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A Systematic Review and Meta-analysis of Medications for Stimulant Use Disorders in Patients with Co-Occurring Opioid Use Disorders

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Abstract

Background: Stimulant (cocaine and/or methamphetamine) use has increased among people with opioid use disorder. We conducted a systematic review of medications for stimulant use disorders in this population.

Methods: We searched for randomized controlled trials in multiple databases through April 2019, and dual-screened studies using pre-specified inclusion criteria. Primary outcomes were abstinence defined as stimulant-negative urine screens for ≥3 consecutive weeks; overall use as the proportion of stimulant-negative urine specimens; and retention as the proportion of participants who completed treatment. We rated strength of evidence using established criteria and conducted meta-analyses of comparable interventions and outcomes.

Results: Thirty-four trials of 22 medications focused on cocaine use disorder in patients with opioid use disorder. Most studies enrolled participants stabilized on opioid maintenence therapy, generally methadone. None of the six studies that assessed abstinence found significant differences between groups. We found moderate-strength evidence that antidepressants (desipramine, bupropion, and fluoxetine) worsened retention. There was moderate-strength evidence that disulfiram worsened treatment retention (N=605, RR 0.86, 95% CI 0.77 to 0.95). We found

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low-strength evidence that psychostimulants (mazindol and dexamphetamine) may reduce cocaine use, though the difference was not statistically significant (standard mean difference 0.35 [95% CI −0.05 to 0.74]). There was only 1 trial for methamphetamine use disorder, which showed insufficient-strength evidence for naltrexone.

Conclusions: Co-occurring stimulant/opioid use disorder is an important problem for targeting future research. Medication trials for methamphetamine use disorder are lacking in this population. Most of the medications studied for cocaine use were ineffective, although psychostimulants warrant further study.

Keywords

pharmacotherapy; substance use disorder; cocaine; amphetamine; stimulant; systematic review

1. INTRODUCTION

While the United States (U.S.) is in the midst of an opioid epidemic, stimulant use disorders have been increasing in people with existing opioid use disorder (OUD). Among treatment-seeking people with OUD, reports of past-month methamphetamine use nearly doubled from 18.8% to 34.2% between 2011 and 2017 (Ellis et al., 2018). Similarly, amongst people with prescription OUD in 2015, 31.5% reported cocaine use disorders in the prior year (Han et al., 2017). While there are Food and Drug Administration (FDA)-approved medications for OUD (Substance Abuse and Mental Health Services Administration (SAMHSA), 2018), untreated stimulant use disorders complicate treatment and are associated with poorer outcomes, including increases in hospitalization and overdose deaths (Centers for Disease Control and Prevention; Seth et al., 2018; Winkelman et al., 2018). In previous systematic reviews (SRs) (Chan et al., 2019a; Chan et al., 2019b) we examined various medications for stimulant use disorders; however, many of the studies reviewed excluded populations with co-occurring OUD. We sought to conduct a more in depth review the evidence for medications for stimulant use disorder treatment specifically in people with co-occurring OUD.

2. METHODS

2.1 Data sources and search strategies

This SR is part of a larger report commissioned by the U.S. Veterans Health Administration (VHA) that examined the benefits and harms of medications for cocaine and methamphetamine use disorders (Chan et al., 2018). We searched Ovid MEDLINE, OvidPsycINFO, and Ovid EBM Reviews Cochrane Database of Systematic Reviews through April 2019 (see online supplement eMethods 1 for full search strategy). 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 study initiation (CRD42018085667). Our methods and reporting follow PRISMA guidelines (Moher et al.).

2.2 Study selection

We included randomized controlled trials (RCTs) that enrolled adults with cocaine or methamphetamine use disorders and co-occurring OUD and compared pharmacotherapies to one another, placebo, usual care, or psychotherapy. We excluded studies and comparisons examining participants with comorbid psychotic spectrum or bipolar disorders. We excluded studies that did not perform urine drug screening (UDS) at least once per week, and/or had less than four-weeks follow-up. The parameters and scope of the review are available in our PICOTS (population, interventions, comparators, outcomes, timing, setting, and study design) table in eMethods 2 of the online supplement, while study selection criteria are detailed in eMethods 3.

We dual reviewed and evaluated titles and abstracts for 13% of the search yield to ensure reliability. Two investigators independently reviewed the full text of all potentially relevant articles for inclusion, and discordant results were resolved through consensus.

2.3 Data abstraction and quality assessment

One investigator abstracted details related to study design; setting; population; intervention and follow-up; co-interventions; outcomes; and harms. A second investigator confirmed the abstraction. Outcomes of interest were defined based on outcomes used in prior reviews, as well as guidance from our Technical Expert Panel (TEP) prior to beginning our review, with focus on standardized measures that would allow for potential meta-analysis, including: abstinence from stimulants, defined as three or more consecutive weeks of negative UDS; overall use, analyzed as the proportion of UDS samples that were cocaine- or methamphetamine-negative; treatment retention defined as the proportion of randomized participants who completed treatment; and harms, specifically, reported adverse effects leading to treatment dropout and severe adverse events. We also noted whether participants in each study were receiving opioid maintenance treatment upon enrollment or not, and whether they were started or continued on concurrent medications for opioid use disorder during the trial.

Two reviewers independently assessed the quality of each included RCT using a tool developed by the Cochrane Collaboration (Higgins and Green, 2011) (quality criteria and ratings are in online supplement eMethods 4 [eTables 1 and 2]), and classified the risk of bias (ROB) as low, unclear, or high. For studies identified in our search that were included in prior SRs, we reviewed the primary studies to confirm enrollment of co-occurring OUD populations and abstracted results from those studies in our analysis.

2.4 Data synthesis and analysis

We qualitatively synthesized the evidence, and combined the findings of trials with comparable interventions and outcome measures in random-effects meta-analyses (DerSimonian and Laird, 1986). We used RevMan 5.3 (Review Manager, 2014) to calculate the overall relative risk (RR) and 95% confidence intervals (CI) for each outcome in the treatment group compared with placebo. We assessed statistical heterogeneity among the pooled studies using the I^2 statistic (Higgins and Thompson, 2002; Higgins et al., 2003).

We assessed the overall strength of evidence (SOE) for each outcome as high, moderate, low, or insufficient using an established method (Berkman et al., 2013). Although the small number of trials for each medication precluded quantitative analysis for publication bias, we assessed publication bias qualitatively by considering whether or not it was likely that negative studies were selectively withheld from publication (Guyatt et al., 2011). We considered factors such as number of positive studies included, review of study sponsorship, and searched clinicaltrials.gov to ensure no studies that should have been reported had remained unpublished.

3. RESULTS

Our search yielded 5,862 publications, of which we selected 486 for full-text review (eFigure 1, online supplement). We included 35 RCTs of 23 different medications, including anticonvulsants, antidepressants, antipsychotics, dopamine agonists, medications for OUD, medications approved by the FDA for other substance use disorders (SUDs) (NIDA), psychostimulants, and various other pharmacotherapies (Table 1). Of the 35 RCTs we included, 24 were reviewed in seven previous SRs, and 11 were newly identified (Table 1) in our search. 34 trials were of treatments for cocaine use disorder, while only one RCT (Tiihonen et al., 2012) studied treatment of amphetamine use disorder using naltrexone implant in participants with comorbid OUD.

A majority (16) of included trials enrolled participants who were already receiving opioid maintenance treatment (OMT), though 10 trials enrolled participants who had not recently received OMT; 9 trials either enrolled a mix of treatment stabilized and treatment naïve or did not include this information. Aside from the five trials of MOUD for stimulant use (Ling et al., 2016; Oliveto et al., 1999; Schottenfeld et al., 2005; Schottenfeld et al., 1997; Tiihonen et al., 2012), the majority of studies used methadone concurrently with the study medication (26); three studies used buprenorphine, and one study used diacetylmorphine.

3.1 Medications for Cocaine Use Disorder in Participants with Opioid Use Disorder

3.1.1 Antidepressants—Ten RCTs studied antidepressants for treatment of cocaine use disorder in populations that were generally stable on methadone maintenance (Table 1).: desipramine in six trials(Arndt et al., 1992; Kolar et al., 1992; Kosten et al., 2003; Kosten et al., 1992; O'Brien et al., 1988; Oliveto et al., 1999), bupropion in two trials(Margolin et al., 1995b; Poling et al., 2006), and fluoxetine in two trials (Table 1). Few studies were high-quality, and most were underpowered.

There was moderate SOE that antidepressants worsen treatment retention (10 RCTs, combined N=1,006; RR of dropout 1.22, 95% CI 1.05 to 1.41) and withdrawals due to adverse events (five RCTs, combined N=492; RR 2.47, 95% CI 1.03 to 5.90) compared to placebo (Pani et al., 2011). Only one unclear-ROB study examined cocaine use during the trial period and found no difference between the antidepressant bupropion and placebo (Poling et al., 2006). None of the antidepressant trials reported abstinence outcomes,

3.1.2 Anticonvulsants—Three placebo-controlled trials of anticonvulsants were reviewed in two previous SRs (Castells et al., 2009; Minozzi et al., 2015b): one unclear-

ROB trial of tiagabine, one unclear-ROB trial with separate arms for gabapentin and tiagabine, and one low-ROB trial of topiramate (Table 1).

Combined retention data from all three trials (N=292) show moderate-strength evidence of worse retention with anticonvulsants compared with placebo (RR 0.86, 95% CI 0.76 to 0.97;; Figure 3), and low-strength evidence for no effect on cocaine use or abstinence in cocaine users with comorbid OUD.

3.1.3 Antipsychotics—Two antipsychotic medications were studied as interventions of cocaine use disorder in participants with OUD: risperidone (Grabowski et al., 2004) and aripiprazole (Moran et al., 2017). These studies provide insufficient-strength evidence for treating cocaine use disorder with antipsychotics in people with comorbid OUD.

The risperidone study included a two-week medically supervised stabilization period prior to a 24-week medication trial of risperidone (two or four mg) or placebo; participants were not required to be cocaine-free at the start. This unclear-ROB study reported fewer dropouts with risperidone than placebo, although the difference was not statistically significant (N=96, RR 0.77, 95% CI 0.59 to 1.00) (Indave et al., 2016). The aripiprazole study was conducted among participants recently stabilized on methadone, receiving contingency management and counseling, who completed a 12-week medically-supervised withdrawal from cocaine prior to initiating treatment (Moran et al., 2017). Those who achieved continuous cocaine abstinence during weeks 11 and 12 (N=18) were randomized to 15 mg of aripiprazole or placebo, with contingency management continuing through the two-week induction phase. Time to both lapse (first cocaine-positive UDS; hazard ratio [HR]=0.45, 95% C I0.14 to 1.42, P=0.17) and relapse (two consecutive cocaine-positive UDSs or missed urines; HR= 0.31, 95% CI 0.07 to 1.27, P=0.10) were similar between groups, and there were no differences in abstinence, retention, or harms. The study was discontinued early due to the small number of participants able to achieve abstinence in weeks 11 and 12 (18 of 41 enrolled) and rated high ROB.

3.1.4 Dopamine agonists—Three RCTs of amantadine and one RCT of bromocriptine were conducted in methadone or buprenorphine-maintained participants with cocaine use disorder (Table 1). These studies reviewed in a previous SR (Minozzi et al., 2015a). We pooled retention outcomes from all studies (N=205) and found no difference between dopamine agonists and placebo (RR 0.95, 95% CI 0.84 to 1.07; Figure 3). There were also no differences in cocaine use, and abstinence was not reported. Three of the studies had unclear ROB and the fourth had high ROB (eTable 2, online supplement).). These studies provide low-strength evidence that dopamine agonists are not effective for reducing cocaine use nor improving treatment retention in an OUD population.

3.1.5 Medications for Opioid Use Disorder (MOUDs)—Four trials examined the effects of MOUDs for cocaine use disorder in participants with comorbid OUD. Three trials compared buprenorphine directly with methadone (Ling et al., 2016)(Table 1). One of these studies included four treatment arms with two dose levels of each drug (methadone 20 mg versus 65 mg daily, buprenorphine four mg versus 12 mg daily; (Schottenfeld et al., 1997). For meta-analysis we included only the higher drug dosages from this study, which are

closer (although still lower) to the dosages used in clinical practice and in the other two studies (Oliveto et al., 1999; Schottenfeld et al., 2005). Abstinence was greater for those taking methadone than buprenorphine in our pooled analysis of 2 low-ROB RCTs (N=219; RR 1.85, 95% CI 1.25 to 2.75; Figure 1). Similarly, there was no significant difference in treatment retention when all three studies were pooled (N=309, RR 1.17, 95% CI 0.91 to 1.51; Figure 3). These studies were reviewed in previous SRs (Castells et al., 2009; Pani et al., 2011).

The current search identified one large (N=302), low-ROB trial of buprenorphine in combination with naloxone at two dosages (16–4 mg and 4–1 mg buprenorphine-naloxone; (Ling et al., 2016). The higher dose arm experienced significantly less cocaine use compared with placebo (UDS-negative OR 1.71, P=0.02); the lower dose arm experienced no differences in use (OR 1.09, P=0.11). There were no differences in retention or abstinence at either dosage.

Taken together these studies provide insufficient-strength evidence for the effectiveness of MOUDs for treatment of cocaine use disorder in those with comorbid OUD.

3.1.6 Medications FDA-approved for other substance use disorders—We identified six studies of disulfiram, which is FDA-approved for alcohol use disorder, to treat cocaine use disorder in participants with comorbid OUD (Carroll et al., 2012; George et al., 2000; Kosten et al., 2013; Oliveto et al., 2011; Petrakis et al., 2000; Schottenfeld et al., 2014)(Table 1). Combined retention data from all six studies (N=605) provides moderate-strength evidence that disulfiram worsened treatment retention compared with placebo (RR 0.86, 95% CI 0.77 to 0.95; Figure 3). Combining data on abstinence from one low-ROB RCT (Schottenfeld et al., 2014) and one unclear-ROB RCT (George et al., 2000) revealed no significant differences (N=207, RR 0.89, 95% CI 0.53 to 1.48; Figure 1). Three trials of disulfiram reported conflicting findings on cocaine use; data were not available to conduct meta-analysis. One study (Kosten et al., 2013) found significant reduction in use (RR 1.58, 95% CI 1.39 to 1.79), another study (Oliveto et al., 2011) found significant increase in use (RR 0.61, 95% CI 0.52 to 0.71), and a third study (Carroll et al., 2012) found no difference from placebo. These provide insufficient-strength evidence for the effect of disulfiram on cocaine use in those with OUD.

Varenicline, an FDA-approved treatment for tobacco use disorder, was studied in one small (N=31), unclear-ROB trial that reported no statistically significant differences in cocaine use reduction or treatment retention (Poling et al., 2010). No adverse events occurred in the study, and abstinence was not reported.

3.1.7 Psychostimulants—Four trials of psychostimulant medications were reviewed in three previous SRs; (Castells et al., 2016; Castells et al., 2009; Indave et al., 2016). Mazindol was studied in two unclear-ROB RCTs (Margolin et al., 1995a; Margolin et al., 1997), dexamphetamine in one unclear-ROB RCT (Grabowski et al., 2004), and methylphenidate in one high-ROB RCT (Dursteler-MacFarland et al., 2013). We found no effect of psychostimulants on retention when the four studies were pooled (N=210; RR=0.98, 95% CI 0.71 to 1.36; Figure 3), although the findings were mixed across studies

and statistical heterogeneity was on the margin of significance (P=0.05, I^2=62%; Figure 3). Cocaine-free urinalyses occurred more frequently with psychostimulants than placebo, but the difference was not statistically significant in a pooled analysis that combined cocaine use data from the studies of mazindol and dexamphetamine (N=115, standardized mean difference [SMD]= 0.35, 95% CI −0.05 to 0.74; Figure 2) using data reported in a previous SR (Castells et al., 2009). None of the studies reported abstinence.

3.1.8 Other medications (carvedilol, magnesium L-aspartate hydrochloride, mecamylamine, progesterone)—Four studies examined various other medications for treatment of cocaine use disorder in comorbid OUD participants (Table 1). A study of carvedilol (25 mg, 50 mg, placebo) in 106 methadone-maintained participants did not assess abstinence but found differences in cocaine use based on dosing; the lower (25 mg) dosage arm had lower rates of positive UDS compared to placebo, while the higher (50 mg) dosage arm had higher rates of positive UDS (25 mg 51% versus 50 mg 75% versus placebo 59%, P=0.03). There were no statistically significant differences in retention (76% versus 66% versus 56%, P=0.21) (Sofuoglu et al., 2017). A study of magnesium L-aspartate versus placebo found no differences in cocaine use (74.5% versus 75.5%, P=NS) or treatment retention (10.9 versus 8.9 weeks in treatment, P>0.5) (Margolin et al., 2003). A small study (N=35) of mecamylamine patches versus placebo in OUD participants on either methadone or levomethadyl acetate (LAAM) therapy found no differences in cocaine use reduction or treatment retention (13 of 17 retained versus 17 of 18, P=0.13) (Reid et al., 2005). Another study randomized 45 OUD participants on methadone maintenance therapy to progesterone (up to 600 mg) or placebo and found no differences in treatment retention (73% versus 93%, P=0.12); no data were available for abstinence or use outcomes (Sofuoglu et al., 2007). As a whole these were small trials that provide insufficient-strength evidence for use of these medications to treat cocaine use in people with OUD.

3.2 Medications for Methamphetamine Use Disorder in Participants with Opioid Use Disorder

We identified one RCT that examined a naltrexone implant (not available in the U.S.) for methamphetamine/amphetamine use disorder in participants with co-occurring OUD (Tiihonen et al., 2012). This was a multi-site trial conducted in Russia of 100 participants with co-occurring amphetamine and opioid dependence randomized to naltrexone implant (1000 mg) or placebo for 10 weeks. The treatment group had a greater percentage of negative UDS than placebo, but this difference was not statistically significant (40% versus 24%, P=0.09). Treatment participants had increased retention versus placebo (52% versus 28%, P=0.01) (Tiihonen et al., 2012). This study had high ROB due to changes to the protocol after study initiation and provides insufficient-strength evidence for naltrexone implant treatment of methamphetamine use disorder in people with existing OUD.

3.3 Publication Bias

There were too few trials for any medication to conduct quantitative estimates of publication bias. However, we felt there was low likelihood of publication bias because: 1) the body of evidence is largely negative - we did not find a disproportionate number of positive studies, 2) most of the published studies were not industry sponsored, and 3) we searched

clinicaltrials.gov and did not find additional studies that should have been reported (Guyatt et al., 2011).

4. DISCUSSION

Against a backdrop of increasing co-use of opioids and stimulants and their associated health consequences (Winkelman et al., 2018), this review summarizes 35 RCTs examining multiple classes of medications used for treatment of cocaine and methamphetamine use disorders in people with OUD. Unfortunately, we found no strong evidence that any drug class was effective in increasing abstinence, reducing use, or improving retention rates for stimulant use disorders. We found antidepressants had no effect for cocaine, but there was moderate-strength evidence that they worsened study retention and increased harms (Chan et al., 2019b). While we found low-strength evidence that psychostimulants might reduce cocaine use, these were small trials that may not be replicable. We did find low-strength evidence that methadone may increase cocaine treatment retention over other MOUDs such as buprenorphine; however, it is unclear the degree to which any potential benefit from opioid agonist therapy relates to the medications themselves, the dosages used, or the effect of participation in highly structured opioid treatment programs with frequent behavioral therapy. We also found conflicting evidence for disulfiram reducing cocaine use, but evidence of worsened treatment retention. All other medication classes had insufficient evidence to draw conclusions. We found only one trial of treatment of methamphetamine use disorder in people with OUD.

This review is the first to summarize evidence for medications trialed for stimulant use disorders in patients with OUD. Our review highlights several implications. First, our review found almost no evidence regarding treatment of methamphetamine use disorder in people with OUD. Given that co-use of methamphetamine and opioids is increasing in prevalence (Al-Tayyib et al., 2017; Winkelman et al., 2018), additional research specific to methamphetamine use in people with OUD is urgently needed. While we identified additional trials of medications for methamphetamine use disorder, including a recent trial of mirtazapine that showed reduced methamphetamine use (Coffin et al., 2019), it was unclear whether participants with OUD were included. Second, while we found trials of medications for cocaine use disorder, there were few trials in each class, mainly small studies of varying quality, had high risk of bias, and lacked power to detect differences--larger multi-site trials would strengthen the evidence base.

4.1 Limitations

Through the review process we noted a wide variety of definitions of abstinence. For the purpose of this review we narrowly defined abstinence as at least three weeks of negative UDS in order to compare efficacy across trials—this meant excluding findings from studies that reported other measures of abstinence, decreasing the size of our review. Substance use disorder researchers should seek to standardize outcome definitions in future studies to enable meta-analyses of results. Similarly, the included studies had varied treatment duration, which may have affected treatment retention estimates.

5. CONCLUSIONS

We found little evidence that any drug class was effective in increasing abstinence, reducing use, or improving treatment retention for those with cocaine or methamphetamine use disorder and co-occurring OUD. Antidepressants and disulfiram may worsen treatment retention outcomes when used for treatment of cocaine use disorders in participants with comorbid OUD. Almost no evidence exists of medications to treat methamphetamine use disorder in people with OUD--additional trials would advance the field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Stimulant use has increased among people with opioid use disorder
- Clinical trials have studied 21 medications for cocaine use in people with OUD
- Only one medication has been studied for methamphetamine use in people with OUD
- No medication had clear benefits; antidepressants and disulfiram had worse retention
- Psychostimulant trials showed potential benefits for cocaine use in this population

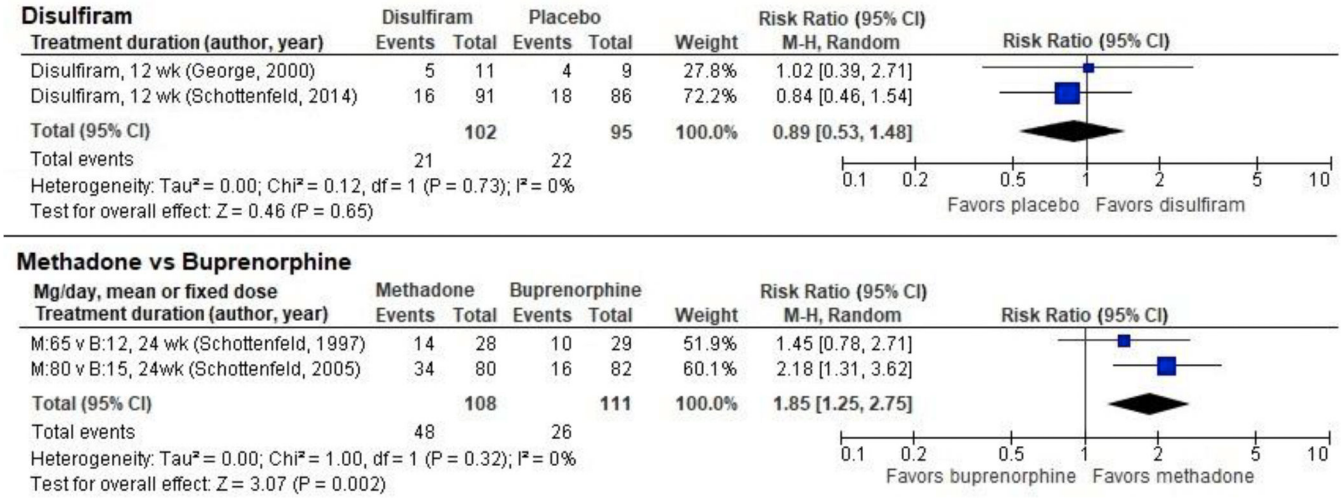

Figure 1.

Abstinence for 3 or more consecutive weeks in randomized controlled trials of disulfiram and opiate agonists in participants with dual cocaine/opioid use disorders

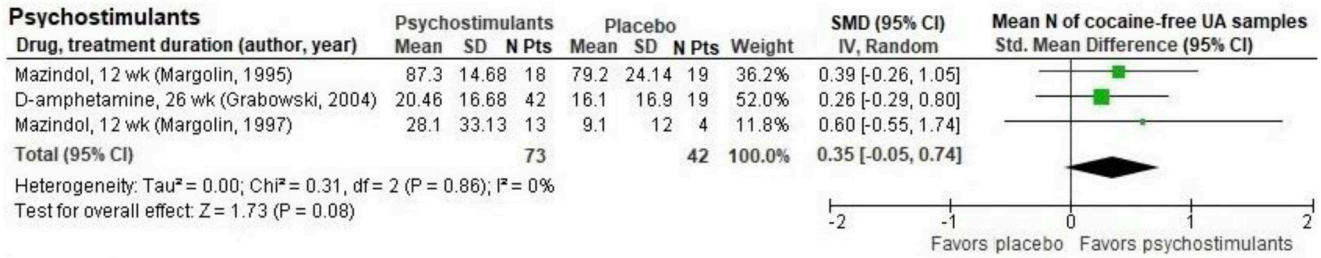

Figure 2.

Cocaine-free urinalysis outcomes in randomized placebo-controlled trials of psychostimulants in participants with dual cocaine/opioid use disorders

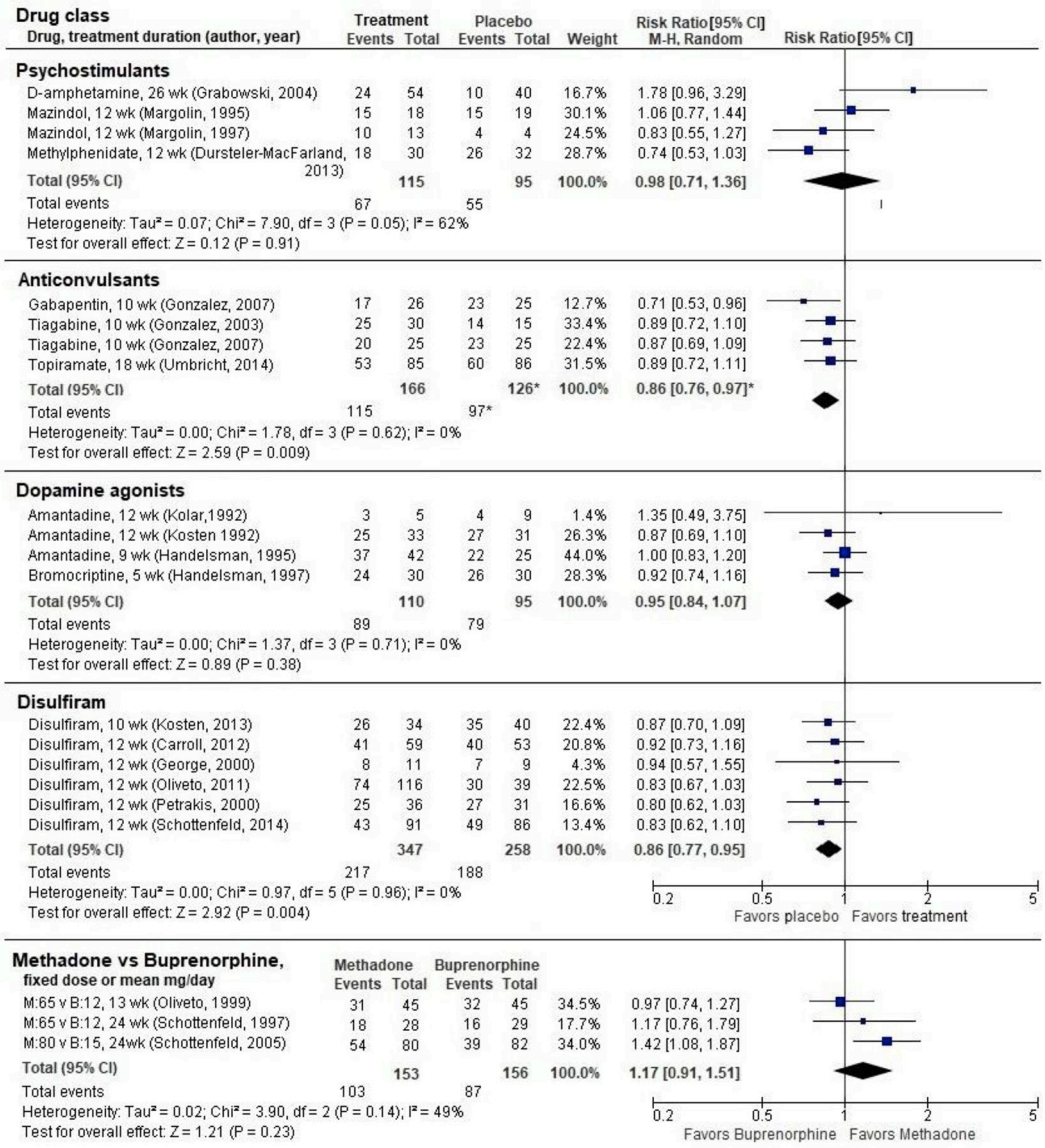

Figure 3. Treatment retention in randomized controlled trials of psychostimulants, anticonvulsants, dopamine agonists, disulfiram, and opiate agonists in participants with dual cocaine/opioid use disorders

* Gonzalez. 2007 included 2 active treatment arms. The weights and combined estimate have been adjusted to represent the placebo arm only once in the analysis.

Table 1.

Pharmacotherapies for stimulant use disorder studied in participants with comorbid opioid use disorder

Drug class	N trials and sources	Drug or drug combination	N trials
Interventions for cocaine use disorder			
Antidepressants	10 RCTs from 4 previous SRs (Castells et al., 2016; Castells et al., 2009; Minozzi et al., 2015a; Pani et al., 2011)	Bupropion	2 (Margolin et al., 1995b; Poling et al., 2006)
		Desipramine	6 (Arndt et al., 1992; Kolar et al., 1992; Kosten et al., 2003; Kosten et al., 1992; O'Brien et al., 1988; Oliveto et al., 1999)
		Fluoxetine	2 (Grabowski et al., 1995; Winstanley et al., 2011)
Anticonvulsants	4 RCTs from 2 previous SRs (Castells et al., 2009; Minozzi et al., 2015b)	Gabapentin	1 (Gonzalez et al., 2007)
		Tiagabine	2 (Gonzalez et al., 2007; Gonzalez et al., 2003)
		Topiramate	1 (Umbricht et al., 2014)
Antipsychotics	2 RCTs: 1 from the current search; 1 from 3 previous SRs (Castells et al., 2016; Castells et al., 2009; Indave et al., 2016)	Aripiprazole	1 (Moran et al., 2017)
		Risperidone	1 (Grabowski et al., 2004)
Dopamine agonists	4 RCTs from 3 previous SRs (Castells et al., 2009; Minozzi et al., 2015a; Pani et al., 2011)	Amantadine	3 (Handelsman et al., 1995; Kolar et al., 1992; Kosten et al., 1992)
		Bromocriptine	1 (Handelsman et al., 1997)
Medications for opioid use disorder	4 RCTs: 1 from the current search; 3 from previous SR (Castells et al., 2009; Pani et al., 2011)	Buprenorphine	3 (Oliveto et al., 1999; Schottenfeld et al., 2005; Schottenfeld et al., 1997)
		Buprenorphine-naloxone	1 (Ling et al., 2016)
		Methadone	3 (Oliveto et al., 1999; Schottenfeld et al., 2005; Schottenfeld et al., 1997)
Medications for other substance use disorders	7 RCTs: 5 from the current search; 2 from 2 previous SRs (Castells et al., 2009; Pani et al., 2010)	Disulfiram	6 (Carroll et al., 2012; George et al., 2000; Kosten et al., 2013; Oliveto et al., 2011; Petrakis et al., 2000; Schottenfeld et al., 2014)
		Varenicline	1 (Poling et al., 2010)
Psychostimulants	4 RCTs included in 3 previous SRs (Castells et al., 2016; Castells et al., 2009; Indave et al., 2016)	Mazindol	2 (Margolin et al., 1995a; Margolin et al., 1997)
		Dexamphetamine	1 (Grabowski et al., 2004)
		Methylphenidate	1 (Dursteler-MacFarland et al., 2013)
Other pharmacotherapies	3 RCTs from the current search; 1 RCT from a previous SR (Castells et al., 2009)	Carvedilol	1 (Sofuoglu et al., 2017)
		Magnesium L-aspartate	1 (Margolin et al., 2003)
		Progesterone	1 (Sofuoglu et al., 2007)
		Mecamylamine	1 (Reid et al., 2005a)
Medications for amphetamine/methamphetamine use disorder			
Medications for other substance use disorders	1 RCT from the current search	Naltrexone	1 (Tiihonen et al., 2012)

Abbreviations: N = number of; RCT = randomized controlled trial; SR = systematic review

Table 2.

Summary of the evidence on pharmacotherapies in participants with comorbid stimulant and opioid use disorders

Outcome	N studies per outcome	Summary of findings by outcome	Strength of Evidence*
Antidepressants (bupropion, desipramine, and fluoxetine)			
Abstinence for ≥3 consecutive weeks	NA	**NA**	No evidence
Use	1 RCT of bupropion (Poling et al., 2006)	**No difference.** One unclear-ROB RCT (N=106) reported no difference in use of cocaine.	Insufficient
Retention	10 RCTs: 6 of desipramine (Arndt et al., 1992; Kolar et al., 1992; Kosten et al., 2003; Kosten et al., 1992; O'Brien et al., 1988; Oliveto et al., 1999); 2 of bupropion (Margolin et al., 1995b; Poling et al., 2006); 2 of fluoxetine (Grabowski et al., 1995; Winstanley et al., 2011)	**Favors placebo.** A previous SR (Pani et al., 2011) found RR for dropout 1.22 (95% CI 1.05 to 1.41) combining 10 RCTs (N=1,006).	Moderate
Harms	5 RCTs: 3 of desipramine (Arndt et al., 1992; Kolar et al., 1992; Kosten et al., 1992); 1 of bupropion (Margolin et al., 1995b); 1 of fluoxetine (Winstanley et al., 2011)	**Favors placebo.** A previous SR (Pani et al., 2011) reported a combined RR of withdrawal due to an adverse event RR of 2.47 (95% CI 1.03 to 5.90; 5 RCTs, N=492). Severe AEs NR.	Moderate
Anticonvulsants (gabapentin, tiagabine, and topiramate)			
Abstinence for ≥3 consecutive weeks	1 RCT of topiramate (Umbricht et al., 2014)	**No difference.** 1 low-ROB RCT (N=171) with 4 arms for topiramate vs placebo, +/− contingency management: longest duration of cocaine abstinence (mean weeks ± SE): 3.8 + 0.8 for TOP/CM, 3.7 ± 0.7 for TOP/Non-CM, 4.4 ± 0.7 for P/CM, for 3.5 ± 0.6 P/Non-CM.	Low
Use	1 RCT of topiramate (Umbricht et al., 2014)	**No difference.** 1 low-ROB RCT (N=171) % of UA that were cocaine-negative: OR: 1.051, 95% CI: 0.6 to 1.84; p = 0.86,	Low
Retention	3 RCTs of 4 medications: 2 of tiagabine (Gonzalez et al., 2007; Gonzalez et al., 2003); 1 of gabapentin (Gonzalez et al., 2007); 1 of topiramate (Umbricht et al., 2014)	**Favors placebo.** Worse retention with anticonvulsants in 3 trials (N=292), pooled RR 0.86 (0.76 to 0.97).	Moderate
Harms	3 RCTs (Gonzalez et al., 2007; Gonzalez et al., 2003; Umbricht et al., 2014)	**No difference.** Severe AEs: None occurred in 2 RCTs. NR in 1 RCT. Dropouts due to AEs: None occurred in 2 RCTs; 6 vs 7 in 1 trial of topiramate.	Low
Antipsychotics (aripiprazole and risperidone)			
Abstinence for ≥3 consecutive weeks	NA	NA	No evidence
Use	1 RCT of aripiprazole (Moran et al., 2017)	**No difference.** A high-ROB RCT of aripiprazole (N=18) found no differences in cocaine use.	Insufficient
Lapse and relapse		**No difference.** A high-ROB RCT of aripiprazole (N=18) found no differences in cocaine lapse or relapse.	Insufficient Insufficient
Retention	1 RCT of risperidone (Grabowski et al., 2004) 1 RCT of aripiprazole (Moran et al., 2017)	**No difference.** A high-ROB RCT of aripiprazole (N=18) and an unclear-ROB RCT of risperidone (N=96) found no difference in retention between groups.	Insufficient
Harms	1 RCT of aripiprazole (Moran et al., 2017)	**No difference.** A high-ROB RCT of aripiprazole found no difference in withdrawal due to AEs between	Insufficient

Outcome	N studies per outcome	Summary of findings by outcome	Strength of Evidence*
		groups. Severe AEs: NR	
Dopamine agonists			
Abstinence for ≥3 consecutive weeks	NA	**NA**	No evidence
Use	4 RCTs: 3 of amantadine (Handelsman et al., 1995; Kolar et al., 1992; Kosten et al., 1992) and 1 of bromocriptine (Handelsman et al., 1997)	**No difference.** There were no differences in cocaine use in 3 studies of amantadine (2 unclear-ROB and 1 high-ROB, or in 1 study of bromocriptine (unclear-ROB).	Low
Retention	4 RCTs: 3 of amantadine (Handelsman et al., 1995; Kolar et al., 1992; Kosten et al., 1992) and 1 of bromocriptine (Handelsman et al., 1997)	**No difference.** Meta-analysis combining 3 studies of amantadine and 1 study of bromocriptine found no difference, without significant heterogeneity: RR 0.95, 95% CI 0.84 to 1.07 (N=205).	Low
Harms	4 RCTs: 3 of amantadine (Handelsman et al., 1995; Kolar et al., 1992; Kosten et al., 1992) and 1 of bromocriptine (Handelsman et al., 1997)	**No difference.** Withdrawal due to AEs: no difference from placebo in 1 study of bromocriptine and 2 studies of amantadine. Severe AEs: None occurred in 1 study of bromocriptine and 1 study of amantadine.	Low
Medications for Opioid Use Disorder (methadone, buprenorphine, and buprenorphine combined with naloxone)			
Abstinence for ≥3 consecutive weeks	2 RCTs of methadone vs buprenorphine (Schottenfeld et al., 2005; Schottenfeld et al., 1997)	**Methadone vs buprenorphine: Favors methadone.** Continuous abstinence more frequent with methadone, combining 2 low-ROB RCTs (N=219): RR 1.85, 95% CI 1.25 to 2.75.	Low
	1 RCT of buprenorphine- naloxone vs placebo (Ling et al., 2016)	**Buprenorphine-naloxone vs placebo: No difference.** 1 low-ROB RCT (N=302). No significant difference in abstinence (days 25–54).	
Use	1 RCT of buprenorphine- naloxone vs placebo (Ling et al., 2016)	**Favors buprenorphine-naloxone: in a** low-ROB RCT (N=302), more UDS(−) at higher dose (16–4 mg buprenorphine-naloxone) OR 1.71, P=0.022. No difference at lower dose (4–1 mg buprenorphine-naloxone) OR 1.09, P=0.105.	Insufficient
	1 RCT of naltrexone implant (Tiihonen et al., 2012)	**Favors naltrexone** in 1 high-ROB RCT; % of drug free UDS (−): 38% vs 16%; P=0.01 Amphetamine: Week 10 UDS (−): 40% vs 24%; P=0.09 Heroin: Week 10 UDS (−): 52% vs 20%, P = 0.001	Insufficient
Retention	3 RCTs of methadone vs buprenorphine (Oliveto et al., 1999; Schottenfeld et al., 2005; Schottenfeld et al., 1997)	**Methadone vs buprenorphine: No difference.** 2 low-ROB and 1 unclear-ROB RCTs (N=309), pooled RR 1.17 (95% CI 0.91 to 1.51).	Low
	1 RCT of buprenorphine- naloxone vs placebo (Ling et al., 2016)	**Buprenorphine-naloxone vs placebo: No difference.** 1 low-ROB RCT (N=302), high dose vs low dose vs placebo: 100% vs 98% vs 99%.	Insufficient
	1 RCT of naltrexone implant (Tiihonen et al., 2012)	**Favors naltrexone in 1 high-ROB RCT:** 26/50 (52%) vs 14/50 (28%); RR=1.86 (1.11–3.12)	Insufficient
Harms	2 RCTs (Oliveto et al., 1999; Schottenfeld et al., 2005)	**Methadone vs buprenorphine: No difference.** Dropouts due to AE: NR Severe AEs: 1	Insufficient
	1 RCT of naltrexone implant (Tiihonen et al., 2012)	**Naltrexone implant vs placebo: No difference.**	Insufficient
Medications FDA-approved for other substance use disorders (disulfiram, varenicline)			
Abstinence for ≥3 consecutive weeks	2 RCTs of disulfiram (George et al., 2000; Schottenfeld et al., 2014)	**No difference. Pooled** RR 0.89 (95% CI 0.53 to 1.48) based on 1 low-ROB RCT and 1 unclear- ROB RCT(N=207)	Low

Outcome	N studies per outcome	Summary of findings by outcome	Strength of Evidence*
Use	1 RCT of varenicline (Poling et al., 2010)	**No difference.** 1 unclear-ROB RCT (N=31) found no difference in slope over time or between groups (Z = 0.20, p < 0.84).	Insufficient
Retention	6 RCTs of disulfiram (Carroll et al., 2012; George et al., 2000; Kosten et al., 2013; Oliveto et al., 2011; Petrakis et al., 2000; Schottenfeld et al., 2014)	**Favors placebo.** Significantly worse treatment retention with disulfiram compared to placebo, 6 studies combined (N=605). RR 0.86, 95% CI 0.77 to 0.95.	Moderate
	1 RCT of varenicline (Poling et al., 2010)	**No difference.** 1 unclear-ROB RCT (N=31) found no difference (log rank $\chi 2 = 1.3, p < 0.26$)	
Harms	6 RCTs of disulfiram (Carroll et al., 2012; George et al., 2000; Kosten et al., 2013; Oliveto et al., 2011; Petrakis et al., 2000; Schottenfeld et al., 2014) 1 RCT of varenicline (Poling et al., 2010)	**No difference.**	Low
Psychostimulants (dexamphetamine, mazindol, and methylphenidate)			
Abstinence for ≥3 consecutive weeks	NA	**NA**	No evidence
Use	3 RCTs: 2 of mazindol (Margolin et al., 1995a; Margolin et al., 1997) 1 of dexamphetamine (Grabowski et al., 2004)	**No difference.** Cocaine-free UDSs occurred more frequently with psychostimulants compared with placebo in 3 Unclear/high ROB RCTs, but the difference did not reach statistical significance (standardized mean difference (SMD) 0.35, 95% CI −0.05 to 0.74; 3 RCTs, N=115).	Low
Retention	4 RCTs: 2 of mazindol (Margolin et al., 1995a; Margolin et al., 1997); 1 of dexamphetamine (Grabowski et al., 2004); 1 of methylphenidate (Dursteler-MacFarland et al., 2013)	**No difference.** (RR 0.98, 95% CI 0.71 to 1.36; N=210), although statistical heterogeneity was on the margin of significance (P=0.05; Figure 3).	Low
Harms	NA	NA	No evidence
Medications for amphetamine/methamphetamine use disorder			
Abstinence for ≥3 consecutive weeks	NA	NA	Insufficient
Use	1 RCT of naltrexone implant (Tiihonen et al., 2012)	**Favors naltrexone** in 1 high-ROB RCT; % of drug free UDS (−): 38% vs 16%; P=0.01 Amphetamine: Week 10 UDS (−): 40% vs 24%; P=0.09 Heroin: Week 10 UDS (−): 52% vs 20%, P = 0.001	Insufficient
Retention	1 RCT of naltrexone implant (Tiihonen et al., 2012)	**Favors naltrexone** in 1 high-ROB RCT: 26/50 (52%) vs 14/50 (28%); RR=1.86 (1.11–3.12)	Insufficient
Harms	1 RCT of naltrexone implant (Tiihonen et al., 2012)	**No difference.**	Insufficient

Abbreviations: AE = adverse event; N = number of; NA = not applicable; P = p-value; RCT = randomized controlled trial; ROB = risk of bias; UDS = urinary drug screen; RR = risk ratio; SMD = standard mean difference; SR = systematic review