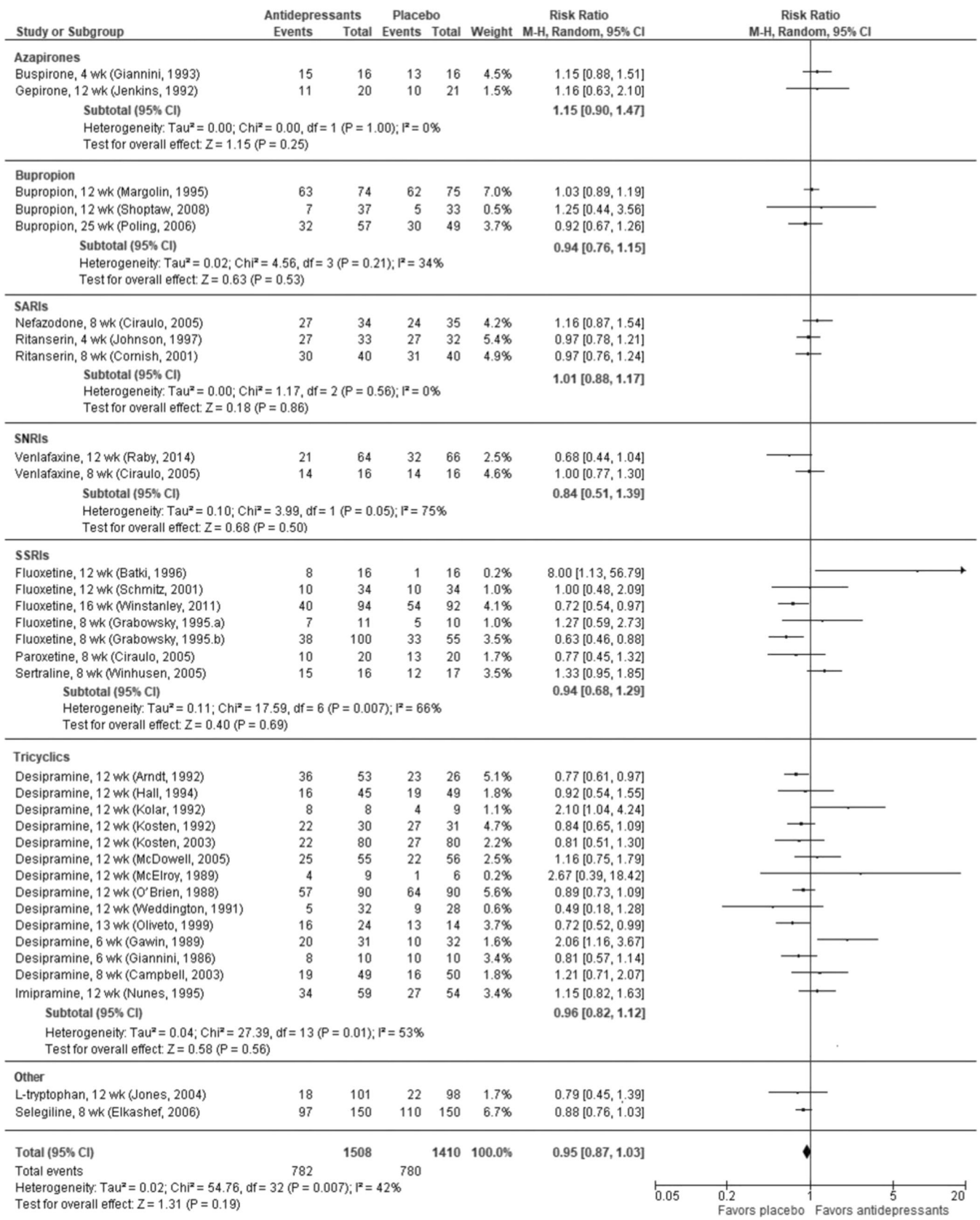

Figure 2 Treatment retention in RCTs of antidepressants vs placebo for cocaine use disorder.

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 SR[5] and one additional RCT[29]—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 SR[4] 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 SR[4] 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

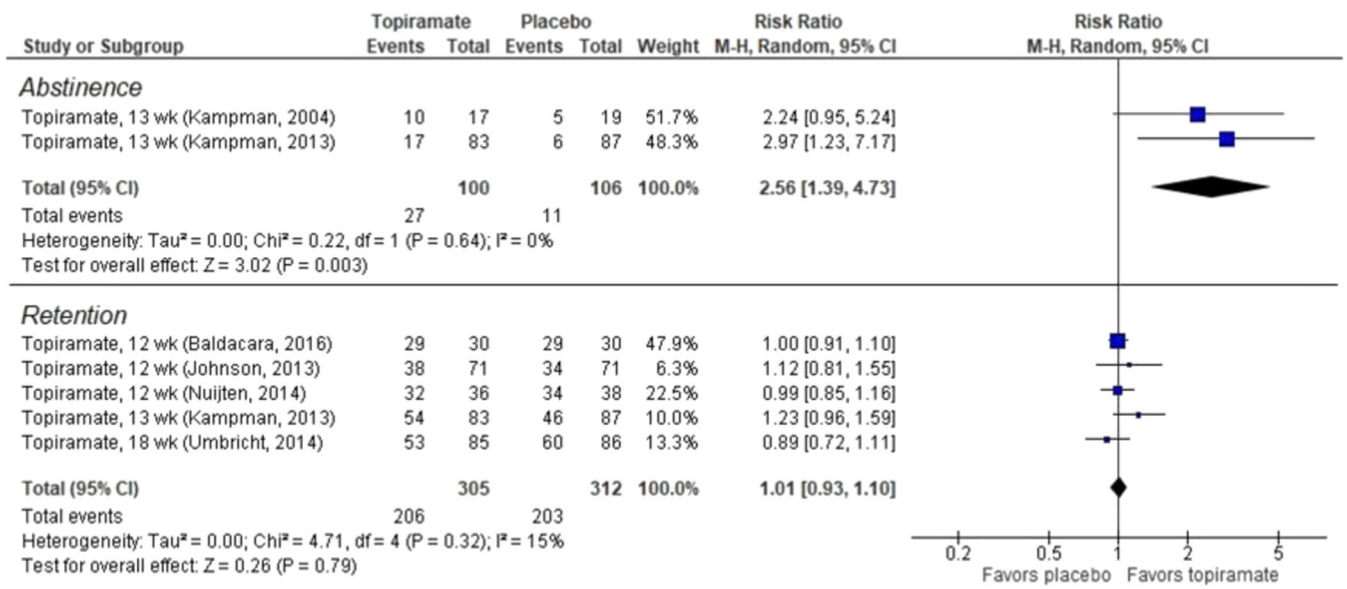

Figure 3 Abstinence and retention in RCTs of topiramate vs placebo for cocaine use disorder.

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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