QUERI

Pharmacotherapy for Stimulant Use Disorders: A Systematic Review

August 2018

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence-based Synthesis Program (ESP)
Portland VA Health Care System
Portland, OR
Devan Kansagara, MD, MCR, Director

Investigators:
Principal Investigator:
Brian Chan, MD, MPH

Co-Investigators:
Karli Kondo, PhD, MA
Chelsea Ayers, BA
Michele Freeman, MPH
Jessica Montgomery, MPH
Robin Paynter, MLIS
Devan Kansagara, MD, MCR

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for 4 ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

Recommended citation: Chan B, Kondo K, Ayers C, Freeman M, Montgomery J, Paynter R, and Kansagara D. Pharmacotherapy for Stimulant Use Disorders: A Systematic Review of the Evidence. VA ESP Project #05-225; 2018.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Portland VA Health Care System, Portland, OR funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Dr. Dominick DePhilippis in conjunction with Dr. Karen Drexler, Deputy National Mental Health Program Director, Office of Mental Health Services, for an evidence review to examine the effectiveness and best practices for pharmacotherapy for stimulant use disorder. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

Karen Drexler
Deputy National Mental Health Program Director
Office of Mental Health Services (10P4M)

Dominick DePhilippis
Education Coordinator, Philadelphia CESATE
Office of Mental Health Services and Philadelphia CESATE

Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

James McKay, PhD
University of Pennsylvania
Philadelphia CESATE
Philadelphia, PA

Eric Hawkins, PhD
University of Washington
VA Puget Sound Health Care System
Seattle, WA

Andrew Saxon, MD
University of Washington

Seattle CESATE
Seattle, WA

Adam Gordon, MD, MPH, FACP
University of Pittsburgh
Pittsburgh VAMC
CHERP
Pittsburgh, PA

Steven Batki, MD
University of California – San Francisco
San Francisco VAMC
San Francisco, CA

Bryon Adinoff, MD
University of Texas Southwestern Medical Center (Dallas)
VA North Texas Health Care System
Dallas, TX

Larissa Mooney, MD
University of California – Los Angeles
VA Greater Los Angeles Health Care System
Los Angeles, CA

Kyle Kampman, MD
University of Pennsylvania
The Charles O'Brien Center for the Treatment of Addictions
Philadelphia, PA

Richard De La Garza, PhD
Baylor College of Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX

Peter Hauser, MD
VA Long Beach Healthcare System
Long Beach, CA

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

TABLE OF CONTENTS

TABLES

FIGURES

EXECUTIVE SUMMARY

INTRODUCTION

Stimulant use disorders, specifically cocaine and methamphetamine use, present ongoing public health problems in the United States, with major medical, psychiatric, cognitive, socioeconomic, and legal consequences.

Currently there are no accepted FDA-approved pharmacotherapy treatment options available for cocaine or methamphetamine use disorders. Several pharmacotherapies have been proposed as possible experimental interventions to promote reduction in use or cessation. Currently, psychotherapy (including cognitive behavioral therapy, drug counseling, relapse prevention, *etc*) is offered as the primary treatment for stimulant addiction. In addition, contingency management strategies use incentives to increase engagement in treatment and reduce drug use. In order to guide future research and policy decisions for the Veterans Health Administration (VHA), the Office of Mental Health and the Seattle and Philadelphia Centers for Substance Abuse Treatment & Education (CESATE) asked the Veterans Affairs Evidence-based Synthesis Program (ESP) to provide an up-to-date examination of the benefits and risks of various pharmacologic treatments of stimulant use disorder. Specifically, this review examined 1) the benefits and harms of pharmacotherapy for cocaine use disorder, 2) subpopulations for whom different forms of pharmacotherapy are most/least effective for cocaine use disorder, 3) the benefits and harms of pharmacotherapy for amphetamine/methamphetamine use disorder, and 4) subpopulations for whom different forms of pharmacotherapy are most/least effective for amphetamine/methamphetamine use disorder.

METHODS

Data Sources and Searches

We developed search strategies in consultation with a research librarian. We searched multiple data sources from database inception through November 2017.

Study Selection

Using pre-specified inclusion criteria, we evaluated titles and abstracts for relevance; a random sample of abstracts was dual-reviewed to ensure reliability between reviewers. The remaining abstracts were decided by a single reviewer. Two independent reviewers assessed articles for inclusion, and discordant results were resolved through consensus. We included systematic reviews of randomized controlled trials (RCTs) that directly compared pharmacological interventions against each other, placebo, usual care, or psychotherapy in adults with cocaine or amphetamine/methamphetamine use disorders. We also included individual RCTs that were more recently published or were not examined by the included systematic reviews. We excluded studies and comparisons examining patients with comorbid psychotic spectrum or bipolar disorders.

Data Abstraction and Quality Assessment

One reviewer abstracted data into a customized database and a second reviewer checked entries for accuracy. From each study, we abstracted the following where available: study setting;

subpopulations; inclusion and exclusion criteria; demographic information; addiction severity at baseline; details of active and comparator arms including concomitant treatments, number of urinalyses (UAs) per week, dose, and duration; outcome data including abstinence, use, retention, and harms including withdrawals from treatment and severe adverse events.

Two reviewers independently assessed the risk of bias (ROB) of each study as low, high, or unclear (Appendix D) using a tool developed by the Cochrane Collaboration.[1]

Data Synthesis and Analysis

We qualitatively synthesized the evidence for each key question, and conducted meta-analyses when combinable outcomes were reported among studies of the same drug or drug class. For studies in which an outcome of interest was collected but not completely reported, we contacted the authors to request the data elements needed for meta-analysis. For trials that had comparable interventions and outcome measures, we combined the trials in meta-analysis using RevMan 5.3 software to estimate odds ratios under the assumption of random effects.[2]

RESULTS

Summary of Results for Key Questions

KQ1: What are the benefits and harms of pharmacotherapy for cocaine use disorder?

We identified 46 RCTs and 7 systematic reviews that examined outcomes of interest of pharmacotherapy for cocaine use disorder.

With some exceptions, we found insufficient to low strength evidence that most of the drug classes examined did not improve abstinence, use, or treatment retention. It is difficult to draw strong conclusions given the limitations of this body of evidence. Many of the studies were small trials with limited power, methodologic deficiencies, and high enough attrition rates to further limit assessment of treatment effectiveness. Across studies there was significant variability in population, setting, co-interventions, number of study visits and UAs per week, and the outcomes reported.

There were several areas for which there may be potential benefit. We found low strength evidence that psychostimulants as a class, the antidepressant bupropion, and topiramate may be effective in increasing continuous abstinence at 2 weeks or more.

There were a few areas for which there was consistent evidence of no effect, or of a negative effect. There is moderate to high strength evidence that antidepressants (specifically, selective serotonin reuptake inhibitors [SSRI]s and tricyclic antidepressants [TCAs]) do not improve abstinence, use, or retention. In addition, there is moderate strength evidence that anticonvulsants do not improve overall use or retention, and low to moderate strength evidence of no benefit of dopamine agonists on abstinence or retention. We found moderate strength of evidence that SSRIs increase risk of study withdrawal due to adverse events, and that disulfiram is associated with lower retention than placebo. We found moderate strength of evidence that patients treated with disulfiram are less likely to complete treatment compared with placebo.

We found mostly insufficient evidence across 3 SRs and 1 trial in individuals with comorbid cocaine and opioid use disorders (OUD). However, we did find moderate strength evidence that

disulfiram and antidepressants as a class, particularly desipramine, are associated with lower retention. Similar to findings for the overall population, we found low strength evidence of a potential benefit of psychostimulants and bupropion for the achievement of sustained abstinence.

KQ2: Are there known subpopulations for whom different forms of pharmacotherapy are most/least effective for cocaine use disorder?

We identified 15 RCTs and 1 systematic review that examined subgroup differences in adults with cocaine use disorder.

Overall, findings are inconclusive due to the limited number of studies examining each subpopulation and are hampered by methodological issues as noted above. However, it is possible that baclofen and naltrexone may be particularly effective when treating long-term cocaine users. In addition, the ability to achieve sustained abstinence or produce a cocaine-negative urine sample may be a good predictor of treatment success. We also found that buspirone and naltrexone may have a lesser or even a negative effect in women, that adults with comorbid depression who experience a clinically significant mood response to venlafaxine may experience a reduction in cocaine use, and that chronic heroin users may benefit from a combination of methadone and aripiprazole. Findings suggest no differences in effect by self-reported cannabis use and the presence of alcohol use disorder or attention deficit disorder (ADHD). In two studies of different drug classes the effects of pharmacotherapy were similar in patients receiving and not receiving a contingency management co-intervention.

KQ3: What are the benefits and harms of pharmacotherapy for amphetamine/methamphetamine use disorders?

We identified 14 RCTs and 1 systematic review that examined outcomes of interest of pharmacotherapy for amphetamine/methamphetamine use disorders.

Similar to the body of research examining pharmacotherapy for cocaine use disorder, studies evaluating pharmacotherapy for amphetamine/methamphetamine use disorders had largely high or unclear ROB and were underpowered. Co-interventions differed widely and rates of retention varied greatly. Some studies examined methamphetamine or amphetamine use disorders exclusively, and others combined the two. For nearly all pharmacotherapies and almost all the outcomes, findings were either null or insufficient to form conclusions. We found low strength evidence that methylphenidate and topiramate may result in a reduction in use.

We identified only 1 RCT (unclear risk of bias) conducted in patients with comorbid amphetamine/methamphetamine and opioid use disorder. The study found that naltrexone improved study retention.

KQ4: Are there known subpopulations for whom different forms of pharmacotherapy are most/least effective for amphetamine/methamphetamine use disorder?

We identified 3 RCTs and 1 systematic review that examine subgroup differences in adults with amphetamine/methamphetamine use disorder.

Overall, findings are inconclusive due to methodological issues, as well as the limited number of studies examining each subpopulation. However, it is possible that bupropion, but not

aripiprazole or psychostimulants, may be more effective in reducing methamphetamine use in individuals who have less addiction severity at baseline, and that topiramate may be more effective in individuals who produce a negative urine drug screen at randomization. In addition, bupropion may be more effective for males with methamphetamine use disorder than for females, and for individuals with comorbid depression. We did not find differences by ADHD diagnosis, lifetime alcohol use disorder, or human immunodeficiency virus (HIV) status. There was insufficient evidence examining whether or not CM co-interventions modified pharmacotherapeutic effects.

Abbreviated Summary of Findings Tables

The tables that follow contain an abbreviated summary of findings for each drug or drug class, and are intended to provide a broad overview of the results. More detailed summary tables on the effects of each drug and the strength of the evidence are provided in the full report.

The abbreviated summary tables convey the direction of the effect and strength of the evidence as follows:

Direction of effect		Strength of Evidence
Unclear (no color)	NA	No evidence or not applicable
No difference	Ø	Insufficient
Evidence of benefit	«	Low
Mixed findings	« «	Moderate
Favors placebo	« « «	High

The tables are listed in the following order:

Table i. Mental health pharmacotherapies for cocaine use disorder
Table ii. Other pharmacotherapies for cocaine use disorder
Table iii. Mental health pharmacotherapies for comorbid cocaine and opioid use disorders
Table iv. Other pharmacotherapies for comorbid cocaine and opioid use disorders
Table v. Pharmacotherapies for amphetamine/methamphetamine use disorder
Table vi. Pharmacotherapies for comorbid opioid and amphetamine/methamphetamine use disorders

Table i. Mental health pharmacotherapies for cocaine use disorder

	Abstinence	Use	Relapse	Lapse	Retention	Harms
All Antidepressants	« «	« «	«	«	« « «	« «
All Antipsychotics	«	«	Ø	Ø	« «	Ø
All Tricyclic Antidepressants	«	Ø	NA	NA	« « «	« «
Aminoketone: Bupropion	«	«	NA	NA	« «	Ø
Anxiolytics: Busiprone	Ø	NA	NA	Ø	Ø	Ø
Atypical Antidepressant: Mirtazapine	NA	Ø	NA	NA	NA	Ø

	Abstinence	Use	Relapse	Lapse	Retention	Harms
Cognitive Enhancing Drugs: Memantine, Atomoxetine	Ø	Ø	Ø	NA	Ø	Ø
First Generation Antipsychotics: Haloperidol	NA	NA	NA	NA	Ø	NA
Other Antipsychotics: Reserpine	Ø	Ø	NA	NA	NA	NA
Psychostimulants: Dexamphetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Lisdexamphetamine, Selegiline (drugs combined in analysis)	«	«	NA	NA	« «	« «
Second Generation Antipsychotics: Aripiprazole, Olanzapine, Risperidone, Quetiapine (drugs combined in analysis)	«	Ø	Ø	Ø	« «	Ø
Selective Serotonin Reuptake Inhibitors (SSRIs): Fluoxetine and Sertraline	NA	NA	«	«	« «	«
Serotonin and Norepinephrine Reuptake Inhibitor (SNRI): Venlafaxine	Ø	Ø	NA	NA	Ø	Ø

Table ii. Other pharmacotherapies for cocaine use disorder

	Abstinence	Use	Retention	Harms
Disulfiram	«	Ø	« «	«
Varenicline	NA	Ø	Ø	Ø
Opioid antagonist: Naltrexone	«	Ø	«	Ø
Camprosate	NA	Ø	Ø	NA
Opioid agonists: Buprenorphine plus naloxone	Ø	Ø	Ø	NA
Opioid agonists: Methadone vs buprenorphine	Ø	NA	Ø	NA
Muscle Relaxant: Baclofen	«	«	«	«
Anticonvulsants: Carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate and vigabatrin (drugs combined in analysis)	NA	« «	« «	NA
Anticonvulsant: Vigabatrin	«	«	«	Ø
Anticonvulsant: Topiramate	«	Ø	« «	Ø

Dopamine agonists: Amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline hydergine, and pramipexole	«	NA	« «	NA

Table iii. Mental health pharmacotherapies for comorbid cocaine and opioid use disorders

	Abstinence	Use	Relapse	Lapse	Retention	Harms
Aminoketone: Bupropion	Ø	Ø	NA	NA	«	Ø
Antipsychotics: Aripiprazole, Risperidone	NA	Ø	Ø	Ø	«	Ø
Any Antidepressant	«	Ø	NA	NA	« «	« «
Psychostimulants: Dexamphetamine, Mazindol	Ø	«	NA	NA	«	NA
Selective Serotonin Reuptake Inhibitor: Fluoxetine	NA	NA	NA	NA	Ø	Ø
Tricyclic Antidepressants: Desipramine	Ø	NA	NA	NA	« «	«

Table iv. Other pharmacotherapies for comorbid cocaine and opioid use disorders

	Abstinence	Use	Retention	Harms
Disulfiram	Ø	Ø	« «	NA
Varenicline	Ø	Ø	Ø	Ø
Opioid agonists: Buprenorphine plus naloxone	Ø	Ø	Ø	Ø
Opioid agonists: Methadone vs buprenorphine	Ø	NA	Ø	NA

Table v. Pharmacotherapies for amphetamine/methamphetamine use disorder

	Abstinence	Use	Retention	Harms
All Antidepressants	« «	Ø	« «	«
Aminoketone: Bupropion	«	«	« «	Ø
Atypical Antidepressant: Mirtazapine	NA	Ø	Ø	Ø
SSRI: Sertraline	Ø	NA	Ø	NA
Atypical Antipsychotics: Aripiprazole	Ø	«	Ø	Ø
Psychostimulants: Modafinil, Dexamphetamine, Methylphenidate*	«	Ø	«	NA
Baclofen vs gabapentin	Ø	Ø	Ø	Ø
Anticonvulsant: Topiramate	NA	«	«	«
Opioid antagonist: Naltrexone	Ø	Ø	«	« «

* We found low strength evidence that methylphenidate may result in a reduction in use.

Table vi. Pharmacotherapies for comorbid opioid and amphetamine/methamphetamine use disorders

	Abstinence	Use	Retention	Harms
Opioid antagonist: Naltrexone	NA	Ø	Ø	Ø

DISCUSSION

We found no strong, consistent evidence that any drug class was effective in increasing abstinence, reducing use, or improving retention rates for participants with cocaine use disorders. Psychostimulants, bupropion, and topiramate may improve cocaine abstinence. Sertraline may be useful to prevent relapse in detoxed/abstinent patients. Antipsychotics may improve treatment retention. In populations with co-morbid opioid use, psychostimulants and antidepressants may increase cocaine abstinence. We found moderate to high strength evidence that antidepressants, disulfiram, and anticonvulsants (apart from topiramate) are unlikely to be effective in non-abstinent patients. For methamphetamine use disorder, we found less promising results, though methylphenidate and topiramate may be effective at reducing use. There are several promising areas deserving of further research including the use of bupropion, the use of topiramate, treatment of abstinent patients to prevent relapse, and treatment of patients with comorbid opioid use disorder. It is possible that the lack of significant findings was due to insufficient power to detect differences. Future studies need to be larger and need to assess clinically relevant and uniform outcomes, including reduction in use and defined periods of abstinence outcomes. Contingency management and behavioral interventions, along with pharmacotherapy, should continue to be explored.

ABBREVIATIONS TABLE

Abbreviation	Term
AA	African American
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
BBCET	Brief Behavioral Compliance Enhancement Treatment
BUP	Buprenorphine
CBT	Cognitive behavioral therapy
CI	Confidence interval
CM	Contingency management
df	Degrees of freedom
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBM	Evidence-based Medicine
EPC	Evidence-based Practice Center
ESP	Evidence-based Synthesis Program
EtOH	Alcohol dependence
FDA	Food and Drug Administration
HAM-D	Hamilton Depression Rating Scale
HIV	Human immunodeficiency virus
hr	Hour
HR	Hazard ratio
HSR&D	Health Services Research and Development Service
IOP	Intensive outpatient
IQR	Interquartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
KQ	Key question
LDA	Longest duration of abstinence
MA	Methamphetamine
MA	Meta-analysis
MET	Motivation Enhancement Therapy
mg	Milligram
MI	Motivational interviewing
min	Minutes
MSM	Men who have sex with men
MTD	Maximum tolerated dose
MTD	Methadone
NA	Not applicable
NCT	National Clinical Trial register number (ClinicalTrial.gov)
NIH	National Institutes of Health
NMDA	N-methyl-D-aspartate
NOS	Not otherwise specified

Abbreviation	Term
NR	Not reported
NS	Not significant
OR	Odds ratio
OUD	Opioid use disorder
P	P-value
PICOTS	Population, interventions, comparators, outcomes, timing, and setting
PLA	Placebo
QUERI	Quality Enhancement Research Initiative
RCT	Randomized controlled trial
RD	Risk difference
ROB	Risk of bias
RR	Relative risk
SAE	Severe adverse event
SD	Standard deviation
SE	Standard error
SEM	standard error of the mean
SERT	Sertraline
SES	Socioeconomic status
SMD	standard mean difference
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SOE	Strength of evidence
SR	Systematic review
Ss	Subjects
SSRI	Selective Serotonin Reuptake Inhibitors
SUD	Substance use disorder
TAU	Treatment as usual
TEP	Technical expert panel
TLFB	Timeline Follow-back Interview
TTM	Transtheoretical Model
tx	Treatment
UA	Urinalysis
US	United States
VHA	Veterans' Health Administration
WD	Withdrawal
wk	Week
XR-NTX	Injectable Extended-Release Naltrexone
yr	Year

EVIDENCE REPORT

INTRODUCTION

Stimulant use disorders, specifically cocaine and methamphetamine use, present ongoing public health problems in the United States, with major medical, psychiatric, cognitive, socioeconomic, and legal consequences.[3] Cocaine use disorder is associated with increased risk of stroke, cardiac abnormalities, and risk of HIV infections.[4] There are more emergency department visits associated with cocaine compared with other illicit substances. In 2013, there were 1.5 million cocaine users aged 12 or older in the United States, and 855,000 of them experienced dependence or abuse during the past year.[5] Potential short-term harms from cocaine use include disturbance in heart rhythm and heart attacks, neurological effects, including seizures, and gastrointestinal complications. Long-term use can lead to increased irritability, restlessness, panic attacks, paranoia, and psychosis. Other health effects associated with long-term cocaine use include malnourishment, damage to the heart and cardiovascular system, and stroke. Cocaine use can be accompanied by drug craving, tolerance, and development of withdrawal symptoms such as depression or anxiety, fatigue, agitation, difficulty concentrating, and physical symptoms (chills, tremors, sleeplessness, muscle aches, and nerve pain), as well as increased craving for cocaine. In some instances, regular daily users of cocaine may have increased rates of suicidal thoughts.

Methamphetamine addiction is a serious public health problem in the United States. Several US cities consider methamphetamine as the drug of abuse associated with the "most serious consequences." Adverse effects of methamphetamine include restlessness, insomnia, hyperthermia, and possibly convulsions. Long-term use can lead to addiction, paranoia, mood disturbances, agitation, psychosis, and cognitive impairment.[6] Following prolonged use, discontinuation of methamphetamine can result in withdrawal symptoms that include dysphoric mood, paranoia, violent behavior, fatigue, sleep disturbances, and increased appetite.[6,7]

Currently there are no accepted FDA-approved pharmacotherapy treatment options available for cocaine or methamphetamine use disorder. Several pharmacotherapies have been proposed as possible experimental interventions to promote reduction in use or cessation. Currently, psychotherapy (including cognitive behavioral therapy, drug counseling, and relapse prevention, among others) is offered as the primary treatment for stimulant addiction. Contingency management is also commonly used in treating stimulant use disorders. We conducted this evidence synthesis to provide an up-to-date examination of the benefits and risks associated with the use of various pharmacotherapy treatments for increasing treatment retention and promoting cessation/reduction of stimulant use.

METHODS

TOPIC DEVELOPMENT

The research questions for this systematic review were nominated by the Office of Mental Health and the Seattle and Philadelphia Centers for Substance Abuse Treatment & Education (CESATE), and were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature, and consultation with internal partners, investigators, and stakeholders. The Key Questions are as follows:

KQ1: What are the benefits and harms of pharmacotherapy for cocaine use disorder?

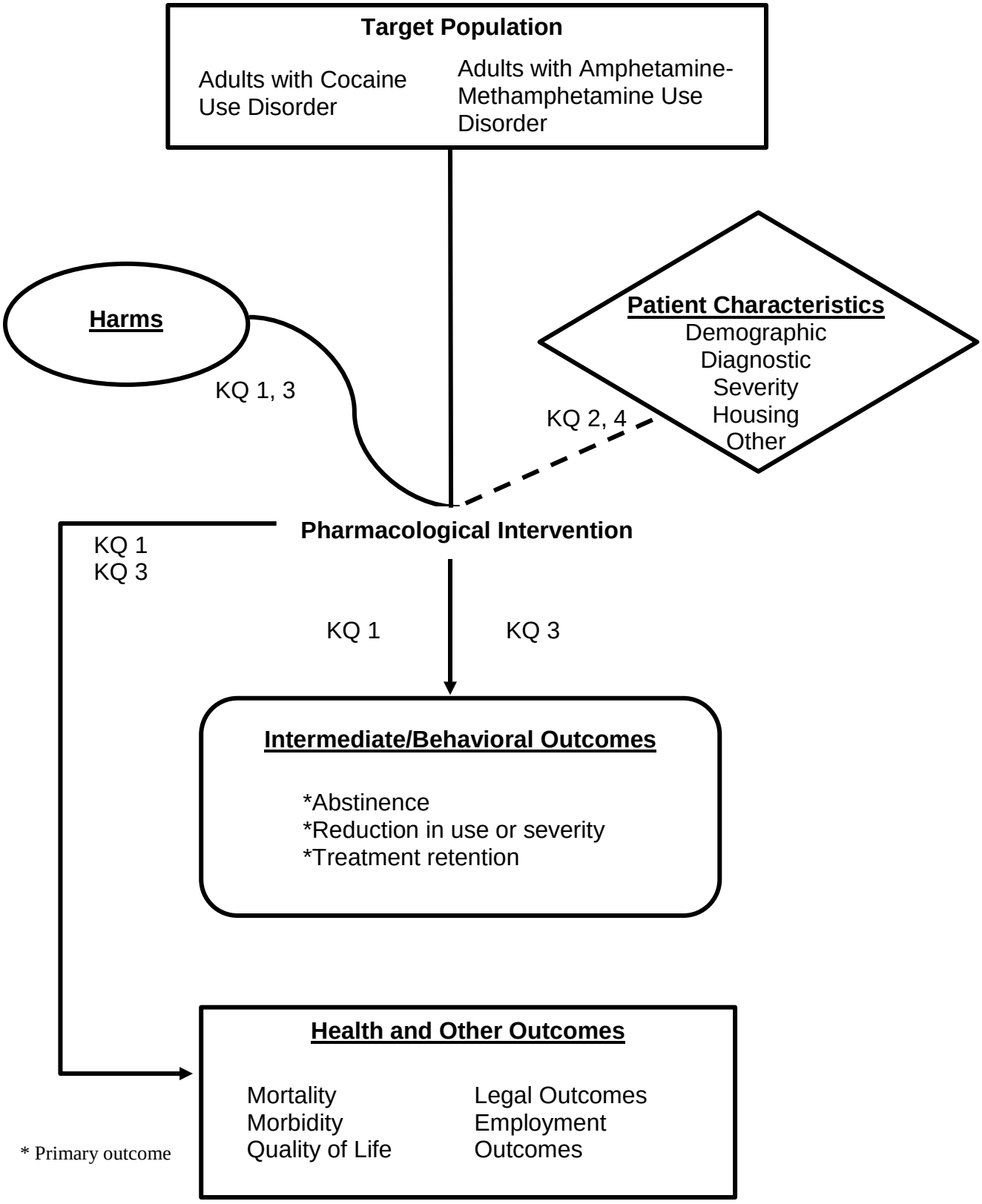
KQ2: Are there known subpopulations for whom different forms of pharmacotherapy are most/least effective for cocaine use disorder?

KQ3: What are the benefits and harms of pharmacotherapy for amphetamine/methamphetamine use disorder?

KQ4: Are there known subpopulations for whom different forms of pharmacotherapy are most/least effective for amphetamine/methamphetamine use disorder?

Our approach was guided by a conceptual framework developed in consultation with our operational partners (see Figure 1). A protocol describing the review plan was posted to a publicly accessible website before the study was initiated (PROSPERO registration number CRD42018085667).

Figure 1. Analytic Framework



SEARCH STRATEGY

Search strategies were developed in consultation with a research librarian, and were peer reviewed by a second research librarian using the instrument for Peer Review of Search Strategies (PRESS; see Appendix A for the search strategy). We searched Ovid MEDLINE, OvidPsycINFO, and Ovid EBM Reviews Cochrane Database of Systematic Reviews (CDSR, DARE, HTA, and Cochrane CENTRAL). We searched all available years of publication from database inception (1946 for Ovid MEDLINE®) through November 2017. 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).

STUDY SELECTION

The criteria for population, interventions, comparators, outcomes, timing, and setting (PICOTS) that apply to each key question were developed in collaboration with our operational partners and Technical Expert Panel (TEP; see Appendix B), and are specified in Table 1.

We included studies that directly compared pharmacological interventions against each other, placebo, usual care, or psychotherapy in adults with cocaine or amphetamine/methamphetamine use disorders. We excluded studies and comparisons examining patients with comorbid psychotic spectrum or bipolar disorders. We examined only randomized controlled trials. We excluded studies that did not perform drug urinalysis (UA) at least once per week. For outcomes related to abstinence and use, we excluded studies that relied on self-reported drug use, with the exception of findings from previous systematic reviews. We used a "best evidence" approach to guide additional study design criteria depending on the question under consideration and the literature available.[8] Appendix C contains the detailed criteria we used for determining study eligibility.

Given the broad scope of this review, we summarized data from existing good-quality systematic reviews, when available, to address each question and outcome of interest, and added individual studies meeting inclusion criteria that were published after the end of the search date of the included review, or were not included in a prior systematic review.

Using pre-specified inclusion criteria, 2 independent reviewers evaluated titles and abstracts for 18.6% of the search yield to ensure reliability between reviewers. A single reviewer evaluated the remainder. Titles and abstracts were screened using Abstrackr,[9] a semi-automated, web-based screening tool. We reviewed funded research for inclusion according to the same pre-specified inclusion criteria. 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.

Table 1. PICOTS by Key Question

Key Question	KQ1: What are the benefits and harms of pharmacotherapy for cocaine use disorder (alone, or as an adjunct or follow-up to psychosocial treatment)?	KQ2: Are there subpopulations for whom different forms of pharmacotherapy are most/least effective for cocaine use disorder?	KQ3: What are the benefits and harms of pharmacotherapy for amphetamine/ methamphetamine use disorder (alone, or as an adjunct or follow-up to psychosocial treatment)?	KQ4: Are there subpopulations for whom different forms of pharmacotherapy are most/least effective for amphetamine/ methamphetamine use disorder?
Population	Included: Non-pregnant adults with cocaine use disorder. Excluded: subjects with psychotic spectrum disorder, bipolar disorder.	Subpopulations may include: - Demographic factors - Housing status - Severity - Comorbid mental and substance use disorders (*eg*, HIV, mood and anxiety disorders, ADHD, alcohol use, opioid use/methadone maintained) - Other clinical conditions	Included: Non-pregnant adults with amphetamine/ methamphetamine use disorder. Excluded: subjects with psychotic spectrum disorder, bipolar disorder.	Subpopulations may include: - Demographic factors - Housing status - Severity - Comorbid mental and substance use disorders (*eg* HIV, mood and anxiety disorders, ADHD, alcohol use, opioid use/methadone maintained) - Other clinical conditions
Intervention	Included: Pharmacotherapies identified as a potential treatment for cocaine use disorder (common adjuncts may be med management; interpersonal therapy; contingency management (or motivational incentives); CBT (including matrix therapy, relapse prevention) Excluded: treatment for temporary psychosis associated with stimulant overdose.		Included: Pharmacotherapies identified as a potential treatment for amphetamine/methamphetamine use disorder (common adjuncts may be med management; interpersonal therapy; contingency management (or motivational incentives); CBT (including matrix therapy, relapse prevention) Excluded: treatment for temporary psychosis associated with stimulant overdose.	
Comparators	Usual care, placebo, or other interventions (control groups should receive the same adjunctive treatments)		Usual care, placebo, or other interventions (control groups should receive the same adjunctive treatments)	

Key Question	KQ1: What are the benefits and harms of pharmacotherapy for cocaine use disorder (alone, or as an adjunct or follow-up to psychosocial treatment)?	KQ2: Are there subpopulations for whom different forms of pharmacotherapy are most/least effective for cocaine use disorder?	KQ3: What are the benefits and harms of pharmacotherapy for amphetamine/ methamphetamine use disorder (alone, or as an adjunct or follow-up to psychosocial treatment)?	KQ4: Are there subpopulations for whom different forms of pharmacotherapy are most/least effective for amphetamine/ methamphetamine use disorder?
Outcomes	· Intermediate/Behavioral outcomes - Abstinence (UA only. Self-report only in addition to UA) Also of interest when available: Longest Duration of Abstinence (LDA), and whether patients reach at least 3 Consecutive Weeks (21 or more days) of abstinence. - Cocaine use (quantitative urine levels) - Retention in treatment · Health and other outcomes - Morbidity/mortality - Quality of Life - Legal/employment outcomes · Harms - Study withdrawal due to AE, and severe AE (as reported in the trials)		· Intermediate/Behavioral outcomes - Abstinence (UA only. Self-report only in addition to UA) Also of interest when available: Longest Duration of Abstinence (LDA), and whether patients reach at least 3 Consecutive Weeks (21 or more days) of abstinence. - Cocaine use (quantitative urine levels) - Retention in treatment · Health and other outcomes - Morbidity/mortality - Quality of Life - Legal/employment outcomes · Harms - Study withdrawal due to AE, and severe AE (as reported in the trials)	
Timing	· Minimum study duration (including follow-up) 4 weeks			
Settings	· Outpatient · Inpatient · Incarceration/detention centers, correctional facilities		· Outpatient · Inpatient · Incarceration/detention centers, correctional facilities	
Study design	· Randomized controlled trials. · Systematic reviews		· Randomized controlled trials · Systematic reviews	

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; AE = Adverse event; KQ = key question; LDA = longest duration of abstinence; CBT = Cognitive Behavioral Therapy; HIV = human immunodeficiency virus; UA = urinalysis

DATA ABSTRACTION

Data from studies meeting inclusion criteria were abstracted into a customized database by one reviewer and confirmed by a second. From each primary study identified in our search, we abstracted the following where available: study setting; subpopulations; inclusion and exclusion criteria; demographic information; addiction severity at baseline; details of active and comparator arms including concomitant treatments, number of UAs per week, dose, and duration; outcome data including abstinence, use, retention, and harms including withdrawals from treatment and severe adverse events. To combine data from studies included in previous systematic reviews with data from more recent trials identified in our search, in most cases we transferred outcome data presented in forest plots of meta-analyses conducted by the previous systematic reviews, rather than directly from the primary studies. In cases where a systematic review did not analyze continuous abstinence, we examined the primary studies identified by the systematic review to abstract data on continuous abstinence.

QUALITY ASSESSMENT

Two reviewers independently assessed the risk of bias of each study (Appendix D). Disagreements were resolved through discussion. To assess the risk of bias of trials we used a tool developed by the Cochrane Collaboration.[1] Each trial was given an overall summary assessment of low, high, or unclear risk of bias. In cases where we analyzed data from individual trials that were included in a previous systematic review, we summarized the risk of bias based on the study quality assessments previously made by the authors of the systematic review.

DATA SYNTHESIS

We qualitatively synthesized the evidence for each key question, and conducted meta-analyses when combinable outcomes were reported among studies of the same drug or drug class. For studies in which an outcome of interest was collected but not completely reported, we contacted the authors to request the data elements needed for meta-analysis. We used RevMan 5.3[2] to estimate relative risk across studies, under the assumption of random effects. For key questions 1 and 3, we provide findings across all studies, as well as for studies limited to individuals with comorbid opioid use disorder. For studies which did not fall under any of the principal drug categories, and for which there was only 1 RCT per pharmacotherapy, we described them qualitatively in brief in KQ 1 and 3 under “other pharmacotherapies.” We were aware of the National Institute on Drug Abuse (NIDA)’s Cocaine Rapid Efficacy Screening Trial (CREST) program that studied a broad a variety of drugs in single, small trials, and those that met our inclusion criteria are described in these sections. As there was only 1 study of each drug, we did not grade their strength of evidence or include them in summary tables.

RATING THE BODY OF EVIDENCE

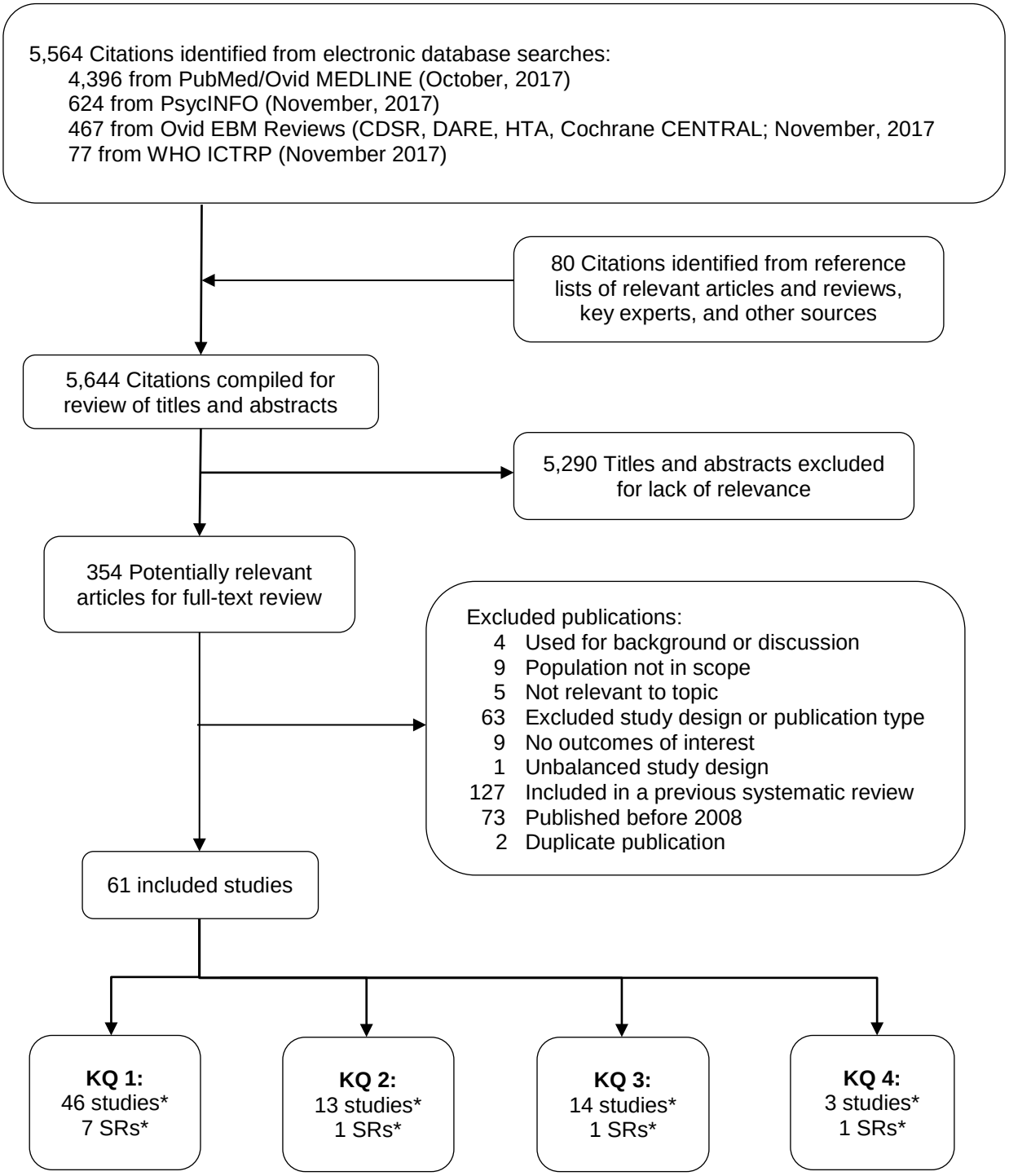
We assessed the overall strength of evidence for outcomes using a method developed for the Agency for Healthcare Research and Quality’s (AHRQ) Evidence-based Practice Centers (EPCs).[10] The AHRQ EPC method considers study limitations, directness, consistency, precision, and reporting bias to classify the strength of evidence for individual outcomes independently for randomized controlled trials (RCTs). Ratings were based on the following criteria:

- High = Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies, the findings are stable, and another study would not change the conclusions.
- Moderate = Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies and the findings are likely to be stable, but some doubt remains.
- Low = Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient = No evidence, unable to estimate an effect, or no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

LITERATURE FLOW

Our search of electronic databases, bibliographies, and other sources resulted in a total of 5,564 studies. After title and abstract review, 354 met inclusion criteria. Upon full-text review, we included a total of 8 systematic reviews and 61 RCTs. Several RCTs and systematic reviews provide data for more than one key question. See Figure 2 for the literature flow. Table 2 lists the numbers of previous systematic reviews and more recent trials identified in our search according to drug and drug class, stratified by substance use disorder.

Figure 2. Literature Flow Diagram



*Several studies addressed more than one key question.

Table 2. Number of systematic reviews and primary trials by drug and drug class, stratified by substance use disorder

SRs	Trials not in previous SRs	Drug category	Drug
Cocaine use disorder			
3	4	Antidepressants	Bupropion, mirtazapine, sertraline, venlafaxine
1	---	Antipsychotics	Aripiprazole, haloperidol, lamotrigine, olanzapine, quetiapine, reserpine, risperidone
---	1	Antipsychotics	Aripiprazole
---	1	Anxiolytics	Buspirone
---	2	Cognitive enhancement	Memantine
1	---	Dopamine agonists	---
1	14	Medications for other SUDs	Acamprosate (1 RCT) Disulfiram (6 RCTs, 1 SR) Naltrexone (6 RCTs) Varenicline (2 RCTs)
---	2	Muscle relaxants/anticonvulsants	Baclofen
1	1	Muscle relaxants/anticonvulsants	Topiramate
---	19	Other pharmacotherapies	1 trial of each: Amlodipine, carvedilol, celecoxib, citicoline, D-Cycloserine, Dehydroepiandrosterone/ DHEA, Doxazosin, Galantaeine, Magnesium L-aspartatehydrochloride, Mecamylamine, metyrapone + oxazepam, mixed amphetamine salts + topiramate, N-acetylcysteine, ondanseteron, pioglitazone, piracetam, gingko biloba, progesterone, propranolol, cocaine-metabolizing fusion protein TV-1380 (AlbuBChE),
Amphetamine/methamphetamine use disorder			
---	3	Opiate agonists	buprenorphine + naloxone; buprenorphine vs methadone
1	---	Psychostimulants	Bupropion
---	1	Anticonvulsants	Baclofen vs gabapentin
---	3	Antidepressants	Bupropion, mirtazapine, sertraline
---	2	Antipsychotics	Aripiprazole
---	4	Medications for other SUD	Naltrexone
---	1	Muscle relaxants/ anticonvulsants	Topiramate
---	3	Other pharmacotherapies	1 trial of each: citicoline, ondansetron, PROMETA

Abbreviations: RCT = randomized controlled trial; SR= systematic review; SUD = substance use disorder

KEY QUESTION 1: What are the benefits and harms of pharmacotherapy for cocaine use disorder?

Summary of Findings

Our search of pharmacotherapies for cocaine use disorder identified 7 systematic reviews[5,11-16] and 46 RCTs[17-62] that were not included in previous systematic reviews. Table 2 lists the pharmacotherapies examined by the included studies.

It is difficult to draw strong conclusions given the limitations of this body of evidence. Many of the studies were small trials with limited power, methodologic deficiencies, and high enough attrition rates to further limit assessment of treatment effectiveness. Across studies there was significant variability in population, setting, co-interventions, the number of study visits and UAs per week, and the outcomes reported. Overall, we found insufficient to low strength evidence that most of the drug classes examined did not improve abstinence, use, or retention.

There were a handful of exceptions with findings suggesting a positive benefit of pharmacotherapy over placebo. We found low strength evidence that bupropion and topiramate were more effective than placebo in achieving sustained abstinence of 2 or more weeks. In addition, we found low strength evidence that for participants who are abstinent at baseline, sertraline is better than placebo at preventing both lapse (first cocaine-positive UA) and relapse (2 consecutive cocaine-positive UAs). For study retention, there is moderate strength evidence of better retention for participants receiving any antipsychotic. However, we found no benefit on retention when examining first- or second-generation antipsychotics (as classes), or any specific antipsychotic individually.

We also found evidence of potential downsides to the use of certain pharmacotherapies. A meta-analysis of 7 RCTs[20,21,31,40,52,63,64] provides moderate strength evidence for lower rates of study retention among participants randomized to disulfiram (compared to placebo). In addition, there is moderate strength evidence of a higher risk of study withdrawal due to adverse events associated with SSRIs versus placebo.

Studies of individuals with comorbid cocaine and opioid use disorders were limited. Similar to the entire cocaine use disorder population, the vast majority of findings were either null or were insufficient from which to draw conclusions. We did find low strength evidence that participants receiving antidepressants as a class and bupropion specifically were more likely to achieve sustained abstinence. However, in the meta-analysis comparing disulfiram to placebo for study retention, 6[21,31,40,52,63,64] of 7 included trials were conducted in subjects with comorbid opioid use disorder, and provide moderate strength evidence that participants randomized to disulfiram are less likely to complete treatment.

Antidepressants

Summary of Findings

One systematic review[16] and 4 subsequent trials[17,36,41,46] provide evidence on the use of antidepressants for cocaine use disorder. One additional systematic review provides data on the use of bupropion.[5] Overall, studies found a non-significant trend favoring antidepressants as a class over placebo for sustained abstinence (SOE moderate), and no difference in study period

use (SOE moderate), retention (SOE high), or harms (SOE moderate/low). There is low strength evidence that bupropion is significantly better than placebo for sustained abstinence. There is also low strength evidence that in participants who are abstinent at baseline, sertraline is better than placebo at preventing lapse and relapse. Finally, there is moderate strength evidence of a higher risk of withdrawal from treatment due to adverse events associated with SSRIs versus placebo. No other significant differences were identified.

Detailed Findings

A previous systematic review[16] and 4 more recent trials[17,36,41,46] provide evidence on the use of antidepressants for cocaine use disorder. The systematic review[16] included 37 studies (3,551 participants) of tricyclics (18 studies), selective serotonin reuptake inhibitors (SSRIs; 8 studies), and other antidepressants including bupropion, nefazodone, and venlafaxine. One additional systematic review provides data on the use of bupropion.[5] Our search identified more recent trials of sertraline,[36,41] venlafaxine,[46] and mirtazapine.[17]

There is moderate strength evidence that antidepressants as a class are no better than placebo for sustained abstinence; however, there is a trend favoring antidepressants. The systematic review included 8 RCTs (N=942) comparing any antidepressant to placebo on 3-or-more-week abstinence rates and found no significant difference (combined RR 1.22 [95% CI 0.99 to 1.51]).[16] Similarly, a recent study (N=130) reported no difference between venlafaxine and placebo on the number of participants achieving negative UAs for a period of 3 weeks or longer.[46] We found moderate strength evidence of no difference between antidepressants and placebo for benefit on cocaine use during the trial period. Findings were consistent across 4 RCTs from the systematic review (N=251; combined RR 1.05 [95% CI 0.91 to 1.21]) and 2 additional RCTs.[17,46] Twenty-seven RCTs from the systematic review[16](N= 2,417; combined RR 1.01 [95% CI 0.91 to 1.12]) and 3 additional RCTs[36,41,46]provide high strength evidence that antidepressants are no better than placebo for study retention, and we identified no difference between antidepressants and placebo on severe adverse events or the number of study withdrawals due to adverse events.

We identified evidence from 2 studies[36,41] of antidepressants in participants who were abstinent from cocaine at baseline. These studies combined provide low strength evidence that antidepressants are better than placebo for preventing both lapse and relapse (see Table 3 for study-level data and Conclusions Table A for a summary of findings).

Tricyclic Antidepressants: Desipramine

One systematic review provided evidence of the effect of tricyclic antidepressants (TCAs) for cocaine use disorder.[16] The review included 18 studies examining tricyclics, 17 of which examined desipramine. There is low strength evidence of no difference between TCAs/desipramine and placebo for sustained abstinence. Although 5 RCTs in the review favor TCAs over placebo for sustained abstinence (N=367; combined RR 1.55 [95% CI 1.10 to 2.17]), no difference remained when limiting analyses to trials requiring a DSM diagnosis of cocaine use disorder (N=234; combined RR 1.41 [95% CI 0.93 to 2.14]). Findings from 2 underpowered RCTs in the review indicate no difference between desipramine and placebo for cocaine use during the trial period; however, the evidence is insufficient (2 RCTs; N=37; combined RR 0.85 [95% CI 0.34 to 2.11]). There is moderate strength of evidence that there is no difference between desipramine and placebo for retention (13 RCTs; N=1,011; combined RR 1.06 [95% CI 0.95 to 1.20]) or treatment withdrawals due to adverse events (4 RCTs; N=268; combined RR 1.42 [95% CI 0.68 to 2.96]) (see Conclusions Table A for a summary of findings). No other significant differences were found.

Selective Serotonin Reuptake Inhibitors (SSRIs)

One systematic review[16] and 2 additional trials[36,41] examine the use of SSRIs, specifically paroxetine, fluoxetine, and sertraline, for cocaine use disorder (the review also grouped nefazodone, a serotonin antagonist and reuptake inhibitor, as an SSRI). There is no evidence examining the effect of SSRIs on sustained abstinence or study period cocaine use in participants who were not abstinent at baseline. Two studies[36,41] provide low strength evidence that sertraline is better than placebo for preventing lapse and relapse in participants who have achieved abstinence (see sertraline below for more detail). Two low-ROB RCTs[36,41] and 7 RCTs in the systematic review provide moderate strength evidence that SSRIs do not improve study retention (N=527; combined RR 0.99 [95% CI 0.70 to 1.71]), and 3 RCTs in the systematic review provide moderate strength evidence of a higher risk of study withdrawal due to adverse events associated with SSRIs versus placebo (N=251; combined RR 3.55 [95% CI 1.11 to 11.34]). No trials provided evidence comparing SSRIs to placebo on serious adverse events (see Table 3 for study-level details and Conclusions Table A for a summary of findings).

Fluoxetine

Five trials in the systematic review examined fluoxetine.[16] We found no evidence examining the effect of fluoxetine on sustained abstinence, study period cocaine use, or serious adverse events. Four RCTs in the systematic review provide moderate strength evidence that fluoxetine performs worse than placebo on study retention (N=430, combined RR 1.30 [95% CI 1.08 to 1.57]). Similarly, 2 RCTs in the review provide low strength evidence of a higher risk of treatment withdrawal due to adverse events associated with fluoxetine (N=218; combined RR 3.60 [95% CI 1.03 to 12.62]). Conclusions Table A provides a summary of findings.

Sertraline

Two low risk of bias trials provide evidence examining sertraline for the treatment of cocaine use disorder in participants with comorbid depression (N=133).[36,41] There is low strength evidence of lower risk for both lapse (combined RR 0.79 [95% CI 0.62 to 1.00]; P= 0.05) and relapse (combined RR 0.74 [95% CI 0.57 to 0.96]; P = 0.02) for participants receiving sertraline (see

Figures 3 and 4). Both studies were 12-week trials, with a 2-week residential stay, followed by 10 weeks of outpatient study visits. Only participants achieving abstinence by the end of week 2 progressed to the outpatient phase. Participants received 200mg of sertraline or placebo, along with contingency management, and once weekly CBT. Neither study found a difference between groups in study retention (see Table 3 for study-level details and Conclusions Table A for a summary of findings).

Figure 3. Lapse after initial abstinence in studies comparing sertraline vs placebo for cocaine use disorder

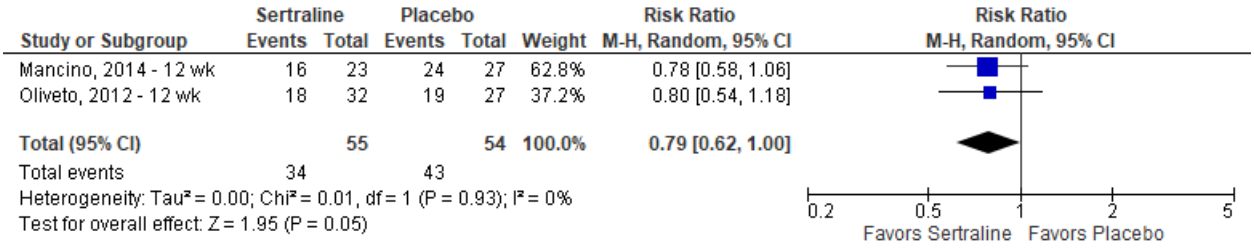
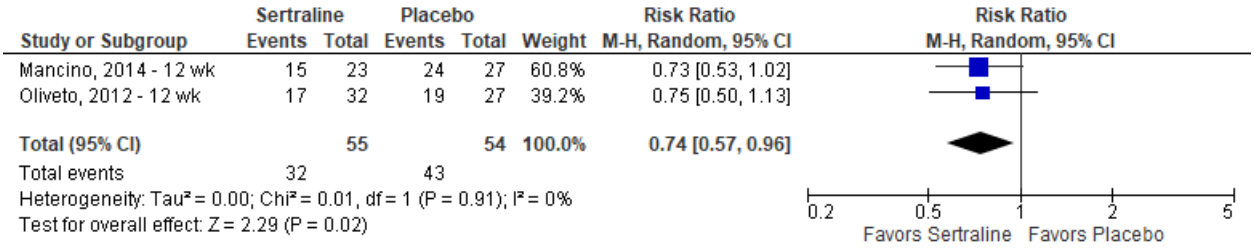


Figure 4. Relapse after initial abstinence in studies comparing sertraline vs placebo for cocaine use disorder



Serotonin and Norepinephrine Reuptake Inhibitor (SNRI): Venlafaxine

One low-ROB, 12-week, placebo-controlled trial examined venlafaxine for cocaine use disorder (N=130) in adults with comorbid depression.[46] Participants received up to 300mg of venlafaxine or placebo, along with motivational interviewing and weekly manualized relapse prevention therapy. No significant differences in sustained abstinence, study period negative UAs, retention, or harms were reported (see Table 3 for study-level details and Conclusions Table A for a summary of findings).

Atypical Antidepressant: Mirtazapine

One small, high-ROB, 20-week trial (N=24) compared mirtazapine to placebo for adults with cocaine dependence and clinically significant depressive symptoms.[17] Participants received 45mg of mirtazapine or placebo for 12 weeks (plus tapering up and down by 15mg every 3 days), in addition to weekly relapse prevention therapy. No difference was reported for study period use, and no treatment withdrawals due to adverse events or severe adverse events were reported (see Table 3 for study-level details and Conclusions Table A for a summary of findings).

Aminoketone: Bupropion

Bupropion as a treatment for cocaine use disorder was included in systematic reviews examining both antidepressants[16] and psychostimulants.[5] Outcomes reported were slightly different and we include the most comprehensive. Two RCTs in one systematic review[5] provide low strength evidence that bupropion is more beneficial than placebo for sustained abstinence (N=176; combined RR 1.63, 95% CI 1.03 to 2.59). No difference was found for cocaine use during the trial period (SOE low),[5] study retention (SOE moderate),[16] or harms (see Table 3 for study-level details and Conclusions Table A for a summary of findings).[16]

Table 3. Trials of antidepressants for treating cocaine use disorder

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Findings: T vs C Overall use, UA-confirmed	Findings: T vs C Retention in treatment	Findings: T vs C Treatment withdrawals due to AE; Severe AEs	Risk of bias
ATYPICAL ANTIDEPRESSANTS: *Mirtazapine*							
Afshar, 2012[17] NR sites (US) N=24 20 wks follow-up	11 vs 13 Mitrazapine 45 mg/day 12 wks 60 mins 1x/wk individual relapse prevention counseling NR (UA1+ /wk)	71% male Age: 45.5 Race: 8% White, 79% AA/Black Education & Employment: NR	NR	Use declined significantly for both groups, with no difference between groups.	NR	WD: 0 Severe AEs: None	High
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs): *Sertraline*							
Mancino, 2014[36] 1 site (US) N=107 residential, 74 outpatient 13 wks follow-up	Residential: 35 vs 34 vs 38 Outpatient (analyzed): 23 vs 24 vs 27 Sertraline 200 mg/day; Sertraline 200 mg/day + Gabapentin 1200mg 12 wks Wks 1-2: residential treatment. Wks 3-12: CM + 60 min 1x/wk individual CBT UA 3x/wk	77% Male Age: 39.5 (7.3) Race: 71.6% AA/Black; White NR Employment: 62% unemployed Education: 57% High school or less	N (%) Lapse: 16 (69.6%) vs 17 (70.8%) vs 24 (88.9%), P = NS N (%) Relapse: 15 (65.2%) vs 17 (70.8%) vs 24 (88.9%) SERT vs PLA, P = 0.04 No difference in the time to lapse or relapse.	NR	74 of 107 completed residential phase: 23 (66%) vs 24 (71%) vs 27 (71%) 23 of 74 completed outpatient phase: 8 (35%) vs 9 (38%) vs 6 (22%)	WD (during residential phase): 0 (0%) vs 1 (3%) vs 0 (0%). Severe AEs: NR	Low

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	Risk of bias
Oliveto, 2012[41] 1 site (US) N=94 residential, 64 outpatient, 59 analyzed 13 wks follow-up	Residential: 50 vs 44 Outpatient (analyzed): 32 vs 27 Sertraline 200 mg/day 12 wks Wks 1-2: Residential Wks 3-12: CM + 60 min 1x/wk CBT UA 3x/wk	61% male Age: 38.3 Race: 27% White, 66% AA/Black Education: 8.9 yrs (4.2) Employment: 66% unemployed or less than part-time	N (%) Lapse: 18 (56%) vs 19 (70%), P = 0.14 N (%) Relapse: 17 (53%) vs 19 (70%), P = 0.07 M time to Lapse: 26.1 (±16.7) vs 13.2 (±10.5), P = 0.004 M time to Relapse 32.3 (±14.9) vs 21.3 (±10.8), P = 0.02	NR	No significant difference in residential or outpatient retention by group.	WD: 2 (group NR) Severe AEs: NR	Low
SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs): *Venlafaxine*							
Raby, 2014[46] 1 site (US) N=130 12 wks follow-up	64 vs 66 Venlafaxine Up to 300 mg/day 12 wks 1x/wk individual relapse prevention therapy (CBT, MI) UA 2x/wk	72.5% Male Age: 38.5 (8) Race: 39% White, 26% AA/Black Education: 46% high school or less Employment: 16% Unemployed Veteran pop: very few Veterans despite VA study (per author email)	N (%) 3+ wks abstinent: 10 (16%) vs 10 (15%), P = 0.94	Proportion of UA (-): 0.58 vs 0.56, P = 0.738	53 completed study: 21 (33%) vs 32 (49%) No difference in wks to dropout by group.	WD: 1 (2%) vs 3 (5%) Severe AEs: 6 (9%) vs 0 (0%)	Low

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States of America; MA = methamphetamine; mg = milligrams; MI = Motivational Interviewing; MTD = maximum tolerated dose; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; PLA = placebo; ROB = risk of bias; SD = standard deviation; SEM = standard error of the mean; SERT = sertraline; SES = socioeconomic status; sig = statistically significant; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; T = treatment group; TTM = Transtheoretical Model; UA = urinalysis; wk(s) = week(s); yrs = years.

Antipsychotics

Summary of Findings

One systematic review[12] and 1 high-ROB RCT[39] examine the evidence for the use of antipsychotics for the treatment of cocaine use disorder. Overall, there was moderate strength evidence of better retention for participants receiving any antipsychotic. However, there was no benefit on retention when examining first- or second-generation antipsychotics as a class, or any antipsychotic individually. Findings suggest that antipsychotics as a class or individually are no better than placebo for sustained abstinence (*ie*, 2+ weeks; SOE low), study period cocaine use (SOE low), preventing relapse or lapse in abstinent participants, or harms.

Detailed Findings

One high-ROB RCT of methadone-maintained participants[39] and 1 systematic review[12] of 14 RCTs (n = 719) that largely examined second-generation antipsychotics (*ie*, aripiprazole, olanzapine, quetiapine, risperidone), along with haloperidol, lamotrigine, and reserpine, provided evidence for antipsychotics for the treatment of cocaine use disorder. Overall, findings indicate low strength evidence of no difference between antipsychotics and placebo for both sustained abstinence[12] and cocaine use during the study period,[12,39] and insufficient evidence for lapse and relapse in participants abstinent at baseline.[39] Based on findings from 8 RCTs in the systematic review (N=397; combined RR 0.75 [95% CI 0.57 to 0.97]),[12] moderate strength evidence exists to support the benefit of antipsychotics over placebo for study retention. We found no difference between antipsychotics as a class and placebo in treatment withdrawal due to adverse events (see Table 4 for study-level details and Conclusions Table A for a summary of findings).[39]

First-generation (Typical) Antipsychotics/Haloperidol

One RCT in 1 systematic review[12] found no difference between haloperidol and placebo in study retention. In addition, a head-to-head trial found no difference between haloperidol and olanzapine (N=31; RR 1.50 [95% CI 0.63 to 3.57]). We found no evidence for the effect of any typical antipsychotic on sustained abstinence, study period cocaine use, or harms (see Conclusions Table A for a summary of findings).

Second-generation (Atypical) Antipsychotics

One systematic review[12] and 1 small, high-ROB RCT of methadone-maintained participants[39] examined atypical antipsychotics aripiprazole, olanzapine, quetiapine, and risperidone for the treatment of cocaine use disorder. Findings from the systematic review indicate no difference between atypical antipsychotics and comparators for sustained abstinence (SOE low), study period use of cocaine, retention (SOE moderate), or harms;[12] moreover, no difference was found in relapse or lapse in methadone-maintained participants at baseline.[39] Head-to-head trials in the systematic review found no difference in retention between olanzapine and haloperidol (1 RCT; N=31), olanzapine and risperidone (1 RCT; N=28), and aripiprazole and ropinirole (1 RCT; N=28; see Table 4 for study-level details and Conclusions Table A for a summary of findings).[12]

Aripiprazole

One small, high-ROB RCT[39] examined aripiprazole, along with contingency management and individual counseling, in opioid-dependent methadone-maintained adults. Participants first went

through a 12-week methadone stabilization phase that included contingency management and (unspecified) treatment, and those who achieved cocaine abstinence in weeks 11 and 12 were randomized to 15mg of aripiprazole or placebo (N=18), with contingency management continuing through the 2-week induction phase. Time to both lapse (first cocaine-positive urine sample; HR=0.45, 95% CI [0.14 to 1.42], P=0.17) and relapse (2 consecutive cocaine-positive urine samples or missed urines; (HR= 0.31, 95% CI [0.07 to 1.27], P=0.10) were similar between groups, and there was no difference in the longest duration of abstinence. The study was discontinued early due to the small number of participants (18 of 41 enrolled) able to achieve abstinence in weeks 11 and 12. One additional RCT in a systematic review[12] compared aripiprazole to ropinirole and found no difference in retention (see Table 4 for study-level details and Conclusions Table A for a summary of findings).

Risperidone

Evidence examining risperidone for the treatment of cocaine use disorder comes from 1 systematic review.[12] One small RCT (N=31) in the systematic review found no difference between risperidone and placebo in the use of cocaine during the study period. In addition, 4 RCTs in the systematic review found a non-significant trend in favor of risperidone for study retention (N=176; combined RR 0.81 [95% CI 0.63 to 1.04]; SOE low), and a head-to-head trial found no difference between risperidone and olanzapine (N=28). No other outcomes were examined (see Conclusions Table A for a summary of findings).

Olanzapine

One systematic review provides evidence examining the use of olanzapine for the treatment of cocaine use disorder.[12] Two underpowered RCTs found no difference between olanzapine and placebo, but provide insufficient evidence for the effect on end-of-study abstinence (N=79, combined RR 1.37 [95% CI 0.71 to 2.61]). In addition, there were no differences in participants completing RCTs comparing olanzapine to placebo (N=30; RR 2.00 [95% CI 0.20 to 19.78]), haloperidol (N=31; RR 1.50 [95% CI 0.63 to 3.57]), and risperidone (N=28; RR 2.00 [95% CI 0.78 to 5.14]; see Conclusions Table A for a summary of findings).

Quetiapine

One systematic review provides evidence examining quetiapine for adults with cocaine use disorder.[12] One RCT (N=60) in the review found no difference between quetiapine and placebo for end-of-trial abstinence (last 2 weeks), and 2 RCTs found no difference in study retention (N=72; combined RR 0.64 [95% CI 0.20 to 2.03]). No other outcomes of interest were examined (see Conclusions Table A for a summary of findings).

Other Antipsychotics: Reserpine

One RCT in a systematic review[12] compared reserpine to placebo for cocaine use. No differences were found between groups during the study. No other outcomes of interest were examined (see Conclusions Table A for a summary of findings).

Table 4. Trials of antipsychotics for treating cocaine use disorders

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Time to lapse and relapse, UA-confirmed	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
ATYPICAL ANTIPSYCHOTICS: *Aripiprazole*							
Moran, 2017[39] 1 site (US) N=18 (41 enrolled) All Ss abstinent at baseline 41wks follow-up	9 vs 9 Aripiprazole 15mg/day (MTD) 12 wks CM during 2-week induction UA 3x /wk	94% Male Age: 46 Race: 12.5% White, 81% AA/Black Education: 12.5 yrs Unemployed: 12.5%	M (SEM) longest duration of abstinence: 20.11 (4.87) vs 14.89 (4.19), P = 0.43 Time to Lapse: There was no difference in time to lapse (HR = 0.51, 95% CI [0.18, 1.48], P = 0.21]. Time to Relapse: There was no difference in time to lapse.	M% (SEM) of UA (-) samples: 58% (12%) vs 55% (11%), P = 0.66	8 (89%) vs 6 (67%)	WD: 0 (0%) vs 1 (11%) Severe AEs: NR	High

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States of America; MA = methamphetamine; mg = milligrams; MI = Motivational Interviewing; MTD = maximum tolerated dose; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SEM = standard error of the mean; SES = socioeconomic status; sig = statistically significant; T = treatment group; TTM = Transtheoretical Model; UA = urinalysis; wk(s) = week(s); yrs = years

Psychostimulants

Summary of Findings

We identified 1 systematic review[5] examining psychostimulants for the treatment of cocaine use disorder. Overall, studies found low strength evidence favoring the use of psychostimulants as a class for sustained abstinence generally, and dexamphetamine and mixed amphetamine salts specifically (both insufficient SOE). There was moderate strength evidence of no differences for retention and harms. Note, this body of literature is hampered by low-quality studies, with consistent concerns related to incomplete outcome data.

Detailed Findings

A 2016 systematic review[5] included 26 trials (N=2366) and examined modafinil, mazindol, methylphenidate, dexamphetamine, lisdexamfetamine, methamphetamine, mixed amphetamine salts, and selegiline. The review also included studies of bupropion, which was also examined in the included systematic review for antidepressants.[16] We have classified bupropion as an antidepressant (see Conclusions Table A for a summary of findings).

Findings from 14 RCTs in the systematic review indicate low strength evidence that psychostimulants as a class are better than placebo for sustained abstinence (N=1,549; combined RR 1.36 [95% CI 1.05 to 1.77]). One bupropion study was included in the combined estimate; however, its removal does not change the conclusion.[65] There were no significant differences between groups for cocaine use during the trial period (SOE low), study retention (SOE moderate), or harms (SOE moderate; see Conclusions Table A for a summary of findings).

Dexamphetamine

Findings come from 1 systematic review[5] that included 4 RCTs examining dexamphetamine. Three high-ROB RCTs in the review examined sustained abstinence and found that dexamphetamine was significantly better than placebo (N=154; combined RR 1.98 [95% CI 1.12 to 3.52]). The strength of evidence however, is insufficient due to concerns about incomplete outcome data for all 3 studies and questions related to random sequence generation and blinding. No other significant differences between dexamphetamine and placebo were identified (see Conclusions Table A for a summary of findings).

Mazindol

Four RCTs in the systematic review examine mazindol for the treatment of cocaine use disorder.[5] One underpowered, high-ROB trial in the review found no significant difference between mazindol and placebo for sustained abstinence, and 4 underpowered RCTs (2 unclear, 2 high-ROB) in the systematic review found no difference between groups in study retention (N=121; combined RR 0.96 [95% CI 0.76 to 1.21]). No other outcomes of interest were examined (see Conclusions Table A for a summary of findings).

Methamphetamine

One high-ROB RCT in the systematic review[5] found no significant difference between methamphetamine and placebo in retention or study withdrawals due to adverse events in the

treatment of cocaine use disorder. No other outcomes of interest were examined (see Conclusions Table A for a summary of findings).

Methylphenidate

Four high-ROB RCTs in the systematic review[5] examined methylphenidate for the treatment of cocaine use disorder. One RCT found that methylphenidate did not differ from placebo on sustained abstinence. Three trials (N=203) found no difference between groups for cocaine use during the trial period (SMD -0.09 [95% CI -0.36 to 0.19]; SOE low) or retention (combined RR 0.91 [95% CI 0.68 to 1.21]; SOE low).Three RCTs found no difference between groups in study withdrawals due to adverse events (N=216; combined RD -0.01 [95% CI -0.05 to 0.03]; SOE low; see Conclusions Table A for a summary of findings).

Mixed Amphetamine Salts

One unclear-ROB RCT in the systematic review[5] compared mixed amphetamine salts to placebo for the treatment of cocaine use disorder. Although the evidence is insufficient due to the single study and questions related to blinding and incomplete outcome data, the study found that mixed amphetamine salts performed better than placebo for sustained abstinence (N=126; RR 3.63 [95% CI 1.15 to 11.48]). No differences were reported for retention or harms (see Conclusions Table A for a summary of findings).

Modafinil

Eight RCTs in the systematic review[5] examined modafinil for the treatment of cocaine use disorder. All but 2 included RCTs were high-ROB, with concerns about incomplete outcome data, as well as questions about random sequence generation, allocation concealment, and blinding. The review found no significant differences between groups for abstinence (6 RCTs; N=644; combined RR 1.32 [95% CI 0.85 to 2.04]; SOE low), use (1 RCT; N=57), retention (7 RCTs; N=723; combined RR 1.04 [95% CI 0.89 to 1.21]; SOE moderate), or harms (4 RCTs; SOE moderate; see Conclusions Table A for a summary of findings).

Lisdexamphetamine

One small, high-ROB study (N=43) in the systematic review[5] compared lisdexamphetamine to placebo for the treatment of cocaine use disorder. No significant differences on retention or harms were reported. No other outcomes of interest were examined (see Conclusions Table A for a summary of findings).

Selegiline

One high-ROB study (N=300) in the systematic review[5] examined selegiline for the treatment of cocaine use disorder. No differences were reported for sustained abstinence, study retention, or harms. No other outcomes of interest were examined (see Conclusions Table A for a summary of findings).

Cognitive Enhancing Drugs

Summary of Findings

Two small RCTs[19,61] examined cognitive enhancing drugs plus contingency management for the treatment of cocaine use disorder. One low-ROB trial compared memantine to placebo,[19] and the second was an unclear-ROB trial comparing atomoxetine to placebo.[61] Neither study reported significant differences on any outcome of interest.

Detailed Findings

Two small RCTs[19,61] examined cognitive enhancing drugs plus contingency management for the treatment of cocaine use disorder. One low-ROB, placebo-controlled trial (N=81) that had a 2-week placebo lead in to encourage abstinence examined memantine,[19] and the second, an unclear-ROB trial (N=50) compared atomoxetine to placebo.[61] Neither study reported significant differences on any outcome of interest.

Memantine

One low-ROB trial[19] compared memantine (a NMDA receptor antagonist) to placebo for the treatment of cocaine use disorder. Participants (N=112) began the trial with 2 weeks of (single-blind) placebo lead-in to encourage abstinence. All participants received Motivation Enhancement Therapy (MET; weeks 1-4), high-value contingency management (weeks 1-4), and Cognitive Behavioral Treatment-Relapse Prevention (CBT-RP; weeks 3-16). In week 3, remaining participants were randomized (n=81) to 40mg of memantine or placebo. There was no difference between groups for sustained abstinence ($c^2(1)= 0.29$, P=0.59), cocaine use (β=0.03, SE=0.17, $c^2(1)=0.03$, P=0.87), or study retention ($c^2(3)=0.89$, P=0.83). In addition, among those participants who had achieved abstinence at baseline, there was no significant difference in relapse or time to relapse (see Table 5 for study-level details and Conclusions Table A for a summary of findings).

Atomoxetine

One small, 12-week, unclear-ROB trial[61] compared 80mg of atomoxetine, a cognitive enhancing serotonin norepinephrine reuptake inhibitor (SNRI), to placebo, along with contingency management and optional weekly CBT-based relapse prevention counseling for the treatment of cocaine use disorder. Findings indicate no significant differences in cocaine use during the study (c^2=0.2, P=0.66; OR=0.89 [95% CI 0.41 to 1.74]), study retention (Cox analysis c^2=0.72, P=0.40; Hazard Ratio 1.48 [95% CI 0.62 to 3.39]), or treatment withdrawal due to adverse events (see Table 5 for study-level details and Conclusions Table A for a summary of findings).

Table 5. Trials of cognitive-enhancing drugs for treating cocaine use disorder

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence or relapse UA-confirmed: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	Risk of bias
Memantine							
Bisaga, 2010[19] 1 site (US) N=112 16 wks follow-up	39 vs 42 Memantine 40 mg/day 12 wks CM (weeks 1-4), MET (weeks 1-4), 1x/week relapse prevention therapy (CBT) UA 3x/wk	79% Male Age: 40 Race: 41% White 40% AA/Black Education: 48% high school Unemployment: 42% unemployed	N (%) Relapse among subjects who achieved abstinence at baseline (N=36): 15 (80%) vs 15 (88%) N (%) 3+ wk abstinence among subjects who achieved abstinence at baseline (N = 36): 11 (58%) vs 10 (59%) Median time to relapse among subjects who achieved abstinence at baseline (N = 36): 2 wks vs 3 wks, P = 0.32 N (%) 3+ wk abstinence among those not abstinent at baseline (N=45): 4 (19%) vs 3 (13%), P = 0.59	No difference, P = 0.87	49 completed study: 22 (56%) vs 27 (64%)	WD: 2 (5%) vs 0 (0%) Severe AEs: 0 (0%) vs 2 (5%)	Low

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence or relapse UA-confirmed: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	Risk of bias
Cognitive enhancing SNRI: *Atomoxetine*							
Walsh, 2013[61] 1 site (US) N=50 24 wks follow-up	25 vs 25 Atomoxetine 80 mg/day 12 wks CM + Optional 1x/week individual relapse prevention therapy (CBT and coping skills) UA 3x/wk	72% Male Age: 43.1 Race: 32% White, 68% AA/Black Education: 12.55 yrs Employment: 76% unemployed	NR	% of study period UA (-): 26% vs 33%, P = 0.66	28 completed study: 12 (48%) vs 16 (64%), P = 0.40 M days completed: 51.6 (±6.7) vs 57.4 (±7)	WD: 1 (4%) vs 0 (0%) Severe AEs: NR	Unclear

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States of America; MA = methamphetamine; MET = motivational enhancement therapy; mg = milligrams; MI = Motivational Interviewing; MTD = maximum tolerated dose; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SEM = standard error of the mean; SES = socioeconomic status; sig = statistically significant; T = treatment group; TTM = Transtheoretical Model; UA = urinalysis; wk(s) = week(s); yrs = years.

Anxiolytics

Summary of Findings

We identified 1 RCT examining an anxiolytic for the treatment of cocaine use disorder. A small, multi-site, high-ROB RCT compared buspirone to placebo for treatment and relapse prevention.[62] No significant differences were reported for any outcome of interest.

Detailed Findings

Buspirone

One small, multi-site, 16-week, high-ROB RCT (N=62) compared 60mg of buspirone to placebo, along with contingency management and once-weekly optional individual or group psychosocial treatment for treatment and relapse prevention in adults with cocaine use disorder.[62] Participants were randomized to buspirone or placebo, then spent 12-19 days in residential treatment before continuing care in an outpatient setting. Urinalyses were performed once weekly. No differences were reported for the mean number of post-discharge days abstinent ($c^2(1)=0.05$, P=.82) or time to lapse ($c^2(1)=0.15$, P=0.70). Rates of retention were similarly high in both groups, and 3 participants receiving buspirone experienced a severe adverse event (see Table 6 for study-level details and Conclusions Table A for a summary of findings).

Table 6. Trials of anxiolytics for treating cocaine use disorder

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Findings: T vs C Abstinence or relapse UA-confirmed: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	Risk of bias
ANXIOLYTICS: *Buspirone*							
Winhusen, 2014[62] 6 sites (US) N=62 12-19 days residential, remaining outpatient 16 wks follow-up	35 vs 27 Buspirone 60 mg/day or MTD 15 wks CM, Inpatient/residential (psychosocial TAU, Outpatient TAU (min of 60 min 1x/wk individual or group psychosocial treatment) UA 1x/wk	63% Male Age: 46 Race: 22.6% White, 72.6% African Am Education: 11.6 yrs (1.8) Employment: NR	M (SD) days of continuous (post-discharge) abstinence: 39.7 (31.4) vs 42.1 (31.1), P = 0.82 No significant difference in days to first cocaine use, P = 0.70	NR	33 (94%) vs 25 (93%)	WD: None Severe AEs: 3 (9%) vs 0 (0%)	High

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States of America; MA = methamphetamine; MET = motivational enhancement therapy; mg = milligrams; MI = Motivational Interviewing; MTD = maximum tolerated dose; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; ROB = risk of bias; TAU = treatment as usual

Pharmacotherapies That are Prescribed for Other Substance Use Disorders

Disulfiram

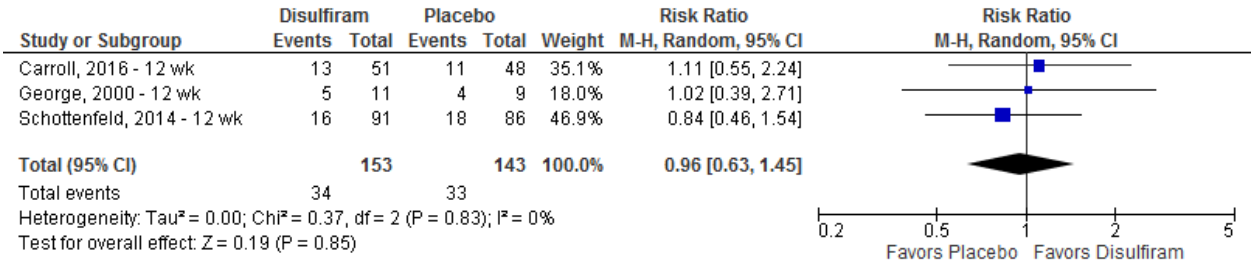
Summary of Findings

Findings from 5 RCTs[20,21,31,40,52] identified in our search and 2 RCTs[63,64] identified by a previous systematic review[15] indicate that subjects randomized to disulfiram were less likely to complete treatment compared with placebo (moderate SOE). The increased attrition with disulfiram was marginally significant in a meta-analysis combining the 7 trials. The effects of disulfiram on overall cocaine use were heterogeneous (insufficient SOE). No effect on abstinence was observed (low SOE). No difference in harms was reported (low SOE).

Abstinence

From 2 low-ROB RCTs[20,52] (N=276) combined with 1 unclear-ROB RCT (N=20),[63] there was low strength of evidence of no significant difference in the number of patients who achieved abstinence for 2 or more consecutive weeks (RR 0.96, 95% CI 0.63 to 1.45). Statistical heterogeneity among the studies combined in this analysis was not significant (p=0.83; See Figure 5 for meta-analysis, Table 7 for study-level data and Conclusions Table B for a summary of findings).

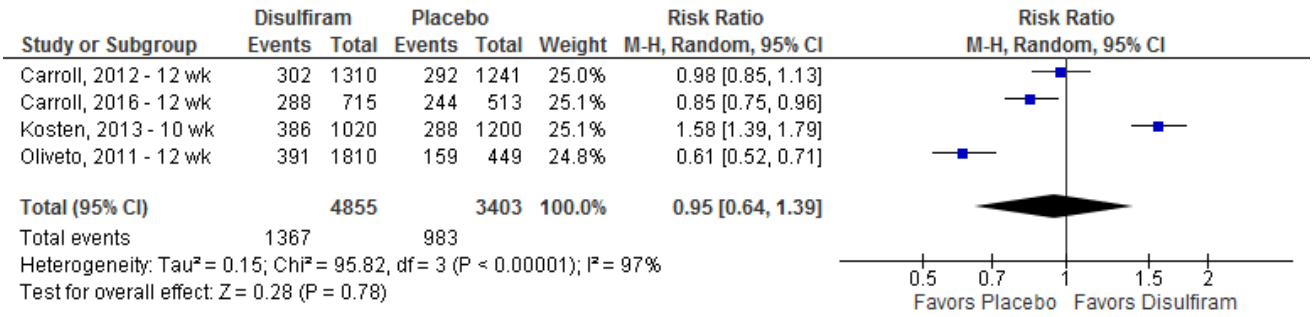
Figure 5. Abstinence for 2+ consecutive weeks in studies comparing disulfiram vs placebo in patients with cocaine use disorder



Use

Among 4 low-ROB RCTs[20,21,31,40] (N=440) there was insufficient strength of evidence for no significant difference in the total number of cocaine-negative UA samples among patients treated with disulfiram compared with placebo (RR 0.95, 95% CI 0.64 to 1.39). The effects of treatment varied markedly, however, and statistical heterogeneity among the studies combined in this analysis was highly significant (P <.00001; See Figure 6 for meta-analysis, Table 7 for study-level data, and Conclusions Table B for a summary of findings).

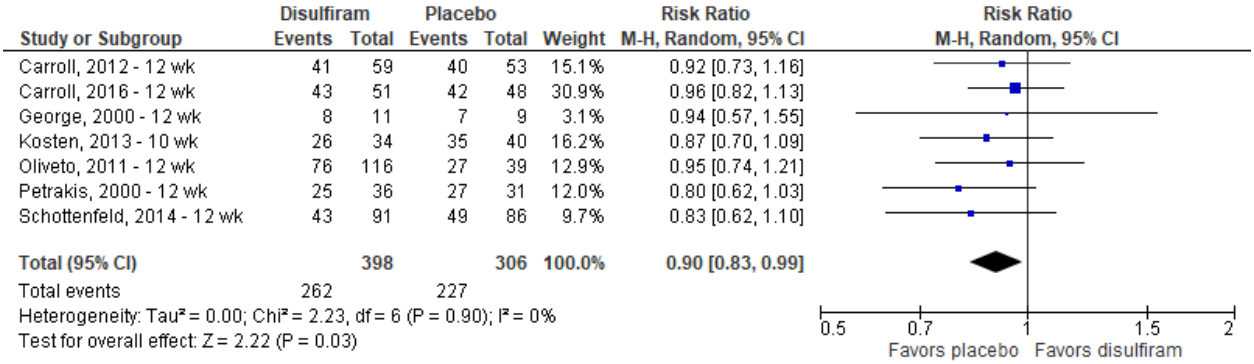
Figure 6. Overall use: Total cocaine-negative UA samples in studies comparing disulfiram vs placebo in patients with cocaine use disorder



Retention

We found moderate-strength evidence that treatment retention tended to be lower among patients treated with disulfiram compared with placebo for cocaine use disorder based on 5 low-ROB RCTs (N=617),[20,21,31,40,52] combined with 1 small (N=20) unclear-ROB RCT[63] and 1 high-ROB RCT[64] (N=67). In a meta-analysis combining the 7 trials, decreased retention with disulfiram was marginally significant (RR 0.90, 95% CI 0.83 to 0.99). The findings were statistically homogeneous among studies, with a P-value of .90 for heterogeneity. See Figure 7 for meta-analysis, Table 7 for study-level data, and Conclusions Table B for a summary of findings.

Figure 7. Treatment retention in studies comparing disulfiram vs placebo in patients with cocaine use disorder



Harms

Withdrawals due to AEs ranged from 0% to 5.9% among the 4 RCTs (N=548) identified in our search, for reasons that included elevated liver enzymes and rash.[21,31,40,52] The occurrence of severe adverse events was not otherwise reported. The strength of evidence for harms is therefore considered low.

Naltrexone

Five low-ROB RCTs compared naltrexone with placebo.[23,42,43,50,51] No differences were reported for any of the outcomes of interest. See Table 7 for study-level data and Conclusions Table B for a summary of findings.

Acamprosate

One low-ROB trial (N=60) compared acamprosate with placebo in patients with cocaine use disorder. The study found no significant differences in retention or overall use.[28] Effects on abstinence and adverse effects were not reported. See Table 7 for study-level data and Conclusions Table B for a summary of findings.

Varenicline

Two unclear-ROB trials (N=68) compared varenicline with placebo, with mixed results. Cocaine use was lower with varenicline in 1 study, though this finding did not reach statistical significance (OR 0.495, p = 0.08).[44] The other study was conducted in opioid-dependent patients (N=31) and reported similar cocaine use between varenicline and placebo groups.[45] No differences in study retention were observed, and continuous abstinence was not reported in either study.

Opiate Agonists

Buprenorphine vs Methadone

Two low-ROB, head-to-head RCTs (N=278) compared methadone to buprenorphine in patients with comorbid cocaine and opioid use, and reported mixed findings on retention and abstinence.[53,54] Longer abstinence and better retention with methadone was found in 1 RCT. Use outcomes favored methadone over buprenorphine (P<.05); however, the strength of evidence was insufficient. See Table 7 for study-level data and Conclusions Table B for a summary of findings.

Buprenorphine plus Naloxone

In 1 low-ROB RCT (N=302), there was no difference in abstinence and retention outcomes. There were mixed findings in use, with significantly less use in those receiving 16mg of buprenorphine plus 4mg of naloxone, versus placebo. However, there was no difference in the lower dose (4 mg buprenorphine plus 1 mg naloxone). The strength of evidence was insufficient.[34] See Table 7 for study-level data and Conclusions Table B for a summary of findings.

Table 7. Trials to treat cocaine use disorder using pharmaceuticals prescribed for other substance use disorders

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) or longest consecutive period/ time to relapse, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
Disulfiram							
Carroll, 2012[21] Single site - US N=112 12 wks	59 vs 53 Disulfiram 250mg/day dissolved in methadone 12 wks 12-step facilitation weekly vs. standard counseling sessions UA 3x weekly	Subgroup: Opioid, EtOH 59% Male Race: 22% AA, 64% white SES: NR	NR	NR	76% who initiated T completed full course. P=ns	WD: 1 SAE: None	Low
Carroll, 2016[20] single site - US N=99 12 wks	51 vs 48 Disulfiram 250mg/day 12 weeks CBT +/- CM UA 3x/wk	Subgroup: EtOH Male: 74% Race: 49.5% AA SES: NR	13/51 (25.5%) vs 11/48 (22.9%)	NR	F test 3.13, p=.08 Favors disulfiram	NR	Low
Oliveto, 2011[40] 2 sites -US N=155 12 wks	3 arms: 37/38/39 vs 38, Disulfiram 62.5mg/125mg/ 250mg daily Methadone maintenance and weekly CBT UA 3x/wk	Subgroup: Opioid Male: 48.7% Race: White 78%; AA 10.5% SES: NR	NR	UA(-): 391/1810 (21.6%) vs 159/449 (35.4%) P<.05	72/116 (62.1%) vs 29/39 (74.4%) P=ns	WD: 6 No severe AE reported	Low

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse or Relapse: ≥2 weeks, N (%) or longest consecutive period/ time to relapse, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	Risk of bias
Schottenfeld, 2014[52] single site - US N=177 12 wks	91 vs 86 Disulfiram 250mg, 6 days/wk 12 wks Buprenorphine 16mg/day Weekly manual guided group drug counseling UA 3x/wk	Subgroup: Opioid Male: 71.8% Race: 69% White SES: NR	abstinence ≥3 wks: 18% vs 21% P=0.57	Mean (SD) UA(-) samples: 10.7 (11.5) vs 10.0 (11.4), P=ns	43/91 (47%) vs 49/86 (56.9%)	WD: 8 due to SAE	Low
Kosten, 2013[31] 2 sites - US N=74 12 wks	34 vs 40 Disulfiram 250mg/day 12 wks Methadone maintenance and weekly CBT UA 3x/wk	Subgroup: Opioid Male: 64.9% Age: 39 Race: NR SES: NR	NR	NR	77% vs 87% No significant difference	WD: 6 SAE: 4	Low
Naltrexone							
Hersh, 1998[23] single site - US N=64 8 wks	31 vs 33 50mg NTX/day 8 wks Individual relapse prevention psychotherapy 1-2/wk UA 2x/wk	Subgroup: EtOH Male: 93.5% Age: 35.2(6.0) Race: 77.5% White	Time to relapse: 2.5 (2.8) wks vs 2.1 (2.4) wks Difference not significant	NR	NR	WD: 1/31 (3.2%) vs 2/33 (6%), P=ns Severe AE: 2/31 (6.5%) vs 11/33 (33.3%) P=0.097	Low

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) or longest consecutive period/ time to relapse, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
Pettinati, 2008[43] Single site - US N=164 12 wks	82 vs 82 150mg/day naltrexone 12 wks CBT - 45 min/wk vs BRENDA (a type of medical management) - 30 min/wk UA 1x/wk	Subgroup: EtOH, gender Male: 70.8% Age: 39.1 (7.0) SES: NR	NR	NR	55/82 (67%) vs 50/82 (61%), P = ns	NR	Unclear
Pettinati, 2014[42] Single site - US N=80 8 wks	39 vs 41 One 380mg XR-NTX injection or placebo injection at randomization, and again at 4 weeks CBT 1x/week UA 3x/week	Subgroup: EtOH Male: 81.3% Age: 47.9 (6.6) Race: 87.5% AA/Black SES: NR	Abstinence ≥3 consecutive wks 17.9% vs 17.1% P = .918	NR	28/39 (72%) vs 34/41 (83%	WD: None SAE: 5/39 (12.8%) vs 4/41 (9.8%) P = ns	Low
Schmitz, 2004[51] single site, US N=80 12 wks	40 vs 40 naltrexone 50mg/day 12 wks Individual therapy sessions 1-2x/week UA 1x/week	Subgroup: EtOH Male: 83.7% Age: 35.9 (6.4) Race: 51.2% AA SES: NR	NR	No differences by medication; NOS	Overall 33% completed; no significant difference (p=0.47); NOS	NR	Low
Schmitz, 2009[50] single site, US N=87 12 wks	45 vs 42 Naltrexone 100mg/day 12 wks CBT vs CBT+CM UA 3x/week	Subgroup: EtOH Male: 87.3% Age: 34.41 (4.55) Race: 71.3% AA/Black SES: NR	NR	NR	25 (33%) Ss completed treatment; No significant difference; NOS	NR	Low

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse or Relapse: ≥2 weeks, N (%) or longest consecutive period/ time to relapse, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	Risk of bias
Acamprosate							
Kampman, 2011[28] single site, US N=60 8 wks	34 vs 26 Acamprosate 666mg 3x/daily 8 wks weekly individual CBT UA 2x/week	Subgroup: EtOH Male: 75% Age: 45 Race: 85% AA/Black SES: NR	NR	% UA (-): 22% vs 23% P=0.44	18/34 (53%) vs 18/26 (69%)	NR	Low
Varenicline							
Plebani, 2012[44]	18 vs 19 2 mg/d 9 wks CBT 1x/wk UA 3x/wk	Male; 70% Age: Race: 89 vs 67% AA/Black (p<.03) SES: NR	NR	Trend toward lower use w varenicline: OR 0.495, (p = 0.08)	77% with no significant difference in time to last visit (F=2.77, p = 0.10); not otherwise specified	NR	Unclear
Poling, 2010[45]	13 vs 18 2 mg/d 12 wks Methadone up to 140 mg/d CBT 1x/wk UA 3x/wk	Subgroup: tobacco and opioid dependent Male; 81% Age: 36.5 Race: 23% AA/Black, 13% Hispanic SES: 12.7y educ	NR	"No significant changes in slope for either group and these slopes do not differ from each other (Z = 0.20, p < 0.84)."	5 subjects dropped out; no difference between groups (log rank $\chi 2$ = 1.3,p < 0.26); not otherwise specified	None occurred	Unclear

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse or Relapse: ≥2 weeks, N (%) or longest consecutive period/ time to relapse, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	Risk of bias
Opiate Agonists							
Buprenorphine plus naloxone							
Ling, 2016[34] multi-site, US N=302 8 wks + 3 mo f/up	BUP 4mg + Nalox 1mg (N=100) vs Bup 16mg + Nalox 4mg (N=100) vs Placebo (N=100) All Ss received 380 mg XR-NTX injection at wks 1 & 5 Bup: naloxone tablets 4:1 mg/day vs 16:4 mg/day 8 wks UA 3x/week	Subgroup: Opioid Male: 78.4% Age: 46.4 Race: 63% AA/Black; 25.8% white SES: NR	100% abstinent during weeks 5-8: BUP4 17/95 (17.9%) BUP16 18/97 (18.6%) Placebo 16/100 (16%) BUP4 vs Placebo, P=0.362 BUP16 vs Placebo, P=0.318	UA(-): BUP4 50.4% BUP16 50.9% Placebo 45.8% BUP4 vs Placebo, P=0.105 BUP16 vs Placebo, P=0.022	Retention defined as % who received 2nd XR-NTX injection at week 5: Placebo: 89/102 (87.3%) Bup4: 86/100 (86.0%) Bup16: 88/100 (88.0%)	NR	Low
Buprenorphine vs methadone							
Schottenfeld, 1997[54] single site, US N=116 24 wks	4 groups (MTD65, Bup12, MTD20, Bup4): 28 vs 29 vs 30 vs 29 Buprenorphine 12mg or 4 mg or Methadone 65mg or 20 mg 24 wks 60 min group counseling 1x/wk UA 2-3x/week	Subgroup: Opioid Male: 69% Age: 32.6 Race: 70.7% White SES: NR	Abstinence ≥3 wks: 50.0% vs 34.5% vs 40.0% vs 20.7% P=0.14	NR	Rates of Completion: 64.3% vs 55.2% vs 46.7% vs 34.5% P=.09 Combined doses: 41% vs 27.6%, P=ns	NR	Low

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse or Relapse: ≥2 weeks, N (%) or longest consecutive period/ time to relapse, mean (SD)	Findings: T vs C Overall use, UA-confirmed	Findings: T vs C Retention in treatment	Findings: T vs C Treatment withdrawals due to AE; Severe AEs	Risk of bias
Schottenfeld, 2005[53] 1 site, US N=162 24 weeks	80 Methadone 35mg/d (40 CM, 40 PF) vs 82 Buprenorphine 4mg/d (39 CM, 43 PF) Manual guided counseling 2x/wk UA 3x/wk	Subgroup: Opioid Male: 66% Age: 36.2 (6.3) Race: 52% White; 36% AA/Black SES: NR	Max consecutive wks abstinence, mean (SD): MTD 5.5 (6.5) vs Bup 2.7 (4.7) P < .05	% UA(-), mean (SD): MTD 45.2% (34.3%) vs Bup 29.3% (31.2%) P<.05	54/80 (67.5%) vs 38/82 (46.3%) P<.05	SAE: 1	Low

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; BUP = Buprenorphine; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States; MA = methamphetamine; mg = milligrams; MI = Motivational Interviewing; MTD = Methadone; NOS = Not otherwise specified; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; PF = performance feedback; ROB = risk of bias; SAE = severe adverse event; SES = socioeconomic status; WD = withdrawal; wk = week; XR-NTX = Injectable Extended-Release Naltrexone

Anticonvulsants and Muscle Relaxants

Anticonvulsants

Summary of Findings

One systematic review and 1 newer trial provide evidence on the use of anticonvulsants for cocaine use disorder. The systematic review found moderate strength of evidence for no overall effect for anticonvulsants on cocaine use and treatment retention. One newer RCT found significantly lower cocaine use with topiramate, although the strength of evidence is insufficient. We found a significant increase in continuous abstinence in studies of topiramate, though the strength of evidence is low owing to methodological limitations. The effect of vigabatrin on continuous abstinence was unclear based on 2 studies with low strength of evidence. A meta-analysis of treatment retention in topiramate trials found moderate strength evidence of no difference in study retention between topiramate and placebo.

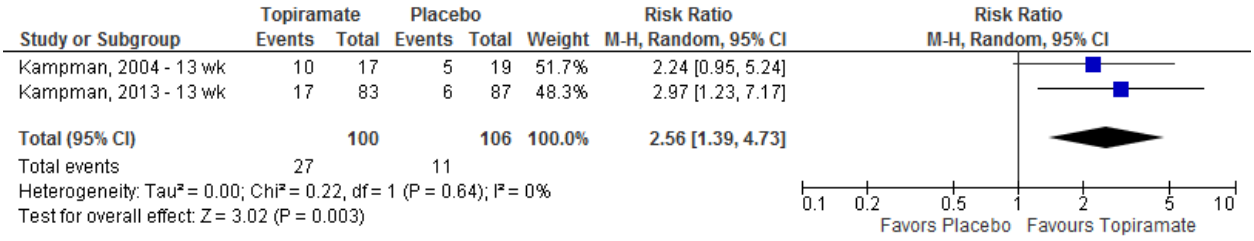
Detailed Findings

One previous systematic review (15 RCTs; N=1066) of anticonvulsant drugs examined carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and vigabatrin.[14] The review found moderate strength of evidence of no effect on dropout (RR 0.95; 95% CI: 0.86 to 1.05) or cocaine use (RR 0.92; 95% CI: 0.84 to 1.02) outcomes for any anticonvulsant.[14] In analyzing a single anticonvulsant versus placebo, they found no difference in dropout from treatment for any pharmacotherapy except gabapentin (significant difference favoring placebo [RR 2.78; 95% CI: 0.67 to 11.61]) and vigabatrin (favors treatment, although the results did not reach statistical significance [RR 0.74; 95% CI: 0.53 to 1.02]). For the cocaine use outcome there was no difference for any single pharmacotherapy versus placebo.[14]

Topiramate

Our search identified 1 additional, recent RCT of topiramate that showed promising abstinence (participants with all UA samples negative: P=0.002 for weeks 1-4 and 5-10, and P<.001 for weeks 11-12) and cocaine use results (the OR of obtaining a negative UA was 8.687; P<.001).[18] Retention between groups was identical. While we determined the risk of bias to be low, the trial had a relatively small sample size (N=60).[18](See Table 8 for study-level data, and Conclusions Table C for a summary of findings). Because the systematic review did not examine continuous abstinence as an outcome we also analyzed continuous abstinence data for those RCTs included in the SR which reported this outcome. Two unclear-ROB RCTs[66,67] examining topiramate provided low SOE of benefit (RR 2.56 [95% CI 1.39 to 4.73]) of topiramate for 2 or more weeks of continuous cocaine abstinence (see Figure 8a).

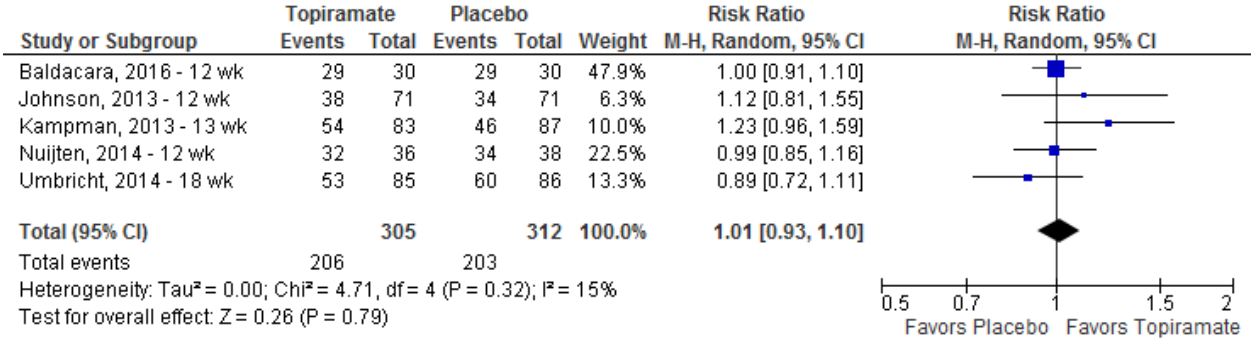
Figure 8a. Abstinence for 2+ continuous weeks in RCTs of topiramate vs placebo for cocaine use disorder



We also performed a meta-analysis of the study retention outcome for topiramate combining the new RCT[18] and 4 studies[67-70] included in the previous systematic review.[14] We found no difference in study retention between the topiramate and placebo groups; the combined OR for study completion was 1.13 (95% CI: 0.80 to 1.61). See Figure 8b for results.

Topiramate continues to be studied. One Phase II trial is under way studying the combination of Adderall-ER and topiramate for cocaine use disorder (NCT01811940). The results of this study were not available.

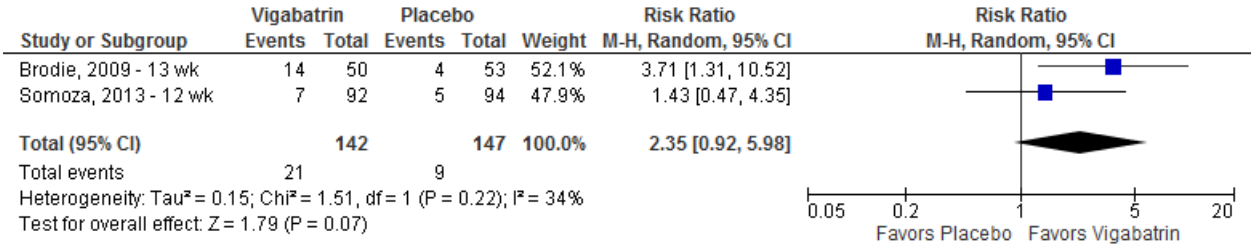
Figure 8b. Retention in studies comparing topiramate vs placebo for cocaine use disorder



Vigabatrin

Aside from the aforementioned retention findings in the previous systematic review, we analyzed data on continuous abstinence from individual RCTs included in the review. Two RCTs (1 unclear-,1 high-ROB) found low strength of evidence for unclear effects on continuous abstinence (RR 2.35; 95% 0.92 to 5.98).[71,72] These studies suffered from inconsistent findings and methodologic issues (incomplete data reported on continuous abstinence for the full trial period in both studies). See Figure 9 for details.

Figure 9. Abstinence for 2+ consecutive weeks in trials comparing vigabatrin vs placebo for cocaine use disorder



Muscle Relaxants

Summary of findings

From 2 trials we found low strength of evidence of no effect of baclofen on all outcomes of interest. There was no evidence for any other muscle relaxants.

Detailed findings

There is a paucity of evidence for the use of muscle relaxants for cocaine use disorder. No previous systematic reviews exist. We identified 2 trials of the muscle relaxant baclofen. One smaller study (N=70) was quality rated unclear for insufficient information reporting, and found no significant difference between groups on abstinence, cocaine use, or retention.[56] The other trial was larger (N=160), and had better reporting, but did not take frequent enough urine samples (one time per week) to validate the abstinence findings.[26] Cocaine use and retention findings were not significantly different.[26] Overall, there is low strength of evidence for no effect on any outcomes of interest with the use of muscle relaxants. See Table 8 for study-level data and Conclusions Table C for a summary of findings.

We performed a meta-analysis of the treatment retention outcome across these 2 studies (N=230).[26,56] One study enrolled 160 patients for 12 weeks,[26] and the other study enrolled 70 patients with 20 weeks follow-up.[56] Overall retention was much lower in the 20-week study (24.3% vs 71.9%), but in both studies there was no significant difference in retention between the treatment groups; the combined OR of study completion was 1.09 (95% CI 0.61 to 1.96). See Figure 10.

Figure 10. Retention in studies that compared baclofen vs placebo for cocaine use disorder

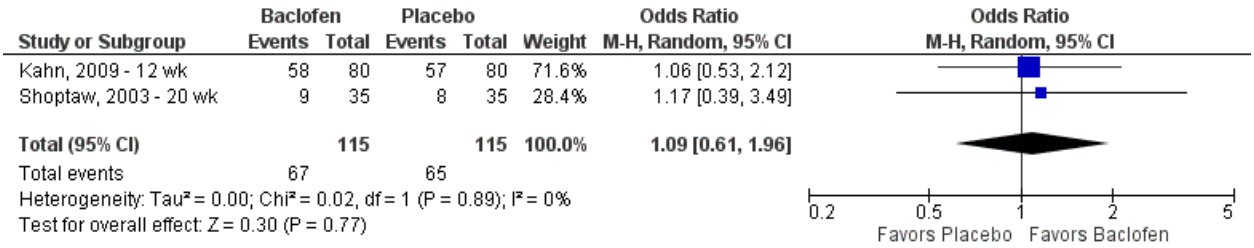


Table 8. Placebo-controlled trials of anticonvulsants/muscle relaxants for treating cocaine use disorder

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Abstinence, Lapse or Relapse, UA-confirmed: ≥2 weeks, N (%)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
Topiramate							
Baldacara, 2016[18] Single-site, outpatient (Brazil) N=60 12 wks follow-up	30 vs 30 Topiramate (200 mg/day) 12 wks 8 motivational interviews + group therapy 1x/wk; UA 2x/wk	100% Male Age: 28.6 (4.7) Race/SES: NR	N (%) with all UA(-) samples: Wks 1-4: 18 (60%) vs 6 (20%), P=.002 Wks 5-10: 19 (63.3%) vs 7 (23.3%), P=.002 Wks 11-12: 20 (66.7%) vs 4 (13.3%), P<.001	OR of obtaining a UA(-) over 12 wks: 8.687, P<.001	58 completed study: 29/30 (96.7%) vs 29/30 (96.7%)	WD: None Severe AEs: None	Low
Baclofen							
Kahn, 2009[26] 8 sites, outpatient (US) N=160 12 wks follow-up	80 vs 80 Baclofen (60mg/day) 8 wks 1 hr individual CBT weekly UA 1x/wk	78.8% Male Age: 42.3 (8.2) Race: 24% White; 63.3% AA/Black Education yrs: 13.0 (2.1) Employment: NR	Longest abstinence, days: 6.1 (6.8) vs 7.4 (9.7), P=.37	% who reduced use days to 75% or less of baseline rate: Baclofen 42.9, placebo 46.1, P= 0.75 % who reduced use days to 50% or less of baseline rate: Baclofen 15.6, Placebo 19.2, P=0.67	115 completed study: 58/80 (72.5%) vs 57/80 (71.3%) P=0.84	WD: NR Severe AEs: 3 (3.75%) vs 6 (7.5%)	Unclear; UA frequency not clearly specified

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse or Relapse, UA-confirmed: ≥2 weeks, N (%)	Findings: T vs C Overall use, UA-confirmed	Findings: T vs C Retention in treatment	Findings: T vs C Treatment withdrawals due to AE; Severe AEs	Risk of bias
Shoptaw, 2003[56] Single-site, outpatient (US) N=70 20 wks follow-up	35 vs 35 Baclofen 20mg/day 16 wks CBT group counseling 3x/wk UA 3x/wk	68.57% Male Age: 34.03 (6.4) Race: 20% White, 40% AA/Black Education yrs: 12.83 (2.5) Employment: days worked in month prior: 10.11 (9.8) vs 12.5 (13.1) P= 0.04	N (%) with 3 consecutive wks abstinence: 6 (17.14) vs 4 (11.43), P=ns Longest abstinence, days: 11.81 (17.7) vs 11.06 (21.5), P=ns	% of UA(-) samples, mean (SD): 64.23 (36.3) vs 52.44 (40.4), P=ns	17 completed study: 9/35 (25.7%) vs 8/35 (22.9%), P=ns	WD: 1 (2.9%) vs 0 Severe AEs: 3 (8.6%) vs 0	Unclear; insufficient information reported

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AA = African American; AE = adverse event; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); US = United States of America; MA = methamphetamine; mg = milligrams; NR = not reported; NS = not significant; OR = odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SES = socioeconomic status; sig = statistically significant; T = treatment group; UA = urinalysis; WD = withdrawal; wk(s) = week(s); yrs = years

Dopamine Agonists

A 2015 systematic review of 24 trials found no differences between any dopamine agonist and placebo on retention (moderate SOE), abstinence (low SOE), or adverse events (moderate SOE).[13] See Conclusions Table D for a summary of findings. Our search did not yield any recent trials of dopamine agonists for cocaine use disorder.

Other Pharmacotherapies

Nineteen additional studies examined the effects of other drugs or drug combinations for cocaine use disorder. Positive findings on abstinence and use reduction were reported in studies of doxazosin,[57] ondansetron,[24] propranolol,[29] and topiramate combined with mixed amphetamine salts.[38] As there was only one study on each of these medications, the strength of evidence for each is considered insufficient. Studies of amlodipine, carvedilol, celecoxib, citicoline, cocaine-metabolizing fusion protein TV-1380 (AlbuBChE), D-cycloserine, dehydroepiandrosterone (DHEA), galantamine, ginkgo biloba, magnesium L-aspartate hydrochloride, mecamylamine, metyrapone combined with oxazepam, N-acetylcysteine, pioglitazone, piracetam, and progesterone found no benefit on study retention, use, or abstinence.[22,25,27,30,32,33,35,37,38,47-49,55,58-60]

Pharmacotherapies for Comorbid Cocaine and Opioid Use Disorders

Antidepressants

Summary of Findings

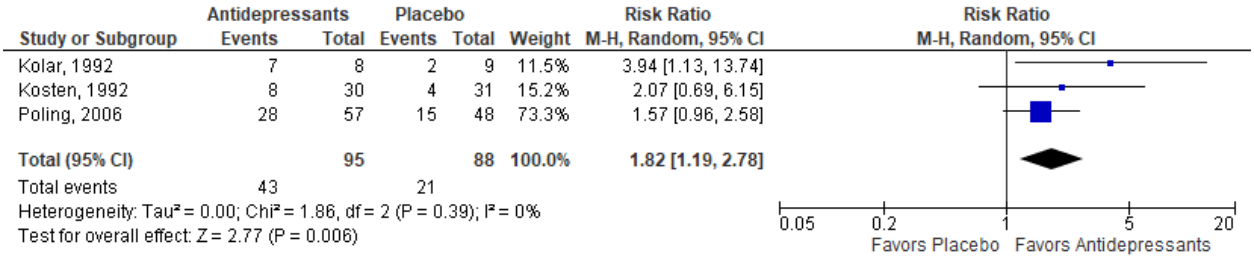
Data from 3 systematic reviews contribute to the evidence examining antidepressants (desipramine, fluoxetine, bupropion) for the treatment of cocaine use disorder in adults with comorbid opioid use disorder.[5,11,16] In general, there were very few high-quality studies, and a good number of studies were underpowered. As a class, there is low strength evidence that antidepressants are more effective than placebo for sustained abstinence.[11] There is moderate strength evidence that antidepressants are less effective than placebo for study retention and treatment withdrawals due to adverse events.[16] Although the evidence is insufficient due to small samples and quality concerns, studies in the systematic reviews reported that both desipramine[11] and bupropion[5,11] were more effective than placebo for sustained cocaine abstinence. There is moderate strength evidence that desipramine has no benefit for study retention, low strength evidence of no benefit of both fluoxetine and bupropion on retention, and low strength evidence of no difference between desipramine and placebo for treatment withdrawals due to adverse events.[16]

Detailed Findings

Evidence examining antidepressants for the treatment of cocaine use disorder in adults with comorbid opioid use disorder comes from 2 systematic reviews.[5,16] 3 RCTs[65,73,74] in a systematic review[11] contribute to low strength evidence that antidepressants are more effective than placebo for sustained abstinence (N=183; combined RR 1.82 [95% CI 1.19 to 2.78]; see Figure 11). There is moderate strength evidence that antidepressants are less effective than placebo for study retention (10 RCTs, N=1,006; combined RR 1.22 [95% CI 1.05 to 1.41]) and treatment withdrawals due to adverse events (5 RCTs, N=492; combined RR 2.47 [95% CI 1.03 to 5.90]).[16] Only 1 unclear-ROB study, included in both systematic reviews, examined cocaine use

during the trial period, and found no difference between antidepressants and placebo (see Conclusions Table E for a summary of findings).[5,11]

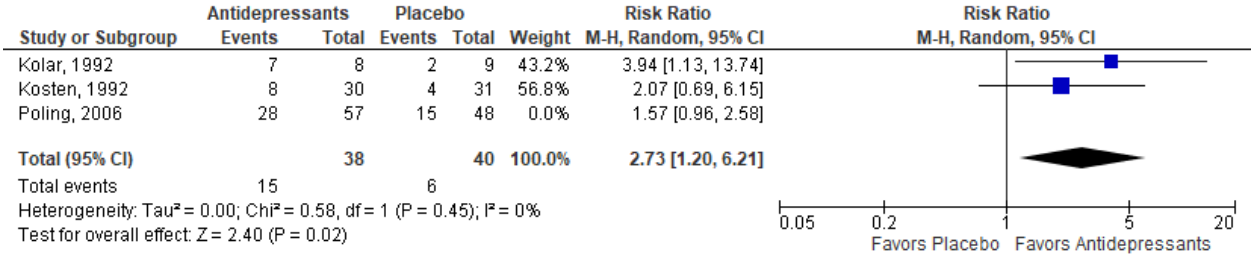
Figure 11. Abstinence in studies of antidepressants vs placebo in patients with dual opioid and cocaine use disorders



Tricyclic Antidepressants: Desipramine

Findings from 2 systematic reviews provide evidence examining desipramine for the treatment of cocaine use disorder in adults with comorbid opioid use disorder.[11,16] Two small, underpowered RCTs[73,74] in a systematic review[11] found that desipramine was more effective than placebo for sustained cocaine abstinence (N=78; combined RR 2.73 [95% CI 1.20 to 6.21]; see Figure 12); however the strength of evidence is insufficient due to the small sample and population heterogeneity. Six RCTs in a systematic review provide moderate strength evidence that desipramine is less effective than placebo for study retention (N=544; combined RR 0.86 [95% CI 0.74 to 0.99]), and the same review included 3 RCTs that provided low-strength evidence that desipramine is similar to placebo on treatment withdrawals due to adverse events (N=157; combined RR 1.66 [95% CI 0.35 to 7.96]).[16] We identified no evidence comparing desipramine to placebo on rates of severe adverse events in adults with comorbid cocaine and opioid use disorders (see Conclusions Table E for a summary of findings).

Figure 12. Abstinence in studies of desipramine vs placebo in patients with dual opioid and cocaine use disorders



Note. Poling, 2006[65] which examines bupropion is listed, but data are not included in the combined risk ratio.

Selective Serotonin Reuptake Inhibitors: Fluoxetine

Two (1 low-, 1 high-ROB) RCTs in a systematic review provide evidence examining fluoxetine for the treatment of cocaine use disorder in adults with comorbid opioid use disorder.[16] Both RCTs in the review provide low strength evidence that fluoxetine has no benefit over placebo for study retention, and a single low-ROB RCT provides insufficient evidence that treatment withdrawals due to adverse events may be greater in those receiving fluoxetine. No other outcomes of interest were reported (see Conclusions Table E for a summary of findings).

Bupropion

Two (1 unclear-, 1 high-ROB) RCTs in 2 systematic reviews provide evidence examining bupropion for the treatment of cocaine use disorder in adults with comorbid opioid use disorder.[5,16] One unclear-ROB RCT included in both reviews examined both cocaine use and sustained cocaine abstinence. Findings indicate better rates of sustained abstinence in participants receiving bupropion; however, there was no difference in study period cocaine use (SOE insufficient). Both RCTs contribute to low strength evidence of no difference between bupropion and placebo for study retention, and 1 high-ROB RCT provides insufficient evidence of similar rates of treatment withdrawals due to adverse events (see Conclusions Table E for a summary of findings).[16]

Antipsychotics

Summary of Findings

Evidence on the effectiveness of antipsychotics (aripiprazole, risperidone) for the treatment of cocaine use disorder in adults with comorbid opioid use disorder comes from a systematic review[12] and 1 very small RCT.[39] Findings indicate no difference between aripiprazole and placebo for cocaine use during the trial period, prevention of lapse and relapse, retention, and harms in participants abstinent at baseline, and no difference between risperidone and placebo for retention (SOE insufficient for all outcomes).

Detailed Findings

Aripiprazole

Evidence on the effectiveness of aripiprazole for the treatment of cocaine use disorder in adults with comorbid opioid use disorder comes from a systematic review[12] and 1 very small RCT.[39] The high-ROB RCT[39] compared aripiprazole to placebo, along with contingency management and individual counseling in methadone-maintained adults. Participants first went through a 12-week methadone stabilization phase that included contingency management and (unspecified) treatment, and those who achieved cocaine abstinence in weeks 11 and 12 were randomized to 15mg of aripiprazole or placebo (N=18), with contingency management continuing through the 2-week induction phase. Time to both lapse (first cocaine-positive urine sample; HR=0.45, 95% CI [0.14 to 1.42], P=0.17) and relapse (2 consecutive cocaine-positive urine samples or missed urines; (HR= 0.31, 95% CI [0.07 to 1.27], P=0.10) were similar between groups, and there was no difference in the longest duration of abstinence, retention, or harms. The study was discontinued early due to the small number of participants (18 of 41 enrolled) able to achieve abstinence in weeks 11 and 12 (see Table 9 for study details and Conclusions Table E for a summary of findings).

Risperidone

One unclear-ROB RCT in a systematic review provides insufficient evidence of no difference between risperidone and placebo on study retention.[12] No other outcomes of interest were reported (see Conclusions Table E for a summary of findings).

Table 9. Trials of antipsychotics for treating cocaine use disorder in patients with comorbid opioid use disorder

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Time to lapse and relapse, UA-confirmed	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
ATYPICAL ANTIPSYCHOTIC: *Aripiprazole*							
Moran, 2017[39] 1 site (US) N=18 (41 enrolled) All participants were abstinent at baseline 41 wks follow-up	9 vs 9 Aripiprazole 15mg/day (MTD) 12 wks CM during 2-week induction UA 3x /wk	94% Male Age: 46 Race: 12.5% White, 81% AA/Black Education: 12.5 yrs Unemployed: 12.5%	M (SEM) longest duration of abstinence: 20.11 (4.87) vs 14.89 (4.19), P = 0.43 There was no difference in time to lapse (HR = 0.51, 95% CI [0.18, 1.48], P = 0.21]. There was no difference in time to lapse.	M% (SEM) of UA (-) samples: 58% (12%) vs 55% (11%), P = 0.66	14 completed study: 8 (89%) vs 6 (67%)	WD: 0 (0%) vs 1 (11%) Severe AEs: NR	High

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States of America; MA = methamphetamine; mg = milligrams; MI = Motivational Interviewing; MTD = maximum tolerated dose; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SEM = standard error of the mean; SES = socioeconomic status; sig = statistically significant; T = treatment group; TTM = Transtheoretical Model; UA = urinalysis; wk(s) = week(s); yrs = years.

Psychostimulants

Summary of Findings

Evidence related to the effectiveness of psychostimulants (dexamphetamine, mazindol) for the treatment of cocaine use disorder in adults with comorbid opioid use disorder comes from 2 systematic reviews.[5,11] There is low strength evidence that psychostimulants as a class are more effective in preventing cocaine use during studies[11] and that there is no difference between psychostimulants and placebo for sustained abstinence[11] and retention.[5] One RCT in a systematic review found that dexamphetamine was more effective than placebo for sustained cocaine abstinence (SOE insufficient).[5] There were no differences across other outcomes for both dexamphetamine and mazindol.

Detailed Findings

Two systematic reviews provide evidence related to the effectiveness of psychostimulants (dexamphetamine, mazindol) for the treatment of cocaine use disorder in adults with comorbid opioid use disorder.[5,11] Pooled findings from three (2 unclear-, 1 high-ROB) RCTs[75-77] in the review provide low strength evidence both that psychostimulants as a class are more effective in preventing cocaine use during trials (N=115; SMD 0.35 [95% CI -0.05 to 0.74] see Figure 13).[11] Two (1 unclear-, 1 high-ROB) RCTs[75,76] in the systematic review provide pooled evidence of no difference between psychostimulants and placebo for sustained cocaine abstinence (see Figure 14).[11] No difference was reported for study retention (1 unclear-, 2 high-ROB RCTs; see Conclusions Table E for a summary of findings).[5]

Figure 13. Cocaine-free UA samples in studies of psychostimulants vs placebo in patients with dual opioid/cocaine use disorder

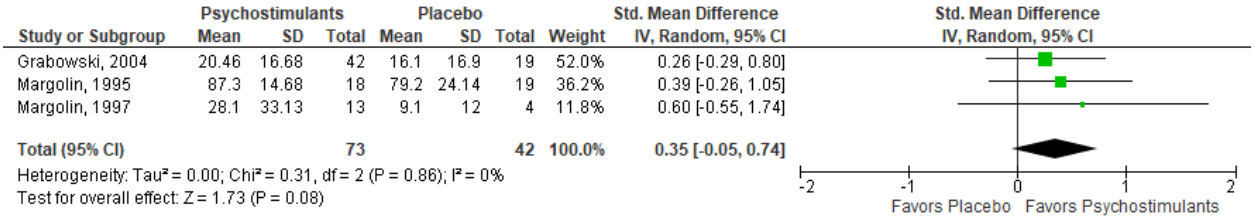
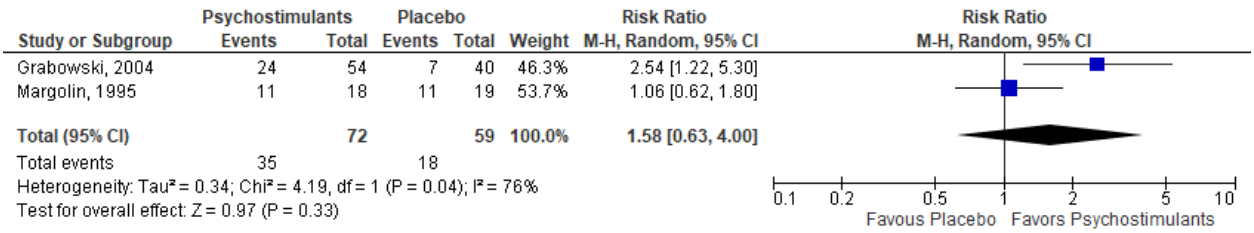


Figure 14. Abstinence in studies comparing psychostimulants vs placebo in patients with dual opioid/cocaine use disorders



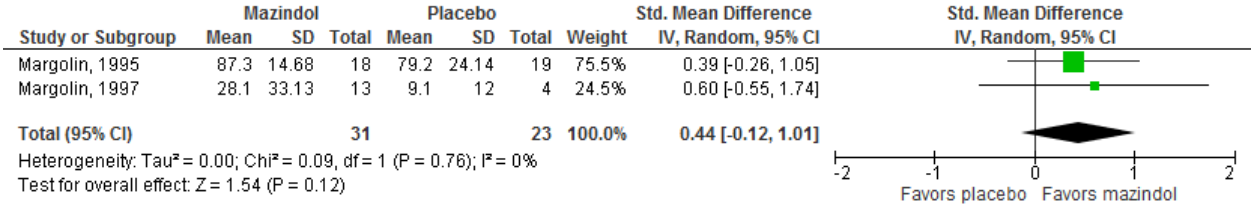
Dexamphetamine

One high-ROB RCT[75] included in 2 systematic reviews[5,11] provides evidence examining the use of dexamphetamine for the treatment of cocaine use disorder in adults with comorbid opioid use disorder. There is insufficient evidence suggesting that dexamphetamine may be more effective than placebo in the achievement of sustained cocaine abstinence (N=94; RR 2.54 [95% CI 1.22 to 5.30]).[5,11] No differences were found for cocaine use during the trial period (N=61; SMD 0.26 [95% CI -0.29 to 0.80])[11] or retention (N=94; RR 1.78 [95% CI 0.96 to 3.29])[5] (SOE insufficient). No evidence related to harms was reported (see Conclusions Table E for a summary of findings).

Mazindol

Two small, unclear-ROB RCTs[76,77] included in 2 systematic reviews[5,11] provide insufficient evidence examining the use of mazindol for the treatment of cocaine use disorder in in adults with comorbid opioid use disorder. One small unclear-ROB RCT found no difference in sustained cocaine abstinence (N=37; RR 1.06 [95% CI 0.62 to 1.80]),[11] and 2 underpowered unclear-ROB RCTs found no difference on cocaine use (N=54; SMD 0.44 [95% CI -0.12 to 1.01]; see Figure 15)[11]and study retention (see Conclusions Table E for a summary of findings).[5]

Figure 15. Cocaine-free UA samples in studies of psychostimulants (Mazindol) vs placebo in patients with dual opioid/cocaine use disorder



Anticonvulsants

Summary of Findings

In a previous systematic review, a meta-analysis of 2 trials of the GABAergic drugs tiagabine and gabapentin found no difference in abstinence.[11] The combined RR was 1.02 (95% CI 0.56 to 1.89).[11]

Varenicline

An unclear-ROB study conducted in 31 patients with dependence on multiple substances (cocaine, tobacco, and opioids) reported no differences in retention between varenicline and placebo, or cocaine use throughout the study.[45] See Conclusions Table F for a summary of findings.

KEY QUESTION 2: Are there known subpopulations for whom different forms of pharmacotherapy is most/least effective for cocaine use disorder?

Summary of Findings

We identified 11 RCTs and 1 systematic review that examine subgroup differences in adults with cocaine use disorder. Included subgroups are: cocaine severity at baseline,[23,56] cocaine abstinent or negative at baseline,[19,46] gender,[19,43,62] comorbid or lifetime alcohol use disorder,[19-21] comorbid opioid use disorder,[39] cannabis use,[56] comorbid ADHD,[5] comorbid depression,[46] and genetic variations.[78,31]

Overall, findings are inconclusive due to the limited number of studies examining each subpopulation and are hampered by the methodological issues frequently observed in studies of this population. However, it is possible that baclofen and naltrexone may be particularly effective when treating chronic/long-term cocaine users.[23,56] In addition, the ability to achieve abstinence or produce a cocaine-negative urine sample may be a good predictor of treatment success[19,46]; certain drug therapies such as buspirone and naltrexone may have a lesser,[43] or even a negative effect in women than in men[62]; adults with comorbid depression who experience a clinically significant mood response to venlafaxine may experience better results[46]; and chronic heroin users may benefit from a combination of methadone and aripiprazole.[39] Findings suggest no differences in effect by self-reported cannabis use,[56] the presence of alcohol use disorder[19-21] or ADHD,[5] and it is possible that genetic variations may play a role in treatment response.[78]

Findings by Subpopulation

Cocaine Severity at Baseline

Two RCTs examined differences in cocaine use by cocaine addiction severity at baseline.[23,56] Trials examined included baclofen[56] and naltrexone[23] in combination with CBT. In both studies, participants who were more severely addicted at baseline experienced greater benefit from the treatment, as compared to control. For participants receiving baclofen, baseline severity of cocaine use was positively related to a reduction in cocaine use over the study period (P=.001), with more severe use at baseline significantly associated with a greater reduction in use. In addition, findings indicate that although baclofen was more effective than placebo for a reduction in cocaine-positive UAs for the full sample, the greatest benefit was experienced by participants who presented with patterns of chronic use.[56] Findings for naltrexone indicate a non-significant trend favoring naltrexone over placebo in the increase of cocaine-negative UAs for heavy users. No such trend was identified for the full sample (see Table 10 for more detail).[23]

Cocaine Abstinent or Negative at Baseline

Two RCTs examined differences in the effect of pharmacotherapy by baseline abstinence.[19,46] Trials examined memantine[19] and venlafaxine[46] in combination with relapse prevention therapy. One study compared differences in participants who achieved abstinence during a 2-week placebo lead-in,[19] and the other reported differences by the baseline cocaine UA.[46] Neither study found a significant interaction between the treatment and cocaine abstinence or negative UAs; however, participants who had achieved abstinence or who provided a negative sample at baseline had more study period cocaine-negative UAs[19,46] and a higher rate of achieving

sustained abstinence,[19] regardless of condition. No difference was found for study retention (see Table 10 for more detail).

Gender

Three RCTs examined the differential impact of gender on pharmacological treatments for cocaine use disorder.[19,43,62] Trials examined naltrexone,[43] buspirone,[62] and memantine.[19] One RCT,[62] which compared buspirone to placebo in abstinent adults, found that although there was no benefit of buspirone on outcomes of interest in the full sample, women receiving buspirone experienced an increase in cocaine use (c^2 [1]=6.06, P=0.01) early in the study. In addition, there was a nonsignificant trend for a shorter time to lapse in women receiving buspirone (c^2[1]=3.20, P=.067). No such relationship was identified for men. The second RCT,[43] that compared naltrexone to placebo found a significant difference in the rates of increase of cocaine use by gender (Z=2.21, P = 0.03). For men with comorbid alcohol and cocaine use disorders, 150mg/day of naltrexone was more effective than placebo. However, in women naltrexone was less effective. Finally, in a RCT comparing memantine to placebo,[19] there was no difference in cocaine-negative samples by gender during the study, and the interaction between treatment and gender was nonsignificant (see Table 10 for more detail).

Comorbid or Lifetime Alcohol Use Disorder

Three RCTs examined the differential effect of pharmacological treatments for cocaine use disorder in adults with and without comorbid or lifetime alcohol use disorder.[19-21] Two RCTs compared disulfiram to placebo,[20,21] 1 in conjunction with CBT and CM,[20]. Neither trial found a difference between disulfiram and placebo for cocaine use in the full sample. However, when analyses were limited to participants with alcohol use disorder, 1 study found that disulfiram was more effective than placebo (t=4.26, P=.04), and the other did not.[20] The third RCT[19] compared memantine to placebo, and found no difference in cocaine-negative urine samples during the study, and the interaction between treatment and alcohol use disorder was nonsignificant (see Table 10 for more detail).

Comorbid Opioid Use Disorder

One underpowered RCT[39] comparing aripiprazole to placebo in adults with comorbid opioid use disorder explored differences in outcomes by years of heroin use. The study found that years of heroin use was positively related to a longer time to lapse, with a nonsignificant trend for time to relapse. There was no difference in frequency of lapse by years of heroin use (see Table 10 for more detail).

Six of the 7 included trials of disulfiram for cocaine use disorder were conducted in subjects with comorbid opioid dependence.[21,31,40,52,63,64] The findings in KQ1 for disulfiram therefore largely reflect the experience of this subpopulation.

Subjects with comorbid opioid disorder randomized to disulfiram had lower retention compared with placebo (moderate SOE), and the combined estimate became slightly more significant (RR 0.88, 95% CI 0.79 to 0.98) upon excluding the only study conducted in non-opioid dependent subjects.[20]

Abstinence was similar between disulfiram and placebo in two studies[52,63] of patients with comorbid opioid disorder (combined N = 197; low SOE). Statistical heterogeneity between the two studies was not significant for this outcome (P=0.73).

The effects of disulfiram on overall cocaine use were significantly heterogeneous (P<.00001) among the 3 studies in patients with comorbid opioid disorder that reported this outcome (insufficient SOE).[21,31,40]

Cannabis Use

One RCT[56] that compared baclofen to placebo examined differences between participants who self-reported cannabis use at baseline to those who did not. No difference in cocaine-negative urine samples during the trial was identified (see Table 10 for more detail).

Comorbid Attention Deficit Hyperactivity Disorder

A systematic review of 26 RCTs examining psychostimulants (including bupropion) for cocaine use disorder[5] performed subgroup analyses comparing studies with and without comorbid ADHD as a requirement for inclusion. They found no significant differences between participants with and without ADHD on any outcome of interest (see Table 10 for more detail).

Comorbid Depression

One RCT[46] that compared venlafaxine to placebo along with weekly CBT in adults with comorbid depression and cocaine use disorder, examined whether there were differences in cocaine response by mood response. Although they found no significant interaction between mood response and treatment condition, participants who experienced a clinically significant mood response had more cocaine-negative urine samples during the study (P < 0.0068). In addition, mood responders achieved 3 or more weeks abstinence at a higher rate than non-responders, although the trend was not significant (P=0.07; see Table 10 for more detail).

Genetic Variations

One RCT[78] comparing disulfiram to placebo evaluated the role of the ADRA1A gene polymorphism on cocaine-negative urine samples by comparing individuals with at least one T allele of rs1048101 (TT or TC) to those who are homozygous (CC). The study found that for participants with the TT/TC genotype, disulfiram was more effective than placebo for cocaine-negative samples during the study (F=17.1, df=1.358; P<0.00005). There was no difference between disulfiram and placebo for those with the CC genotype.

Another RCT[31] that compared disulfiram to placebo examined the role of the dopamine B-hydroxylase (DBH) gene polymorphism, which reduces DBH enzyme levels, on increasing cocaine-free urines with disulfiram. Participants were divided into two DBH genotype groups: those with a T allele of rs1611115 (CT/TT genotype) to those who were homozygous (CC genotype). The study found that those with normal levels of DBH (CC) had more cocaine-positive urines (F=17.2, P<.00005) than those with lower levels of DBH (CT/TT) (F=1.12, P>.05). See Table 10 for more detail.

Table 10. Subgroup analyses in studies of pharmacotherapy for cocaine use disorder, stratified by population characteristic

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Abstinence, Lapse, Relapse	Use	Retention	Summary of findings
Cocaine Severity at Baseline					
Shoptaw 2003[56]	35 vs 35 Baclofen 20mg/day 16 wks CBT group counseling 3x/wk UA 3x/wk	NR	For participants receiving baclofen, baseline cocaine use was positively related to a reduction in cocaine use over the study period (P=.001), with more severe use at baseline significantly associated with a greater reduction in use. There was no relationship between baseline severity and use in participants receiving placebo.	NR	Baseline severity was positively related to greater reductions in cocaine use for participants assigned to baclofen, but not placebo.
Hersh 1998[23]	31 vs 33 50mg NTX/day 8 wks Individual relapse prevention psychotherapy 1-2/wk UA 2x/wk	NR	In participants with higher pre-treatment cocaine use, there was a nonsignificant trend favoring naltrexone for study period negative UAs (P=0.082).	NR	In participants with higher pre-treatment cocaine use, there was a nonsignificant trend favoring naltrexone for study period negative UAs.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Abstinence, Lapse, Relapse	Use	Retention	Summary of findings
Cocaine Abstinent or Negative at Baseline					
Bisaga, 2010[19] 1 site (US) Baseline N=81, Abstinent at Baseline N=36 16 wks follow-up	Memantine 40 mg/day 12 wks 2 wk placebo lead-in prior to randomization CM (wks 1-4), MET (wks 1-4), 1x/wk relapse prevention therapy (CBT) UA 3x/wk	No difference between memantine and placebo on abstinence. The interaction between treatment and baseline abstinence was nonsignificant. However, more participants who were abstinent at baseline achieved sustained abstinence (P = 0.01).	Participants who were abstinent at baseline had more cocaine-negative urine samples during the study (P < 0.0001); however, the interaction between treatment and baseline abstinence was nonsignificant.	There was no difference in retention by baseline abstinence.	Ss abstinent at baseline achieved sustained abstinence more frequently and had more cocaine-negative urine samples; however, the interaction between treatment and baseline abstinence was nonsignificant. No relationship between baseline abstinence and study retention.
Raby, 2014[46] 1 site (US) N=130 12 wks follow-up	64 vs 66 Venlafaxine Up to 300 mg/day 12 wks 1x/wk individual relapse prevention therapy (CBT, MI) UA 2x/wk	NR	Participants who were provided a cocaine-negative UA at baseline had more cocaine-negative urine samples during the study (P<0.0001); however, the interaction between treatment and baseline abstinence was nonsignificant (P=0.87)	NR	Participants who were abstinent at baseline had more cocaine-negative urine samples during the study; however, the interaction between treatment and baseline abstinence was nonsignificant

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Abstinence, Lapse, Relapse	Use	Retention	Summary of findings
Gender					
Bisaga, 2010[19] 1 site (US) Baseline N=81 (79% Male) 16 wks follow-up	Memantine 40 mg/day 12 wks 2 wk placebo lead-in prior to randomization CM (wks 1-4), MET (wks 1-4), 1x/wk relapse prevention therapy (CBT) UA 3x/wk	NR	There was no difference in cocaine-negative samples by gender during the study, and the interaction between treatment and gender was nonsignificant.	NR	There was no difference in cocaine-negative samples by gender during the study, and the interaction between treatment and gender was nonsignificant.
Winhusen, 2014[62] 6 sites (US) N=62 (63% Male) 12-19 days residential, remaining outpatient 16 wks follow-up	35 vs 27 Buspirone 60 mg/day or MTD 15 wks CM Inpatient/residential (psychosocial TAU, Outpatient TAU (min of 60 min 1x/wk individual or group psychosocial treatment) UA 1x/wk	In women but not men, there was a nonsignificant trend for a shorter time to lapse in participants receiving buspirone (c2=3.20, P=.067).	In women but not men, there was an increase in cocaine use by participants receiving buspirone early in the outpatient treatment phase (c2=6.06, P=0.01).	NR	There was no benefit of buspirone on outcomes of interest in the full sample. However, buspirone may increase cocaine use and may result in a shorter time to lapse in women but not men.
Pettinati, 2008[43] (N=116 men, N=48 women)	82 vs 82 150mg/day naltrexone 12 wks CBT - 45 min/week; vs BRENDA- 30 min, weekly- manualized psychosocial intervention. UA 1x/wk	NR	There were significant differences in the rates of increase of cocaine use by gender (Z=2.21, P = 0.03). For men with comorbid alcohol and cocaine use disorders, 150mg/day of naltrexone was more effective than placebo. However, in women naltrexone was less effective.	NR	For men with comorbid alcohol and cocaine use disorders, 150mg/day of naltrexone was more effective than placebo. However, in women naltrexone was less effective.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Abstinence, Lapse, Relapse	Use	Retention	Summary of findings
Comorbid or Lifetime Alcohol Use Disorder					
Bisaga, 2010[19] 1 site (US) Baseline N=81, Abstinent at Baseline N=36 16 wks follow-up	Memantine 40 mg/day 12 wks CM (wks 1-4), MET (wks 1-4), 1x/wk relapse prevention therapy (CBT) UA 3x/wk	NR	There was no difference in cocaine-negative samples when comparing participants with and without comorbid alcohol use disorder, and the interaction between treatment and alcohol use disorder was nonsignificant.	NR	Comorbid alcohol use disorder was not related to differences in cocaine use during the study.
Carroll, 2012[21] Alcohol use disorder N=70 Comorbid OUD population	59 vs 53 disulfram 250mg/day 12 weeks 12-step facilitation weekly vs. standard counseling sessions UA 3x weekly	NR	There was no benefit of disulfiram on study period cocaine use over placebo for the full sample. However, when limited to participants with alcohol use disorder, disulfiram was more effective than placebo (t=4.26, P=.04).	NR	There was no benefit of disulfiram on study period cocaine use over placebo for the full sample. However, when limited to participants with alcohol use disorder, disulfiram was more effective than placebo.
Carroll 2016[20] Alcohol use disorder N=74	51 vs 48 disulfram 250mg/day 12 weeks CBT +/- CM UA 3x/wk	NR	In both the full sample and in those with comorbid alcohol use disorder, disulfiram (with or without CM) had no effect on study period negative UAs.	NR	There were no differences between disulfiram and placebo for the full sample or for those with alcohol use disorders.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Abstinence, Lapse, Relapse	Use	Retention	Summary of findings
Comorbid Opioid Use Disorder: Years of Heroin Use					
Moran, 2017[39] N=18 (41 randomized) All participants were abstinent at baseline 41wks follow-up	9 vs 9 Aripiprazole 15mg/day (MTD) 12 wks CM+ methadone + 1x/week individual counseling UA 3x /wk	Lapse: More years of heroin use was associated with longer latency to lapse (HR = 0.89 [95% CI 0.80 to 0.99], P < 0.05), but was not related to the risk of lapse (HR = 0.48 [95% CI 0.11 to 2.19], P = 0.35). Relapse: There was a nonsignificant trend towards years of heroin use as predictor of longer latency to relapse (P = 0.07).	NR	NR	Years of heroin use was positively related to a longer time to lapse, with a nonsignificant positive trend for time to relapse. There was no difference in frequency of lapse by years of heroin use.
Cannabis Use					
Shoptaw 2003[56]	35 vs 35 Baclofen 20mg/day 16 wks CBT group counseling 3x/wk UA 3x/wk	NR	There was no relationship between self-reported cannabis use at baseline and cocaine-negative urine samples during the study.	NR	There was no relationship between self-reported cannabis use at baseline and cocaine-negative urine samples during the study.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Abstinence, Lapse, Relapse	Use	Retention	Summary of findings
Comorbid ADHD					
Castells, 2016[5] Systematic review of 26 RCTs	Psychostimulants (includes bupropion)	There was no difference between participants with comorbid ADHD (2 RCTs, N=232) and those without, in the achievement of sustained abstinence (P=0.11).	There was no difference between participants with comorbid ADHD (2 RCTs, N=154) and those without (6 RCTs, N=372) in cocaine-negative urine samples (P=0.21).	There was no difference between participants with comorbid ADHD (3 RCTs, N=180) and those without (21 RCTs, N=1,925) in retention (P=0.34).	There were no significant differences between participants with and without ADHD on any outcome of interest.
Comorbid Depression – Mood Responders					
Raby, 2014[46] 1 site (US) N=130 *Mood responder N=48, Mood non-responder N=82 12 wks follow-up	Venlafaxine 30 mg/day 12 wks 1x/wk individual relapse prevention therapy (CBT, MI) UA 2x/wk	There was a nonsignificant trend towards more participants who experienced a clinically significant mood response achieving 3+ week abstinence (P=0.07); however, the interaction between treatment and mood response was nonsignificant.	Participants who experienced a clinically significant mood response had more cocaine-negative urine samples during the study (P < 0.0068); however, the interaction between treatment and mood response was nonsignificant.	NR	Mood response was significantly related to fewer positive UAs. Although not significant, more mood responders achieved 3+ week abstinence.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Abstinence, Lapse, Relapse	Use	Retention	Summary of findings
Genetic Variations					
Shorter, 2013[78] ADRA1A genotype: TT or TC N=47, CC N=22	Disulfiram 250mg/day 12 wks Methadone maintenance and weekly CBT UA 3x/wk	NR	For participants with the TT/TC genotype, disulfiram was more effective than placebo for cocaine-negative samples during the study (F=17.1, df=1.358; P<0.00005). There was no difference between disulfiram and placebo for those with the CC genotype.	NR	Disulfiram was more effective than placebo for cocaine-negative samples over the study period for participants with the TT/TC genotype, but not the CC genotype.
Kosten, 2013[31]	Disulfiram 250mg/day 12 wks Methadone maintenance and weekly CBT UA 3x/wk	NR	Participants with the CC genotype dropped from 84% to 56% on disulfiram. Those with the CT/TT genotype showed no disulfiram effect.	NR	The DBH genotype of a patient could be used to determine the efficacy of disulfiram pharmacotherapy for cocaine use disorder.

Abbreviations: AA = African American; ADHD = attention deficit hyperactivity disorder; AE = adverse event; BBCET = Brief Behavioral Compliance Enhancement Therapy; CBT = Cognitive Behavioral Therapy; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; HIV = human immunodeficiency virus; P = p-value; MI = Motivational Interviewing; MTD = Methadone; NR = Not reported; P = p-value; RCT = randomized control trial; RR = Risk ratio; Ss = subjects; UA = urinalysis; US = United States

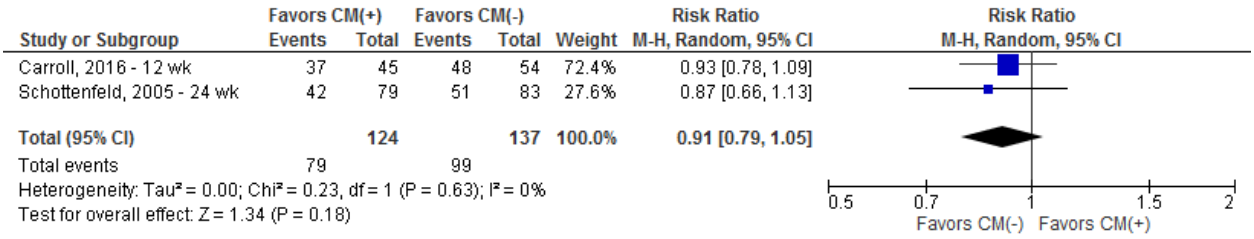
Subgroup Analysis of Contingency Management as a Co-intervention

In the substance use disorder literature there is evidence to support the effectiveness of contingency management (CM) in treatment retention.[79,80] We examined whether the effectiveness of pharmacologic therapy differed according to whether patients were also receiving CM.

Among studies in patients with cocaine use disorder, 6 RCTs representing 4 drug classes provided CM to participants in all study arms.[19,36,39,41,61,62] In 18 other studies,[17,18,21,23,26,28,31,34,40,42-46,50-52,54,56,78] CM was not offered to any participants during the trial, of which 14 provided retention data. Retention among studies that offered CM to all participants was 59.3%, compared with 66.1% among studies that did not offer CM. Because of the variety of pharmacotherapies they used, these studies are not directly comparable.

Three multifactorial trials (representing 3 drug classes) directly compared use versus non-use of CM within active treatment and placebo groups.[20,50,53] Only 2 of these studies provided retention data.[20,53] Patients randomized to receive CM in these studies tended to be less likely to complete treatment compared to patients who did not receive CM (RR 0.91, 95% CI 0.79 to 1.05), although the combined estimate did not reach statistical significance (see Figure 16 for details). Because there were only 2 studies that directly examined the effects of CM, and the medications used in each study were not directly comparable, it is difficult to draw conclusions.

Figure 16. Retention in studies that directly compared CM(+) vs CM(-) in patients with cocaine use disorder



KEY QUESTION 3: What are the benefits and harms of pharmacotherapy for Amphetamine/methamphetamine use disorder?

Summary of Findings

We identified 14 RCTs and 1 systematic review that examined outcomes of interest of pharmacotherapy for amphetamine/methamphetamine use disorder. Pharmacotherapies examined included bupropion, mirtazapine, sertraline, aripiprazole, modafinil, dexamphetamine, methylphenidate, topiramate, baclofen, gabapentin, and naltrexone.

Similar to the body of research examining pharmacotherapy for cocaine use disorder, studies evaluating pharmacotherapy for amphetamine/methamphetamine use disorders were largely of low or unclear quality and underpowered. Co-interventions differed widely, and rates of retention varied greatly. Some studies examined methamphetamine or amphetamine use disorders exclusively, and others combined the two. For nearly all of the pharmacotherapies and almost all of the outcomes, findings were either null or insufficient to form conclusions. We identified only 1 pharmacotherapeutic for which there may be the potential for benefit. There is low strength evidence that methylphenidate may result in a reduction in use.

We identified only 1 unclear risk of bias RCT with a comorbid amphetamine/methamphetamine and opioid use disorder sample. Although the findings are insufficient from which to draw conclusions, the study found that naltrexone improved study retention.

Antidepressants

Summary of Findings

One systematic review[81] and 3 additional trials[82-84] provide evidence on the use of antidepressants for methamphetamine use disorder. Overall, studies found no difference between antidepressants as a class over placebo for sustained abstinence (SOE low), study retention (SOE moderate), or severe adverse events (SOE low), and mixed findings related to methamphetamine use during the trial period. Similarly, no specific antidepressant (*ie*, sertraline, mirtazapine, bupropion) was found to have positive benefit over placebo on any outcome of interest.

Detailed Findings

One systematic review[81] and 3 additional trials[82-84] provide evidence on the use of antidepressants for methamphetamine use disorder. The systematic review[81] focused on psychostimulants for methamphetamine use disorders; however, it included 6 RCTs of bupropion, which we classified as an antidepressant. One newer included trial also examined bupropion,[82] and other trials examined mirtazapine,[84] and sertraline.[83]

Findings from 3 RCTs in the systematic review[81] (N=361; combined OR 1.12 [95% CI 0.54 to 2.33]) and one additional unclear-ROB RCT[83] provide low strength evidence that antidepressants as a class are no different than placebo for the achievement of sustained abstinence. There is moderate strength evidence that antidepressants are not beneficial for study retention (based on 4 RCTs in the systematic review[81] and 3 additional RCTs[82-84]), and low strength evidence that they are similar to placebo in treatment withdrawals due to adverse events (based on 1 unclear[82] and 1 high-ROB RCT[84]). Findings related to methamphetamine use during the studies were mixed, with no benefit of antidepressants on use reported by the systematic review[81] a modest, but non-

significant trend favoring bupropion reported by 1 RCT,[82] and findings of positive benefit reported in a small, high-ROB RCT[84] (see Table 11 for study-level data and Conclusions Table G for a summary of findings).

Selective Serotonin Reuptake Inhibitors (SSRIs): Sertraline

A 12-week, unclear-ROB RCT (N=229)[83] compared 100mg sertraline with and without contingency management (incentivizing negative urine screens) to placebo with and without continency management. All participants received 2 weeks of twice-weekly recovery skills group sessions, followed by 13 weeks of 90 minute thrice-weekly relapse prevention groups. When all 4 groups were compared, significantly fewer participants receiving sertraline alone achieved abstinence, ($\chi^2[3] = 8.6$, $P = 0.035$). When all participants receiving sertraline were compared to those receiving placebo, there was a strong trend favoring placebo ($\chi^2[1] = 3.8$, $P = 0.052$). In addition, participants receiving sertraline were retained for significantly less time than those receiving placebo ($\chi^2[3] = 8.40$, $P < 0.05$). No other outcomes of interest were examined (see Table 11 for study-level data and Conclusions Table G for a summary of findings).

Atypical Antidepressant: Mirtazapine

One small, 12-week, high-ROB RCT (N=60)[84] compared 30mg of mirtazapine to placebo. Participants were men who have sex with men (MSM), and both groups received once-weekly individual substance use counseling. Findings indicate that participants who received mirtazapine had more negative UAs over the study period (RR 0.57; 95% CI [0.35 to 0.93], P = 0.02), but there was no difference in retention or severe adverse events (see Table 11 for study-level data and Conclusions Table G for a summary of findings).

Aminoketone: Bupropion

Four RCTs (1 unclear-, 3 high-ROB) in the systematic review[81] and 1 unclear-ROB RCT from our search of primary studies provide evidence examining the use of bupropion for the treatment of methamphetamine use disorder. The RCT was an 18-week multi-site trial (N=151) comparing 300mg of bupropion to placebo.[82] All participants received 90-minute CBT-relapse prevention group therapy 3 times per week. Results indicate no difference between bupropion and placebo on methamphetamine use during the studies, and a non-significant trend favoring bupropion in the rate of reduction (P=0.09). These findings, along with those of 3 high-ROB RCTs in the systematic review,[81] provide low strength evidence of no difference between bupropion and placebo for reducing methamphetamine use. Combining the 5 RCTs provided moderate strength evidence that bupropion has no benefit over placebo for study retention (OR 1.10 [95% CI 0.73 to 1.67]). Three RCTs in the systematic review provide low strength evidence of no difference between bupropion and placebo on sustained abstinence (N=361; combined OR of 1.12 [95% CI 0.54 to 2.33]). There was no difference in reported severe adverse events (see Table 11 for study-level data and Conclusions Table G for a summary of findings).

Table 11. Placebo-controlled trials of antidepressants for treating methamphetamine use disorder

Setting Total N* Mean follow-up	N, T vs C; Dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Abstinence, UA-confirmed ≥2 weeks, N (%)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
AMINOKETONE: *Bupropion*							
Elkashef 2008[82] 5 sites (US) N=151 18 wks follow-up	79 vs 72 Bupropion SR 300 mg/day 12 wks 90 min/3x weekly CBT-relapse prevention group UA 3x/wk	67% male Age: 36 Race: 75% White, 3% AA/Black Education yrs: 12.5 Employment: NR	NR	N (%) week 12 UA (-): 42 (54%) vs 32 (44%) Modest trend for improvement over the treatment period (favors T), P = 0.09 Rate of reduction, P = 0.15	79 completed study: 41 (51.9%) vs 38 (52.8%)	WD: NR Severe AEs: 5 (6.3%) vs 8 (11.1%)	Unclear
ATYPICAL ANTIDEPRESSANTS: *Mirtazapine*							
Colfax, 2011[84] 1 site (US) N=60 12 wks follow-up	30 vs 30 Mitrazapine 30 mg/day 12 wks 30 min 1x/week individual substance use counseling (CBT/MI) UA 1x/wk	100%Male Age: 40.5 (9.0) Race: 62% White; 18% AA/Black Veteran/homeless: NR Education: 25% high school highest level of attainment Employment: 60% Unemployed	NR	N (%) week 12 UA (-): 18 (56%) vs 13 (37%). % of participants with UA (-) from baseline to week 12: 40% vs 6% UA (-) increased faster for T: RR = 0.57, 95% CI [0.35, 0.93], P = 0.02	56 completed study: 28 (93%) vs 28 (93%)	WD: NR Severe AEs: 1 (3%) vs 1 (3%)	High

Setting Total N* Mean follow-up	N, T vs C; Dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, UA-confirmed ≥2 weeks, N (%)	Findings: T vs C Overall use, UA-confirmed	Findings: T vs C Retention in treatment	Findings: T vs C Treatment withdrawals due to AE; Severe AEs	Risk of bias
SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRI): *Sertraline*							
Shoptaw, 2006[83] 1 site (US) N=229 12 wks follow-up	T+CM = 61, T only = 59 vs P+CM = 54, P only = 55 Combined: 120 vs 109 Sertraline 100mg/day 12 wks CM + 2 wks of 60 min 2x/week recovery skills group, then 90 min/3x weekly CBT-relapse prevention group. UA 3x/wk	62% male Age: 33 Race: 74% White, 0.4% AA/Black Education yrs: 12 Employment: 28% unemployed Severity: used 13 of last 30 days	N (%) 3 wk+ abstinent: 23 (43%) vs 15 (25%) vs 28 (59%) vs 23 (42%), P = 0.035 Collapsed to 2 groups: N (%) 3 wk+ abstinent: 41 (34%) vs 51 (48.6%), P = 0.052	NR	116 completed study: 31 (51%) vs 23 (39%) vs 29 (54%) vs 33 (60%) Collapsed to 2 groups: 54 (45%) vs 62 (57%)	WD: NR Severe AEs: NR	Unclear

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States of America; MA = methamphetamine; mg = milligrams; MI = Motivational Interviewing; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SES = socioeconomic status; sig = statistically significant; SSRI = selective serotonin reuptake inhibitor; T = treatment group; TTM = Transtheoretical Model; UA = urinalysis; wk(s) = week(s); yrs = years.

Antipsychotics

Summary of Findings

Two RCTs (1 unclear-ROB[85] and 1 high-ROB[86]) provide evidence for the use of antipsychotics for the treatment of methamphetamine use disorder. Both trials compared aripiprazole to placebo and found no difference in sustained abstinence, use during the study, retention, or harms.

Detailed Findings

Second-generation Antipsychotic: Aripiprazole

Two RCTs provide evidence for the use of antipsychotics for the treatment of methamphetamine use disorder. One 12-week, unclear-ROB RCT (N=90) compared 20mg of aripiprazole to placebo.[85] All participants received once weekly individual therapy (combination of CBT and MI). The second, a 20-week, high-ROB RCT (N=53) compared 15mg to placebo, with no concurrent interventions.[86] Both studies contribute to low strength evidence of no difference between aripiprazole and placebo on methamphetamine use during trials. The evidence for all other outcomes of interest is insufficient, with neither study reporting a positive benefit associated with the use of aripiprazole (see Table 12 for study-level data and Conclusions Table G for a summary of findings).

Table 12. Placebo-controlled trials of antipsychotics (aripiprazole) for treating methamphetamine use disorder

Setting Total N* Mean follow-up	N, T vs C; Dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Abstinence, UA-confirmed ≥2 weeks, N (%)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
ATYPICAL ANTIPSYCHOTICS: *Aripiprazole*							
Coffin, 2013[85] 1 site (US) N=90 12 wks follow-up	45 vs 45 Aripiprazole 20 mg/day (MTD) 12 wks 30 min/1x weekly individual psychotherapy (combination of CBT, MI) UA 1x/wk	88% male Age: 38.7 (10.8) Race: 50% white, 19% AA/Black Education: 44% high school or less Employment: 74% unemployed	8 (18%) vs 15 (33%), P = 0.15	There was no difference in negative UAs, P = 0.41.	75 completed study: 35 (78%) vs 40 (89%)	WD: 14 (31%) vs 3 (7%), P £ 0.01 Severe AEs: 6 total.	Unclear
Tiihonen, 2007[86] NR sites (Finland) N=53 20 wks follow-up	19 vs 17 Aripiprazole 15 mg/day 20 wks None UA 2x/wk	68% male Age: 35.7 Race: 100% white SES: NR	NR	Positive UA, higher in T vs C (Adj OR = 3.77, 95% CI [1.55, 9.18], P = 0.003).	NR	WD: 2 (11%) vs 0 (0%) Severe AEs: 2 (11%) vs 0 (0%)	High

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AfrAm = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); CM = contingency management; US = United States of America; MA = methamphetamine; mg = milligrams; MI = Motivational Interviewing; MTD = maximum tolerated dose; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SES = socioeconomic status; sig = statistically significant; T = treatment group; UA = urinalysis; wk(s) = week(s); yrs = years.

Psychostimulants

Summary of Findings

A systematic review of 11 RCTs examined evidence for the use of psychostimulants (dexamphetamine, modafinil, methylphenidate) for the treatment of methamphetamine use disorder.[81] Across all outcomes (sustained abstinence, use, retention, harms), there is low strength evidence that psychostimulants provide no benefit over placebo. The systematic review reported no benefit of either modafinil or dexamphetamine over placebo for any outcome of interest. There is low strength evidence of a positive effect of methylphenidate on methamphetamine use during studies. There was low strength evidence for no effect of methylphenidate on study retention.

Detailed Findings

Eleven RCTs in a systematic review provide evidence examining the use of psychostimulants (dexamphetamine, modafinil, and methylphenidate) for the treatment of methamphetamine use disorder.[81] Four RCTs (N=278) in the systematic review provide low strength evidence of a positive effect of methylphenidate on methamphetamine use during the trial period. There is low strength evidence of no difference between methylphenidate and placebo for retention (5 RCTs in the systematic review; N=322). No differences were reported when comparing dexamphetamine or modafinil to placebo on any outcome of interest (SOE low).

Dexamphetamine

Findings come from 1 systematic review[81] that included 2 RCTs (1 low, 1 unclear-ROB) examining dexamphetamine. There is low strength evidence of both no difference between dexamphetamine and placebo on methamphetamine use during trials, and no difference in study retention (combined OR 2.50 [95% CI 0.80 to 7.87]). No other outcomes of interest were examined (see Conclusions Table G for a summary of findings).

Methylphenidate

Six RCTs (1 low, 1 unclear, 4 high-ROB) in the systematic review[81] examined methylphenidate for the treatment of methamphetamine use disorder. Three of 4 studies found participants receiving methylphenidate had significantly lower rates of methamphetamine use during the trial (low strength evidence). Five trials in the review (N=322) found no difference between groups for retention (combined OR 1.29 [95% CI 0.67 to 2.48]; SOE low). Of note, 2 of the trials examined individuals with amphetamine and not methamphetamine use disorder. Removing these trials does not change the findings of no difference. No other outcomes of interest were examined (see Conclusions Table G for a summary of findings).

Modafinil

Three RCTs in the systematic review[81] examined modafinil for the treatment of methamphetamine use disorder. Two high-ROB RCTs in the review contribute to low strength evidence of no difference between modafinil and placebo for sustained abstinence (N=281; combined OR of 0.86 [95% CI 0.46 to 1.61]). Three RCTs (N=361; 1 unclear-, 2 high-ROB) found no difference in methamphetamine use during the trial period (SOE low) or retention

(combined OR 1.00 [95% CI 0.64 to 1.55]; SOE low). No other outcomes of interest were reported (see Conclusions Table G for a summary of findings)

Muscle Relaxants/Anticonvulsants

Topiramate

There are no previous systematic reviews of anticonvulsants for amphetamine/methamphetamine use disorder. We identified 1 moderately-sized (N=140), low-ROB trial of topiramate.[87] There was a significant effect on use reduction greater than or equal to 25% of baseline median methamphetamine urine levels (P=0.03) as well as on use reduction greater than or equal to 50% (P=0.027). There was no difference in treatment retention, and the trial did not report on abstinence.[87] There is low strength of evidence from this trial to support the use of topiramate for methamphetamine use disorder (see Table 13 for study-level data, and Conclusions Table H for a summary of findings).

Baclofen versus Gabapentin

There were no identified systematic reviews or trials addressing muscle relaxants for amphetamine/methamphetamine use disorder. We identified 1 smaller trial (N=88) which was a head-to-head comparing the muscle relaxant baclofen to anticonvulsant gabapentin or placebo.[88] The trial was rated low risk of bias, and there was no statistically significant difference between groups in probability of providing negative urine drug screen (P=0.577), abstinence (P=NS), or retention (P=0.157).[88] This does not offer sufficient strength of evidence to address whether muscle relaxants are an effective treatment for amphetamine/methamphetamine use disorder (see Table 13 for study-level data, and Conclusions Table H for a summary of findings).

Table 13. Trials of anticonvulsants/muscle relaxants for treating methamphetamine use disorder

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Abstinence, Lapse, or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
Topiramate							
Elkashef, 2012[87] 8 sites (US) N=140 17 wks follow-up	69 vs 71 Topiramate 200mg/day 13 wks BBCET 1x/wk UA 3x/wk	63.6% male Age: 38.0 (8.62) Race: 82.9% White, 2.1% AA/Black Education yrs: 12.9 (1.85) Employment: 24.3% unemployed	NR	% of subjects with a UA(-) wk during wks 6-12 (max tx dose): No significant difference, P=0.13 % who reduced use days by ≥25% of baseline: 64.2% vs 42.3%; P=0.03 (wks 6-12) % who reduced use days by ≥50% of baseline rate: 49.1% vs 26.9%; P=0.027 (wks 6-12)	77 completed study: 39/69 (56.5%) vs 38/71 (53.5%)	WD: 2 (2.9%) vs 2 (2.8%) Severe AEs: 13	Low

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C Abstinence, Lapse, or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Findings: T vs C Overall use, UA-confirmed	Findings: T vs C Retention in treatment	Findings: T vs C Treatment withdrawals due to AE; Severe AEs	Risk of bias
Baclofen vs gabapentin							
Heinzerling, 2006[88] Single-site (US) N=88 16 wks follow-up	25 vs 26 vs 37 Baclofen 20mg/day vs Gabapentin 800mg/day 16 wks 90-min relapse prevention group sessions 3x/wk UA 3x/wk	69% male Age: 32 Race: 59% White, .01% AA/Black Education yrs: 12	Longest abstinence, days: Baclofen 25.39 (29.17); Gabapentin 18.85 (21.67); Placebo 21.00 (24.72); P=ns N (%) with 3 consecutive wks abstinence: Baclofen 11 (44%); Gabapentin 9 (34.6%); Placebo 15 (40.5%); P=ns	% UA(-) samples: Baclofen 50.3% (±37%); Gabapentin 37.1% (±35%); Placebo 37.7% (±37%) P=0.577	39 completed study: Baclofen 15 (60%), Gabapentin 9 (35%), Placebo 15 (41%) P=0.157	WD: 1(4%) vs 0 vs 0 Severe AEs: NR	Low

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AA = African American; AE = adverse event; BBCET = Brief Behavioral Compliance Enhancement Treatment; C = control group; CBT = Cognitive Behavioral Therapy; hr = hour(s); MA = methamphetamine; mg = milligrams; NR = not reported; NS = not significant; OR = odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SES = socioeconomic status; sig = statistically significant; T = treatment group; UA = urinalysis; US = United States of America; wk(s) = week(s); WD = withdrawal; yr(s) = year(s).

Pharmacotherapies that are Prescribed for Other Substance Use Disorders

Opioid Antagonists

Naltrexone

Summary of Findings

We identified 4 RCTs for use of naltrexone in treatment of amphetamine/methamphetamine use disorder.[89-92] Overall, there was insufficient evidence related to the effect of naltrexone on sustained abstinence and the reduction of amphetamine/methamphetamine use. There was low strength evidence that naltrexone is more effective than placebo improving treatment retention. We found moderate strength of evidence that naltrexone did not cause harms.

Detailed Results

All trials analyzed had small sample sizes (80-100 participants) with varying lengths of treatment duration (10-24 weeks).Only 1 unclear-ROB trial (N=100) examined abstinence from amphetamine use of greater than 3 weeks as an outcome.[91] This study enrolled men who have sex with men (MSM) at a single site in the US and randomized patients to receive intermuscular XR-NTX (380 mg) or placebo injection once monthly for a total of 12 weeks. All participants also completed weekly cognitive behavioral therapy (CBT) and motivational interviewing (MI) counseling, and provided UA samples once weekly. Few achieved abstinence at trial completion (14% vs 20%; P=0.6). There were no differences in rate of positive UA between groups or treatment retention. (See Table 14 for study-level data and Conclusions Table I for a summary of findings).

The 3 remaining studies took place internationally and did not report abstinence.[89,90,92] Runarsdottir et al randomized Icelandic patients transitioning from inpatient to outpatient setting to receive monthly injection of naltrexone (XR-NTX 380 mg) or placebo for 24 weeks total; both groups received concomitant 4-weeks residential or intensive outpatient (IOP) psychosocial treatment program (consisting of motivational, cognitive behavioral, and relapse prevention counseling) and submitted once-weekly UA for testing. There were no differences in likelihood of having positive UA for methamphetamine between groups (IRR 1.00, 95% CI 0.38-2.68, P=0.99), and retention was similar in both groups. The study reported no serious AEs. There was unclear risk of bias due to unclear blinding procedures and because UA was only assessed weekly. (See Table 14 for study-level data and Conclusions Table I for a summary of findings).

Jayaram-Lindstrom et al, a low-ROB RCT, randomized newly abstinent Swedish patients (*ie*, completed 2-week lead-in period) to receive naltrexone (50 mg/day) or placebo for 12 weeks total. Both groups also received weekly 60-minute relapse prevention therapy and participants submitted once-weekly UAs. The treatment group had a higher percentage of negative UA than placebo (65.2% vs 47.7%, P<.05). There were no significant differences in retention (RR=1.12 95% CI 0.83-1.50). (See Table 14 for study-level data and Conclusions Table I for a summary of findings).

Tiihonen et al, an unclear-ROB multi-site trial in Russia, randomized 100 patients with co-occurring amphetamine and opioid dependence to receive naltrexone implant (Prodetoxon 1000 mg implant) or placebo for 10 weeks. The treatment group had higher percentage of negative UA than placebo but this difference was not statistically significant (40% vs 24%, P=.09). Treatment

participants had increased retention versus placebo (52% vs 28%, P=0.01) (See Table 14 for study-level data and Conclusions Table I for a summary of findings).

Treatment Retention

We conducted a meta-analysis on treatment retention for all 4 studies on naltrexone (see Figure 17). The combined effect on treatment retention was similar between naltrexone and placebo (RR 1.11, 95% CI 0.88 to 1.41). Statistical heterogeneity was significant (P=.05). Patients treated with naltrexone were significantly more likely to complete treatment compared with placebo in one 10-week study with low risk of bias.[90] In an analysis combining 3 studies with treatment of 12 weeks or longer, there was no significant heterogeneity, and no difference in retention between the naltrexone and placebo groups (RR 1.03, [95% CI 0.93 to 1.13] see Figure 18). Due to multiple studies with unclear risk of bias and reporting of inconsistent results, we assessed this as low strength of evidence.

Figure 17. Treatment retention among patients with amphetamine/methamphetamine use disorder in studies that compared naltrexone vs placebo

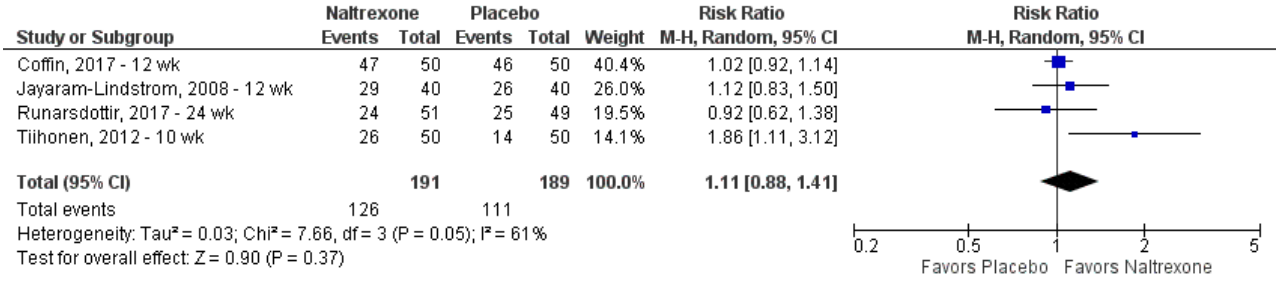


Figure 18. Treatment retention among patients with amphetamine/methamphetamine use disorder in studies that compared naltrexone vs placebo with at least 12 weeks follow-up

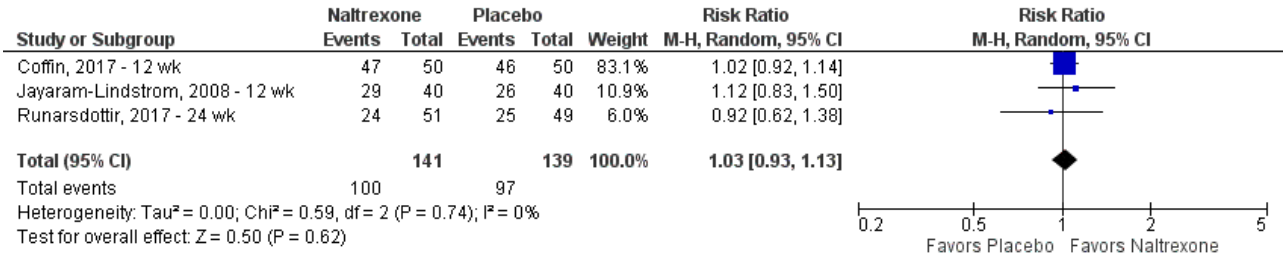


Table 14. Placebo-controlled trials of opioid antagonists for treating amphetamine/methamphetamine use disorder

Setting Total N* Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES %	Findings: T vs C				Risk of bias
			Abstinence ≥2 consecutive weeks, N (%)	Overall use, UA-confirmed	Retention in treatment	Treatment withdrawals due to AE; Severe AEs	
Naltrexone							
Runarsdottir, 2017[89] Single site, inpatient transitions to outpatient (Iceland) N=100 24 wks follow-up	51 vs 49 XR-NTX (380 mg/monthly injection) 24 wks 4-week residential or IOP treatment program UA 1x/wk	75% Male Age: 31.6 (8.6) Race: 100% white Education: 72% general educ or less Employment: 69% unemployed Homeless: 12%	NR	UA (+) IR 1.00, 95% CI 0.38–2.68; P=0.99	49 completed study: 24/51 (47%) vs 25/49 (51%); RR=0.92 (0.62-1.38)	Severe AEs: None WD due to severe AE: None	Unclear
Tiihonen, 2012[90] Multi-site (Russia) N=100 10 wks follow-up	50 vs 50 Naltrexone (Prodetoxon 1000mg implant) 10 wks No concomitant tx UA 1x/wk	89% Male Age: 28 (4.1) Race, education, employment: NR	NR	Proportion UA (-): 40% vs 24%; P=0.09	40 completed study: 26/50 (52%) vs 14/50 (28%); RR=1.86 (1.11-3.12)	Severe AEs: None WD due to severe AE: None	High
Coffin, 2017[91] Single site, outpatient (US) N=100 12 wks follow-up	50 vs 50 XR-NTX (380 mg/month) 12 wks CBT and MI 30min/wk UA 1x/wk	96% Male Age: 43.2 (8.5) Race: 55% White Education: 26% high school or less Employment: 70% unemployed	Achieved abstinence at completion of trial: 7 (14%) vs 10 (20%); P=0.6*	Risk of UA (+): IRR=0.95; 95% CI=0.76–1.20)	93 completed study: 47/50 (94%) vs 46/50 (92%); RR=1.86 (1.11-3.12)	Severe AEs: 3 WD due to severe AE: None	Unclear
Jayaram-Lindstrom, 2008[92] Single-site Inpatient (Sweden) N=80	40 vs 40 Naltrexone (50mg/day) 12 wks	78% Male Age: 39.3 (8.1) Education: 10.7 years (SD 1.6) Race: NR	NR	% UA (-) during trial: 65.2% ±36.1 vs 47.7% ±33.7	55 completed study: 29/40 (72.5%) vs 26/40 (65%);	Severe AEs: None	Low

12 wks follow-up	60 minute relapse prevention therapy/wk UA 1x/wk	Mean number UA (-) significantly higher for tx; P<0.05	RR=1.12 (0.83-1.50)	WD due to severe AE: None

* Descriptors may represent the total study population or the subgroup assigned to active treatment unless a significant difference occurred between study arms at baseline.

Other benefits/harms Not Reported in these studies

Abbreviations: AE = adverse event; AA = African American; C = control group; CBT = Cognitive Behavioral Therapy; CI = confidence interval; hr = hour(s); IOP = Intensive outpatient; MA = methamphetamine; mg = milligrams; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; ROB = risk of bias; SD = standard deviation; SES = socioeconomic status; sig = statistically significant; T = treatment group; UA = urinalysis; US = United States; wk(s) = week(s); yrs = years.

Other Pharmacotherapies

Three additional studies examined the effects of other drugs or drug combinations for methamphetamine use disorder. No effects were reported in studies of citicoline,[93] Ondansetron,[94] or PROMETA (which contains a combination of flumazenil, gabapentin, and hydroxyzine).[95] As there was only 1 study on each of these medications, the strength of evidence for each is considered insufficient.

Pharmacotherapies for Comorbid Amphetamine/Methamphetamine and Opioid Use Disorders

Summary of Findings

We identified only 1 study that examined pharmacotherapies for comorbid amphetamine/methamphetamine and opioid use disorder.[90] This RCT compared naltrexone to placebo and found a nonsignificant trend towards the use of naltrexone for rates of amphetamine-negative UAs. Naltrexone was significantly better than placebo for study retention.

Detailed Findings

There was 1 trial that examined the effect of naltrexone on amphetamine use in an opioid dependent population.[90] This study took place at multiple sites in Russia and randomized 100 patients to receive naltrexone implant (Prodetoxon 100 mg implant) or placebo for 10 weeks. There was no concurrent behavioral health intervention administered. Patients randomized to receive naltrexone had higher rates of negative UA for amphetamines compared to placebo though this was not statistically significant (40% vs 24%, P=0.09). At 10 weeks, the naltrexone arm had improved retention compared to placebo (52% in treatment vs 28% in placebo, P=0.01). As above, there was unclear risk of bias. Strength of evidence was insufficient due to lack of studies (see Conclusions Table J).

KEY QUESTION 4: Are there known subpopulations for whom different forms of pharmacotherapy is most/least effective for amphetamine/methamphetamine use disorder?

Summary of Findings

We identified 3 RCTs[82,85,87] and 1 systematic review[81] that examine subgroup differences in adults with methamphetamine use disorder. Included subgroups are: methamphetamine severity at baseline,[81,82,85] methamphetamine-negative UA at randomization,[87] gender,[82] comorbid or lifetime alcohol use disorder,[87] comorbid ADHD,[82] comorbid depression,[82] and HIV status.[85]

Overall, findings are inconclusive due to methodological issues, as well as the limited number of studies examining each subpopulation. However, it is possible that bupropion,[82] but not aripiprazole[85] or psychostimulants,[81] may be more effective in reducing methamphetamine use in individuals who are less severely addicted at baseline,[82] and topiramate may be more effective in individuals who produce a negative urine screen at randomization.[87] In addition, bupropion may be more effective for males with methamphetamine use disorder than for females, and there is a possibility that some individuals with comorbid depression may experience more benefit than placebo.[82] No differences were found by ADHD diagnosis,[82] lifetime alcohol use disorder,[87] or HIV status.[85]

Findings by Subpopulation

Methamphetamine Severity at Baseline

Two RCTs[82,85] and 1 systematic review[81] examined the differential effect of baseline severity treatment response and outcomes. A RCT[82] comparing bupropion to placebo found that for individuals who had reported using methamphetamine 18 days or fewer in the last 30 days, bupropion was more effective than placebo for increased methamphetamine-negative weeks over time, with greater rates of decrease in negative methamphetamine urine samples and more participants achieving at least 1 methamphetamine-negative week. No such effect was found for those who reported more than 18 days of use.[82] Neither the RCT comparing aripiprazole to placebo,[85] nor the systematic review examining psychostimulants (including bupropion)[81] found significant differences in any outcome of interest by baseline severity (see Table 15 for more detail).

Methamphetamine-negative at Randomization

One RCT comparing topiramate to placebo examined differences in the effect of pharmacotherapy by baseline UA results.[87] Findings indicate that participants with negative final UAs prior to randomization had more methamphetamine-negative weeks (in weeks 6-12 [primary outcome]), regardless of treatment group. There was no difference between topiramate and placebo in week 6; however, over the course of weeks 6-12, participants with negative final UAs assigned to topiramate experienced more methamphetamine-negative weeks (P=0.02). There was no significant treatment effect in the full sample (see Table 15 for more detail).

Gender

One RCT comparing bupropion to placebo examined differential treatment effects by gender.[82] Findings indicate that receiving bupropion was more effective than placebo for increased methamphetamine-negative weeks over time for males (P=0.04), but not for females (P=0.71) (see Table 15 for more detail).

Comorbid Depression

One RCT comparing bupropion to placebo examined the role of comorbid depression in the treatment of methamphetamine use disorder.[82] The study found a nonsignificant trend favoring bupropion associated with increased methamphetamine-negative weeks over time for less-depressed participants (P=0.08), but not for participants with higher rates of depression (P=0.58; see Table 15 for more detail).

Comorbid Attention Deficit Hyperactivity Disorder

One RCT comparing bupropion to placebo examined differences in treatment effects in patients with and without comorbid ADHD.[82] There was no difference between bupropion and placebo in methamphetamine-negative weeks over time by ADHD diagnosis (see Table 15 for more detail).

Comorbid or Lifetime Alcohol Use Disorder

A single RCT that compared topiramate to placebo explored the impact of a lifetime history of alcohol use disorder on treatment effects.[87] The study found that a history of alcohol use disorder was not significantly associated with methamphetamine-negative weeks (in weeks 6-12 [primary outcome]) nor were there differences in treatment effect by history of alcohol use disorder (see Table 15 for more detail).

HIV Status

One RCT compared differences in the effect of aripiprazole versus placebo in participants with and without HIV.[85] Findings indicate no difference between aripiprazole and placebo in methamphetamine-negative samples by HIV status (RR 0.85 [95% CI 0.63 to 1.15], P=0.29; see Table 15 for more detail).

Table 15. Subgroup analyses in studies of pharmacotherapy for amphetamine/methamphetamine use disorder, stratified by population characteristic

Study N	N, T vs C; Tx dose and duration; concurrent intervention UA frequency	Abstinence	Use	Retention	Summary
Addiction Severity at Baseline					
Elkashef 2008[82] 5 sites (US) N=151 18 wks follow-up Lower use (<=18/30 days), N=71 Higher use (>18/30 days) N=80	79 vs 72 Bupropion SR 300 mg/day 12 wks 90 min/3x weekly CBT-relapse prevention group UA 3x/wk	NR	For participants with lower baseline use at baseline, but not higher (0.68), bupropion was more effective than placebo for increased methamphetamine-negative weeks over time (P=0.03), with a greater rate of decrease in negative methamphetamine samples (P=0.04) and more participants achieving at least one methamphetamine-negative week (56% vs 40%).	NR	Bupropion was more effective than placebo for increased methamphetamine-negative weeks over time for participants with lower but not higher rates of baseline use, with greater rates of decrease in negative methamphetamine samples and more participants achieving at least one methamphetamine-negative week.
Coffin, 2013[85] 1 site (US) N=90 12 wks follow-up 3-7 days/wk N=71 < 3 days/wk N=19	45 vs 45 Aripiprazole 20 mg/day (MTD) 12 wks 30 min/1x weekly individual psychotherapy (combination of CBT, MI) UA 1x/wk	NR	There was no difference between aripiprazole and placebo when comparing light (P=0.7) and heavy users (P=0.3) in methamphetamine-negative samples.	NR	There was no difference between aripiprazole and placebo when comparing light and heavy users in methamphetamine-negative samples.

Study N	N, T vs C; Tx dose and duration; concurrent intervention UA frequency	Abstinence	Use	Retention	Summary
Bhatt, 2016[81] 17 RCTs N=1,387	Systematic review of psychostimulants (includes bupropion)	No differences associated with any frequency of use (3 RCTs, N=353; combined OR 0.92 [95% CI 0.54 to 1.54) or low frequency of use (2 RCTs, N=288; combined OR 1.24 [95% CI 0.65 to 1.45]); no difference by frequency of use P=0.67.	NR	No differences associated with any frequency of use (12 RCTs, N=896; combined OR 1.19 [95% CI 0.85 to 1.66) or low frequency of use (2 RCTs, N=288; combined OR 1.29 [95% CI 0.69 to 2.40]); no differences by frequency of use P=0.83.	There were no significant differences between psychostimulants and placebo in sustained abstinence or retention by frequency of use.
Methamphetamine-negative UA at Randomization					
Elkashef, 2012[87] N=140	69 vs 71 Topiramate 200mg/day 13 wks BBCET 1x/wk UA 3x/wk	NA	Ss with negative final UAs prior to randomization had more methamphetamine-negative weeks (in weeks 6-12), regardless of treatment group. No difference between topiramate and placebo in week 6. However, over the course of weeks 6-12, participants with negative final UAs assigned to topiramate experienced more methamphetamine-negative weeks (P=0.02). There was no significant treatment effect in the full sample.	NA	Topiramate was more effective than placebo for methamphetamine-negative weeks over time for only participants with a negative UA just prior to randomization, and not for the entire sample. Similarly, participants with a final negative UA had more methamphetamine-negative weeks regardless of treatment group.

Study N	N, T vs C; Tx dose and duration; concurrent intervention UA frequency	Abstinence	Use	Retention	Summary
Gender					
Elkashef 2008[82] 5 sites (US) N=151 18 wks follow-up Male N=101 Female N=50	79 vs 72 Bupropion SR 300 mg/day 12 wks 90 min/3x weekly CBT-relapse prevention group UA 3x/wk	NR	For males (P=0.04) but not females (P=0.71), receiving bupropion was more effective than placebo for increased methamphetamine-negative weeks over time.	NR	Bupropion was more effective than placebo for increased methamphetamine-negative weeks over time for males but not females.
Comorbid Depression					
Elkashef 2008[82] 5 sites (US) N=151 18 wks follow-up Ham-D <=12 N=121 Ham-D >12 N=30	79 vs 72 Bupropion SR 300 mg/day 12 wks 90 min/3x weekly CBT-relapse prevention group UA 3x/wk	NR	There was a nonsignificant trend favoring bupropion associated with increased methamphetamine-negative weeks over time for less depressed participants (P=0.08), but not for participants with higher rates of depression (P=0.58).	NR	There was a nonsignificant trend favoring bupropion associated with increased methamphetamine-negative weeks over time for less depressed participants, but not for participants with higher rates of depression.
Comorbid ADHD					
Elkashef 2008[82] 5 sites (US) N=151 18 wks follow-up No ADHD N=131 ADHD N=20	79 vs 72 Bupropion SR 300 mg/day 12 wks 90 min/3x weekly CBT-relapse prevention group UA 3x/wk	NR	There was no difference between bupropion and placebo in methamphetamine-negative weeks over time by ADHD diagnosis.	NR	There was no difference between bupropion and placebo in methamphetamine-negative weeks over time by ADHD diagnosis.

Study N	N, T vs C; Tx dose and duration; concurrent intervention UA frequency	Abstinence	Use	Retention	Summary
Comorbid or Lifetime Alcohol Use Disorder					
Elkashef, 2012[87]		NA	A history of alcohol use disorder was not significantly associated with methamphetamine-negative weeks (in weeks 6-12) nor were there differences in treatment effect by the presence of alcohol use disorder.	NA	History of alcohol use disorder was not significantly associated with methamphetamine-negative weeks (in weeks 6-12) nor were there differences in treatment effect by history of alcohol use disorder.
HIV Status					
Coffin, 2013[85] 1 site (US) N=90 12 wks follow-up HIV+ N=28 HIV- N=62	45 vs 45 Aripiprazole 20 mg/day (MTD) 12 wks 30 min/1x weekly individual psychotherapy (combination of CBT, MI) UA 1x/wk	NR	There was no difference between aripiprazole and placebo in methamphetamine-negative samples by HIV status (RR 0.85 [95% CI 0.63 to 1.15], P=0.29).		There was no difference between aripiprazole and placebo in methamphetamine-negative samples by HIV status.

Abbreviations: AA = African American; ADHD = attention deficit hyperactivity disorder; AE = adverse event; BBCET = Brief Behavioral Compliance Enhancement Therapy; CBT = Cognitive Behavioral Therapy; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; HIV = human immunodeficiency virus; P = p-value; MI = Motivational Interviewing; MTD = Methadone; NR = Not reported; P = p-value; RCT = randomized control trial; RR = Risk ratio; Ss = subjects; UA = urinalysis; US = United States

Subgroup Analysis of Contingency Management as a Co-intervention

A multifactorial trial of sertraline for methamphetamine dependence (N=229) compared use versus non-use of CM within both active treatment and placebo groups.[83] Fifty-three percent of participants randomized to the sertraline group completed the trial, compared with 49% in the placebo group. The difference was not statistically significant (RR 1.06, 95% CI 0.82 to 1.37).

SUMMARY AND DISCUSSION

In this systematic review, we examined 7 systematic reviews and 68 trials of a variety of pharmacotherapies for stimulant use disorder (46 for cocaine, 14 for amphetamine and/or methamphetamine), and found largely disappointing results. We found no strong, consistent evidence that any drug class was effective in increasing abstinence, reducing use, or improving study retention rates. As the summary of evidence table shows, a key issue was the absence of good quality evidence: we found insufficient to low strength evidence for all drug classes in amphetamine/methamphetamine use disorder and most of the drug classes in cocaine use disorder, suggesting that further research in these areas may alter conclusions. On the other hand, we also found some areas in which there was consistent evidence of no effect, or negative effect. For patients with cocaine use disorder, we found moderate to high strength evidence that antidepressants (specifically, SSRIs and TCAs) do not improve abstinence, use, or retention; moderate strength evidence that anticonvulsants do not improve use or retention; and low to moderate strength evidence that dopamine agonists do not improve abstinence or retention. We found moderate strength of evidence that SSRIs increase risk of study withdrawal due to adverse events and that disulfiram treatment was associated with lower retention than placebo.

A motivating factor behind this review was to find promising treatments for a devastating condition that has been historically difficult to treat with pharmacotherapy. We identified several potentially effective treatments, though the strength of evidence is low, underscoring the need for further research to strengthen conclusions. First, psychostimulants as a class, and the antidepressant bupropion, may improve abstinence in cocaine use disorder, though the same studies did not find an improvement in reducing cocaine use or treatment retention.[5] The anticonvulsant topiramate may also be effective for continuous cocaine abstinence.[18,66,67] Second, antidepressants and psychostimulants may be effective in patients with comorbid opioid use disorder.[11] Third, topiramate has the potential to be beneficial in those with methamphetamine use disorder (based on the finding from 1 larger, well-done trial).[87] Finally, antidepressants may decrease the risk of relapse in patients who have already achieved abstinence from cocaine.[41,96] The use of pharmacotherapy for relapse prevention is an intriguing finding that warrants exploration. In subgroup analyses, we found that 2-or-more-week abstinence at baseline (confirmed by UA), or a negative UA at screening, were more likely to predict success.[19,46] It is possible that those who are actively using stimulants are not engaged enough in treatment for pharmacotherapy to be effective. Retention rates varied widely across studies (24-97%), but overall low rates of retention could potentially affect the assessment of treatment effectiveness in the majority of studies (attrition was greater than 20% in 68% of the studies reporting retention rates). Unfortunately, pharmacotherapy itself does not appear to be effective in improving 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, or tobacco use disorders). Perhaps the neurobiology of stimulant use disorders makes it more difficult for some to engage in treatment.[97] Whether the negative results we found reflect the biology of disease or lack of efficacy of the pharmacological interventions is unclear.

As such, behavioral interventions (*ie*, contingency management, cognitive behavioral therapy, and community reinforcement approach) continue to be mainstays of treatment and management of stimulant use disorders.[98-100] A systematic review by Minozzi et al found that any

psychosocial treatment likely reduces drop-out rates, and may increase the period of abstinence (most of the studies reviewed involved contingency management in addition to treatment as usual).[100] In our comparison of all included studies with and without CM, we found that pharmacotherapeutic effects were similar in studies with and without a CM co-intervention.

The decision to consider any treatment depends on the anticipated balance of benefits and harms. One might consider use of a medication with lower strength evidence of benefit if the potential for adverse effects was known to be low. In this body of evidence, however, data on harms was poorly reported, resulting in insufficient evidence to draw conclusions about harms for most of the drugs examined in this population. None of these drugs are FDA-approved for this indication. Most have been widely used for other indications for many years and many have well-known adverse effect profiles. There was moderate strength evidence that SSRIs may be associated with a higher rate of treatment withdrawal due to adverse effects, but very few studies reported on the nature and rate of severe adverse effects.

LIMITATIONS

Our review has several limitations. The review scope was very broad and hence we had to rely on existing systematic reviews when available. We sought to minimize the downside of using existing reviews by only including those that met key quality criteria. We also updated reviews and included newer trials, or trials that had been missed in the original reviews. We had to choose a scheme for organizing results by drug class though this scheme could be debated. The definition of abstinence (2 or more weeks) is only a proxy for sustained (long-term) abstinence, but our Technical Expert Panel deemed it a reasonable and clinically important proxy that also reflects the reality of available trial literature. Finally, we limited our search to English language studies, though we believe the risk of missing literature that would have appreciably altered conclusions is low.[101]

There are also a number of limitations to this body of evidence. Many of the studies we included had methodologic flaws including poor outcome reporting, incomplete reporting of allocation methods, and small sample sizes. An anticipated limitation of the body of evidence which proved true was the high rate of attrition in the majority of studies. Because we were interested in treatment retention as an outcome, we did not consider attrition as a sole criterion for assessing study quality. An important and potentially amenable weakness in future studies was the marked variation in outcome reporting across trials. This precluded our ability to conduct meta-analyses in many cases because reported outcomes used various definitions and time points, preventing comparison to one another.

RESEARCH GAPS/FUTURE RESEARCH

Our review offers suggestions for future research. It is possible that the lack of significant findings was due to insufficient power to detect differences. Future studies need to be larger and assess clinically relevant and uniform outcomes, including reduction in use and defined periods of abstinence outcomes. Use of national or international clinical trial networks with standardized protocols may help address these limitations. There are a number of specific areas ripe for future work. In particular, we were surprised by the dearth of evidence in stimulant use disordered patients with co-occurring opioid use disorder. These patients are an important subgroup because they are a sizeable proportion of stimulant use disordered populations. The potentially promising

areas listed above should also be examined further as these results need to be replicated in more studies and larger populations.

Our review corroborates and extends many prior reviews. To our knowledge, this is the first review to broadly summarize drug treatment effects across many different drug classes, and to include both cocaine and amphetamine/methamphetamine use disorder patients. We used outcome measures similar to existing SRs including reduction in stimulant use by proportion of negative UA, sustained abstinence, and retention in treatment.[5,12-16] Unlike prior SRs, our review had international studies that increased external validity and generalizability to different settings.

CONCLUSIONS

We found no strong, consistent evidence that any drug class was effective in increasing abstinence, reducing use, or improving retention rates. We found moderate to high strength evidence that antidepressants, disulfiram, and anticonvulsants (with the exception of topiramate) are unlikely to be effective in non-abstinent patients. There are several promising areas deserving of further research including the use of bupropion, topiramate, treatment of abstinent patients to prevent relapse, and treatment of patients with comorbid opioid use disorder.

Conclusions Table A. Summary of the evidence on mental health 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[a]	Comments and rationale for strength of evidence rating
Antidepressants				
All Antidepressants				
Abstinence	1 SR of 8 RCTs[16] (N=942) 1 Low-ROB RCT[46] (N=130)	No difference. One SR reported a combined 3+ week abstinence RR of 1.22 (95% CI 0.99 to 1.51), and an additional RCT found no difference between study groups.	Moderate	Inconsistency Trend toward benefit disappeared when restricted to studies using strict criteria for cocaine dependence.
Use	1 SR of 4 RCTs[16] (N=251) 1 Low-ROB RCT[46] (N=130) 1 High-ROB RCT[17] (N=24)	No difference. One 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)
Relapse	2 Low-ROB RCTs[41,96] (N= 133)	Favors antidepressants. Participants abstinent at baseline with 2 consecutive cocaine-positive UAs, 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 UA, relapse is 2 consecutive cocaine-positive UAs.
Lapse		Favors antidepressants. Abstinent at baseline participants with one cocaine-positive UA, combined RR 0.79 (95% CI 0.62 to 1.00).	Low	
Retention	1 SR of 27 RCTs[16] (N=2,417) 3 Low-ROB RCTs[41,46,96] (N=263)	No difference. One SR reported RR 1.01 (95% CI 0.91 to 1.12). Three more recent low-ROB RCTs also found no difference in retention between groups.	High	Findings were similar in analyses limited to RCTs specifying DSM cocaine dependence criteria for inclusion.

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Harms	1 SR of 13 RCTs[16] (N=1,396) 1 Low-ROB RCT[46] (N=130) 1 High-ROB RCT[17] (N=24)	No difference. One 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 one low and one 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.
All Tricyclic Antidepressants				
Abstinence	1 SR of 5 RCTs[16] (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[16] (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[16] (N=1,141)	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[16] (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.
Selective Serotonin Reuptake Inhibitors (SSRIs): Fluoxetine and Sertraline				
Abstinence	NA	NA	No evidence	NA
Use	NA	NA	No evidence	NA

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Relapse	2 Low-ROB RCTs[41,96] (N= 133)	Favors sertraline. Participants abstinent at baseline with 2 consecutive cocaine-positive UAs, 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 UA, relapse is 2 consecutive cocaine-positive UAs.
Lapse		Favors sertraline. Abstinent at baseline participants with 1 cocaine-positive UA, combined RR 0.79 (95% CI 0.62 to 1.00).	Low	
Retention	1 SR of 7 RCTs[16] (N=527) 2 Low-ROB RCTs[41,96] (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 one outlier, and no difference was found when further excluding one high-ROB RCT. Indirectness (of population) - 2 more recent RCTs enrolled only patients who had achieved abstinence.
Harms	1 SR of 3 RCTs[16] (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
Serotonin and Norepinephrine Reuptake Inhibitor (SNRI): Venlafaxine				
Abstinence	1 Low-ROB RCT[46] (N=130)	No difference. One RCT found no difference in 3+ week abstinence between groups (P = 0.94).	Insufficient	One single-site study.
Use		No difference. One RCT found no difference in negative UAs between groups (P = 0.738).	Insufficient	
Retention		No difference. One RCT found no difference in retention between groups.	Insufficient	

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Harms		No difference. One RCT found no difference in withdrawals due to adverse events by group. No difference. One RCT found no difference in severe AEs between groups.	Insufficient	
Atypical Antidepressant: Mirtazapine				
Abstinence	NA	NA	No evidence	NA
Use	1 High-ROB RCT[17] (N=24)	No difference. One RCT found no difference in study period use between groups.	Insufficient	One very small underpowered study. Details regarding randomization and allocation concealment NR.
Retention	NA	NA	No evidence	NA
Harms	1 High-ROB RCT[17] (N=24)	No difference. One RCT found no difference in withdrawals due to AEs between groups (none). No difference. One RCT found no difference in severe AEs between groups (because there were none).	Insufficient	One very small underpowered study. Details regarding randomization and allocation concealment NR.
Aminoketone: Bupropion				
Abstinence	1 SR of 2 RCTs[5] (N=176)	Favors bupropion. One SR reported a combined 2+ week abstinence RR of 1.63 (95% CI 1.03 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[16] (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

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Harms	1 SR of 1 RCT[5]	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[12] (N=139)	No difference. One SR reported a combined 2+ 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[12] (N=150) 1 high-ROB RCT[39] (N=18 opioid randomized, 41 enrolled opioid dependent participants)	No difference.	Low	Small body of evidence Methodologic limitations of studies Indirectness of population
Relapse	1 high-ROB RCT[39] (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 UA, relapse is 2 consecutive cocaine-positive UAs.
Lapse		No difference.	Insufficient	
Retention	1 SR of 8 RCTs[12] (N=397) 1 high-ROB RCT[39] (N=18 randomized, 41 enrolled opioid dependent participants)	Favors any antipsychotic. One SR reported RR 0.75 (95% CI 0.57 to 0.97). In addition, 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).
Harms	1 high-ROB RCT[39] (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)
First Generation Antipsychotics: Haloperidol				
Abstinence	NA	NA	No evidence	NA

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Use	NA	NA	No evidence	NA
Retention	1 SR of 1 RCT[12] (N=31)	No difference. One SR reported a RR for participants not completing the trial of 1.50 (95% CI 0.63 to 3.57). One 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
Second Generation Antipsychotics: Aripiprazole, Olanzapine, Risperidone, Quetiapine				
Abstinence	1 SR of 3 RCTs[12] (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[12] (N=31) 1 high-ROB RCT[39] (N=18 randomized, 41 enrolled opioid dependent participants)	No difference. One RCT from one SR and 1 high-ROB RCT of opioid dependent participants found no difference between groups.	Insufficient	Small body of evidence Methodologic limitations of studies Indirectness of population
Relapse	1 high-ROB RCT[39] (N=18 randomized, 41 enrolled opioid dependent participants)	No difference. One 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 UA, relapse is 2 consecutive cocaine-positive UAs.
Lapse		No difference. One high-ROB found no difference in lapse by group.	Insufficient	
Retention	1 SR of 7 RCT[12] (N=365) 1 high-ROB RCT[39] (N=18 randomized, 41 enrolled opioid dependent participants)	No difference. Seven studies in one 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).

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Harms	1 high-ROB RCT[39] (N=18 randomized, 41 enrolled opioid dependent participants)	No difference. One 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).
Other Antipsychotics: Reserpine				
Abstinence	NA	NA	No evidence	NA
Use	1 SR of 1 RCT[12] (N=119)	No difference. One 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
Psychostimulants: Dexamphetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Lisdexamphetamine, Selegiline				
Abstinence	1 SR of 14 studies[5] (N=1,549)	Favors psychostimulants. One SR reported a combined 2+ 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[5] (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[5] (N=2,205)	No difference. Number of participants who did not complete the trial, combined RR 1.00 (95% CI 0.93 to 1.06)	Moderate	Methodologic limitations of many included studies. Heterogeneous population.

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Harms	Withdrawal: 1 SR of 19 RCTs[5] (N=1,601) Serious AEs: 1 SR of 6 RCTs[5] (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. .
Cognitive Enhancing Drugs: Memantine, Atomoxetine				
Abstinence	1 Low-ROB RCT[19] (N=81)	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).	Insufficient	Single small RCT with a 2-week placebo lead-in to encourage abstinence after randomization.
Use	1 Low-ROB RCT[19] (N=81) 1 Unclear-ROB RCT[61] (N=50)	No difference. There was no difference in cocaine-negative UAs between groups.	Insufficient	Small body of evidence. Methodologic limitations of studies.
Relapse	1 Low-ROB RCT[19] (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 UAs.
Retention	1 Low-ROB RCT[19] (N=81) 1 Unclear-ROB RCT[61] (N=50)	No difference. There was no difference in retention by group.	Insufficient	Small body of evidence. Methodologic limitations of studies.
Harms		No difference. There was no difference in retention by group. No difference. 0 participants receiving memantine experienced a SAE compared to 2 who received placebo.	Insufficient	

Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments and rationale for strength of evidence rating
Anxiolytics: Busiprone				
Abstinence	1 High-ROB RCT[62] (N=62)	No difference. One 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 UA, relapse is 2 consecutive cocaine-positive UAs.
Use		NA	No evidence	
Lapse		No difference. One RCT found no difference between groups in number of days to lapse.	Insufficient	
Retention		No difference. One 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	

Abbreviations: AE = Adverse event; CI = Confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; MD = mean difference; NR = no response; P = p-value; RCT = randomized control trial; RD = risk difference; RR = Risk ratio; ROB = Risk of bias; SAE = Severe adverse event; SMD = standard mean difference; SSRI = Selective Serotonin Reuptake Inhibitors; SR = Systematic review; UA = urinalysis

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table B. Summary of the evidence on pharmacotherapies that are prescribed for other stimulant use disorders in studies of patients with cocaine use disorder, stratified by drug

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Disulfiram				
Abstinence	2 RCTs[20,52] (N=276)	No difference. Continuous abstinence disulfiram vs placebo, combined RR (95% CI) 1.22 (0.74 to 2.00)	Low	ROB unclear overall
Use	4 RCTs[20,21,31,40] (N=440)	No difference. Combined RR 0.95 (95% CI 0.64 to 1.39). The effect varied among studies, and statistical heterogeneity was highly significant (P <.00001).	Low	Heterogeneous findings among studies
Retention	1 SR[15] that included 2 RCTs (N=87): 1 unclear-ROB (N=20),[63] 1 high-ROB[64] (N=67) 5 low-ROB RCTs[20,21,31,40,52] (N=617)	Favors placebo. Treatment retention was lower with disulfiram: 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[21,31,40,52] (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	---
Naltrexone				
Abstinence	2 Low-ROB RCT[23,42] 1 Unclear-ROB RCT[102] (N=416)	No difference	Low	---
Use	1 Low-ROB RCT[51] (N=80)	No difference	Insufficient	
Retention	3 Low RCTs[43,50,51] 1 Unclear-ROB RCT[102]	No difference	Low	---

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Harms	1 low RCT[23] (N=64)	No difference	Insufficient	---
Acamprosate				
Abstinence	---	No evidence	---	
Use	1 Low-ROB RCT[28] (N=60)	No difference. % UA (-): 22% vs 23%, P=0.44	Insufficient	Only one small RCT
Retention	1 Low-ROB RCT[28] (N=60)	No difference. 18/34 (53%) vs 18/26 (69%), P=ns.	Insufficient	Only one small RCT
Harms	---	No evidence	---	
Varenicline				
Abstinence	---	No evidence	---	
Use	2 Unclear-ROB RCTs[44,45] (N=68)	Mixed findings	Insufficient	
Retention	2 Unclear-ROB RCTs[44,45] (N=68)	No difference	Insufficient	
Harms	1 Unclear-ROB RCT[45] (N=31)	No difference	Insufficient	
Buprenorphine Plus Naloxone, 2 Doses				
Abstinence	1 Low-ROB RCT[34] (N=302)	No difference	Insufficient	
Use	1 Low-ROB RCT[34] (N=302)	Mixed findings. Significantly less use with Bup 16mg + naloxone 4mg vs placebo. No difference with lower dose	Insufficient	
Retention	1 Low-ROB RCT[34] (N=302)	No difference	Insufficient	
Harms	---	No evidence	---	
Methadone vs Buprenorphine				
Abstinence	2 Low-ROB RCTs[53,54] (N=278)	Mixed findings. Longer abstinence with methadone in 1 RCT; No difference in 1 RCT	Insufficient	Mixed findings
Use	1 Low-ROB RCT[54] (N=116)	Favors Methadone. Lower use with methadone vs buprenorphine (P<.05)	Insufficient	

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Retention	2 Low-ROB RCTs[53,54] (N=278)	Mixed findings. Better retention with methadone in 1 RCT; No difference in 1 RCT	Insufficient	Mixed findings
Harms	1 Low-ROB RCT[53] (N=162)	Elevated LFT in 1 subject	Insufficient	

Abbreviations: AE = Adverse event; CI = Confidence interval; NR = no response; P = p-value; RCT = randomized control trial; RD = risk difference; RR = Risk ratio; ROB = Risk of bias; SAE = Severe adverse event; SMD = standard mean difference; SSRI = Selective Serotonin Reuptake Inhibitors; SR = Systematic review; UA = urinalysis

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table C. Summary of the evidence on anticonvulsants/muscle relaxants for cocaine use disorder, stratified by drug

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and vigabatrin (drugs combined in analysis)				
Abstinence	1 SR[14]	NR	No evidence	These represent the combined results for all drug classes included in the SR.[14] SOE was determined by the SR authors
Use	1 SR of 9 RCTs[14] (N=867)	No difference. Use of cocaine (self-reported or objective), combined RR 0.92 (95% CI 0.84 to 1.02)[14]	Moderate14	
Retention	1 SR that included 17 RCTs[14] (N=1695)	No difference. RR 0.95 (95% CI 0.86 to 1.05)[14]	Moderate14	
Topiramate				
Abstinence	1 Low-ROB RCT[18] (N=60) 2 unclear-ROB RCTs[66,67]	Favors topiramate (3 RCTs). Relapse prevention RCTs: Combined findings from 2 unclear-ROB RCTs[66,67] (RR 2.56 [95% CI 1.39 to 4.73]) for 2 or more weeks of continuous abstinence	Low	
Use	1 Low-ROB RCT[18] (N=60)	Favors topiramate.	Insufficient	Only one small trial
Retention	5 RCTs: 1 High-ROB[69]; 2 Unclear-ROB[67,68]; 2 Low-ROB[18,70] (N=605)	No difference. Combined RR 1.01 (95% CI: 0.93 to 1.10).	Moderate	Methodologic limitations of several trials.
Harms	1 Low-ROB RCT[18] (N=60)	No withdrawals occurred due to AE. No severe AEs occurred.	Insufficient	Only one small RCT
Vigabatrin				
Abstinence	1 Unclear-ROB RCT[71] (N=186) 1 High-ROB RCT[72] (N=103)	No difference. RR 2.35; 95% CI 0.92 to 5.98	Low	Unclear effect overall due to mixed findings between studies; incomplete data was reported for the full trial period in both studies
Use	1 Unclear-ROB RCT[71] (N=186) 1 High-ROB RCT[72] (N=103)	No difference. Total events: 76 (Treatment), 86 (Placebo). RR 0.88; 95% CI 0.69 to 1.13	Low	Analysis from SR[14]

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Retention	1 Unclear-ROB RCT[71] (N=186) 1 High-ROB RCT[72] (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[71] (N=186)	No difference. RR 0.97; 95% CI 0.88 to 1.08	Insufficient	
Baclofen				
Abstinence	2 Unclear-ROB RCTs[26,56] (N=230)	No difference.	Low	
Use	2 Unclear-ROB RCTs[26,56] (N=230)	No difference.	Low	
Retention	2 Unclear-ROB RCTs[26,56] (N=230)	No difference.	Low	
Withdrawal due to AE	1 Unclear-ROB RCT[56] (N=70)	No difference.	Insufficient	
Severe AE	2 Unclear-ROB RCTs[26,56] (N=230)	No difference.	Low	

Abbreviations: AE = Adverse Event; CI = Confidence Interval; RCT = Randomized control trial; ROB = Risk of Bias; RR = Risk Ratio; SR = Systematic review

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table D. Summary of the evidence on dopamine agonists for cocaine use disorder

Treatment; Outcomes	N studies per outcome (N=combined participants)	Summary of findings by outcome	Strength of Evidence	Comments
Amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline hydergine, and pramipexole (drugs combined in analysis)				
Abstinence	1 SR of 11 RCTs[13] (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[13]	Strength of evidence was determined by the SR authors[13]
Use	NR	NR	---	
Retention	1 SR of 20 studies[13] (N=1656)	No difference. RR 1.04 (95% CI 0.94 to 1.14)	Moderate[13]	
Harms	1 SR of 7 studies[13] (N=252)	SAEs and withdrawals due to AE NR.	No evidence[13]	

Abbreviations: AE = adverse event; CI = confidence interval; NR = Not reported; RR = Risk ratio; SAE = severe adverse event; SR = Systematic review

Conclusions Table E. Summary of the evidence on mental health pharmacotherapies for comorbid cocaine and opioid use disorders, stratified by drug class

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence*	Comments
Antidepressants				
Any Antidepressant				
Abstinence	1 SR of 3 RCTs[11] (N=183)	Favors antidepressants. One SR reported a combined 3+ week abstinence RR of 1.82 (95% CI 1.19 to 2.78).	Low	Small body of evidence.
Use	1 SR of 1 RCT[5] (N=108)	No difference. One RCT reported no difference in use of cocaine.	Insufficient	Single study with methodologic limitations.
Retention	1 SR of 10 RCTs[16] (N=1,006)	Favors placebo. One SR reported a combined number of participants not completing the trial of RR 1.22 (95% CI 1.05 to 1.41).	Moderate	Findings were similar in analyses limited to RCTs specifying DSM cocaine dependence criteria for inclusion.
Harms	1 SR of 5 RCTs[16] (N=492)	Favors placebo. One SR reported a combined withdrawal due to an adverse event RR of 2.47 (95% CI 1.03 to 5.90). Severe AEs NR	Moderate	Body of evidence with methodologic flaws. Indirectness of population due to heterogeneity in inclusion criteria. Imprecision.
Tricyclic Antidepressants: Desipramine				
Abstinence	1 SR of 2 RCTs[11] (N=78)	Favors desipramine. One SR reported a combined 3+ week abstinence RR of 2.73 (95% CI 1.20 to 6.21).	Insufficient	Small body of evidence. Imprecision.
Use	NA	NA	No evidence	NA
Retention	1 SR of 6 RCTs[16] (N=544)	Favors placebo. Number of participants who completed the trial, combined RR 0.86 (95% CI 0.74 to 0.99).	Moderate	Body of evidence with methodologic flaws. Indirectness of population due to heterogeneity in inclusion criteria.

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence*	Comments
Harms	1 SR of 3 RCTs[16] (N=157)	No difference. Withdrawal due to an adverse event, combined RR 1.66 (95% CI 0.35 to 7.96) Severe AEs NR	Low	Small body of evidence with methodologic flaws. Indirectness of population due to heterogeneity in inclusion criteria. Imprecision.
Selective Serotonin Reuptake Inhibitor: Fluoxetine				
Abstinence	NA	NA	No evidence	NA
Use	NA	NA	No evidence	NA
Retention	1 SR of 2 RCTs[16] (N=207)	Favors placebo. One low-ROB RCT reported more dropouts in participants receiving fluoxetine. A second small high-ROB RCT found no difference between groups.	Insufficient (Low SOE of no benefit)	Small body of evidence with methodologic flaws. Indirectness of population due to heterogeneity in inclusion criteria. Imprecision.
Harms	1 SR of 1 RCT[16] (N=186)	Favors placebo. One low-ROB RCT reported more withdrawals due to AEs associated with fluoxetine. Severe AEs NR	Insufficient	Small body of evidence. Imprecision.
Aminoketone: Bupropion				
Abstinence	1 SR of 1 RCT[5] (N=108)	Favors bupropion. One RCT reported more 3+ week abstinence in participants receiving bupropion.	Insufficient	Small body of evidence with methodologic flaws. Indirectness of population due to heterogeneity in inclusion criteria. Imprecision.
Use		No difference. One RCT reported no difference in use of cocaine.	Insufficient	
Retention	1 SR of 2 RCTs[16] (N=255)	No difference. Two RCTs in a SR reported no difference in participants completing the trial by group.	Low	
Harms	1 SR of 1 RCT[16] (N=149)	No difference. One RCT found no difference in withdrawals due to AEs by group. Severe AEs NR	Insufficient	

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence*	Comments
Antipsychotics: Aripiprazole, Risperidone				
Abstinence	NA	NA	No evidence	NA
Use	1 high-ROB RCT[39] (N=18 opioid dependent participants)	No difference. One RCT found no difference in use 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 UA, relapse is 2 consecutive cocaine-positive UAs.
Relapse		No difference. One RCT found no difference in relapse by group.	Insufficient	
Lapse		No difference. One RCT found no difference in lapse by group.	Insufficient	
Retention	1 SR of 1 RCT[12] (N=96) 1 high-ROB RCT39 (N=18 opioid dependent participants)	No difference. One high-ROB RCT and one RCT in an SR found no difference in retention between groups.	Low	Small body of evidence. Methodologic limitations of studies.
Harms	1 high-ROB RCT[39] (N=18 opioid dependent participants)	No difference. One found no difference in withdrawal due to AEs between groups. Severe AEs: NR	Insufficient	Small, methodologically limited single trial. Indirectness of population.
Psychostimulants: Dexamphetamine, Mazindol				
Abstinence	1 SR of 2 RCTs[11] (N=131)	Mixed Findings. 3+ week abstinence, RR 1.58 (95% CI 0.63 to 4.00). Findings favor dexamphetamine, but not mazindol.	Insufficient	Small body of evidence with methodologic flaws. Imprecision.
Use	1 SR of 3 RCTs[11] (N=115)	Favors psychostimulants. Use of cocaine, SMD 0.35 (95% CI -0.05 to 0.74).	Low	
Retention	1 SR of 3 RCTs[5] (N=297)	No difference. Three RCTs found no difference in the number of participants who did not complete the trial.	Low	
Harms	NA	NA	No evidence	NA

Abbreviations: AE = adverse event; CI = confidence interval; MD = mean difference; NR = Not reported; RCT = randomized control trial; RD = risk difference; ROB = Risk of bias; RR= risk ratio; SAE = severe adverse event; SMD = standard mean difference; SR = Systematic review; SOE = strength of evidence

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table F. Summary of the evidence on the use of pharmacotherapies prescribed for other stimulant use disorders in studies of patients with comorbid cocaine and opioid use disorders, stratified by drug

Outcome	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Disulfiram				
Abstinence	1 Low-ROB RCT[52] (N=177) 1 Unclear-ROB RCT[63] (N=20)	No difference. RR 0.89 (95% CI 0.53 to 1.48)	Low	P-value for statistical heterogeneity = 0.73
Use	3 Low-ROB RCTs[21,31,40] (N=332)	Mixed findings	Insufficient	Significant statistical heterogeneity among studies (P<.00001)
Retention	4 Low-ROB RCTs[21,31,40,52] (N=341) 1 Unclear-ROB RCT[63] (N=20) 1 High-ROB RCT[64] (N=67)	Favors placebo. RR 0.87 (95% CI 0.77 to 0.98)	Moderate	P-value for statistical heterogeneity = 0.94
Harms	---	No evidence	---	
Varenicline				
Abstinence	---	No evidence	---	
Use	2 Unclear-ROB RCTs[44,45] (N=68)	Mixed findings	Insufficient	
Retention	2 Unclear-ROB RCTs[44,45] (N=68)	No difference	Insufficient	
Harms	1 Unclear-ROB RCT[45] (N=31)	No difference	Insufficient	
Opioid Agonists				
Buprenorphine Plus Naloxone				
Abstinence	1 Low-ROB RCT[34] (N=302)	No difference	Insufficient	
Use	1 Low-ROB RCT[34] (N=302)	Mixed findings	Insufficient	Varies with dose
Retention	1 Low-ROB RCT[34] (N=302)	No difference	Insufficient	
Harms	---	No evidence	Insufficient	
Methadone vs Buprenorphine				
Abstinence	2 Low-ROB RCTs[53,54] (N=278)	Mixed findings	Insufficient	
Use	---	No evidence		
Retention	2 Low-ROB RCTs[53,54] (N=278)	Mixed findings.	Insufficient	
Harms	---	No evidence	---	

Abbreviations: AE = Adverse event; CI = Confidence interval; CM = contingency management; MA = meta-analysis; OR = odds ratio; P = p-value; RCT = randomized control trial; ROB = Risk of bias; SR = Systematic review; UA = urinalysis; wk = week

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table G. Summary of the evidence on mental health pharmacotherapies for amphetamine/methamphetamine use disorder

Treatment comparison	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Antidepressants				
All Antidepressants				
Abstinence	1 SR of 3 RCTs[81] (N=361) 1 Unclear-ROB RCT[83] (N=229)	No difference. One SR reported and one additional unclear-ROB RCT reported similar findings.	Moderate	Body of evidence with methodologic flaws. Consistent findings across studies.
Use	1 SR of 3 RCTs[81] (N=122) 1 Unclear-ROB RCT[82] (N=151) 1 High-ROB RCT[84] (N=60)	Mixed findings. One SR included 2 RCTs that found no difference in negative UAs, and one small trial (N=19) that favored placebo. One additional RCT found no differences in week 12 negative UAs and rate of reduction, but a modest trend towards improvement favoring bupropion (P = 0.09). One small trial of MSM found that participants receiving mirtazapine had more negative UAs, with a larger increase in the number of negative UA participants.	Insufficient	Body of evidence with methodologic flaws. Indirectness of population.
Retention	1 SR of 4 RCTs[81] (N=391) 2 Unclear-ROB RCTs[82,83] (N=380) 1 High-ROB RCT[84] (N=60)	No difference. One SR reported a combined number of participants not completing the trial of OR 1.10 (95% CI 0.73 to 1.67). Two additional RCTs also found no difference in retention, and one RCT reported findings favoring placebo.	Moderate	Body of evidence with methodologic flaws. Indirectness of population. Consistent findings across studies.
Harms	1 Unclear-ROB RCT[82] (N=151) 1 High-ROB RCT[84] (N=60)	Withdrawal due to AEs: NA No difference. Two RCTs found no difference between groups in reported severe AEs.	No evidence: Withdrawal due to AEs. Low: SAEs	Small body of evidence with methodologic flaws.

Treatment comparison	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Aminoketone: Bupropion				
Abstinence	1 SR of 3 RCTs[81] (N=361)	No difference. One SR reported combined abstinence OR of 1.12 (95% CI 0.54 to 2.33).	Low	Small body of evidence with methodologic flaws. Imprecision.
Use	1 SR of 3 RCTs[81] (N=122) 1 Unclear-ROB RCT[82] (N=151)	No difference. One SR included 2 RCTs that found no difference in negative UAs, and one small trial (N=19) that favored placebo. In addition, one RCT found no differences in week-12 negative UAs and rate of reduction, but a modest trend towards improvement favoring bupropion (P = 0.09).	Low	Body of evidence with methodologic flaws.
Retention	1 SR of 4 RCTs[81] (N=391) 1 Unclear-ROB RCT[82] (N=151)	No difference. One SR reported a combined number of participants not completing the trial of OR 1.10 (95% CI 0.73 to 1.67). One additional RCT also found no difference in retention.	Moderate	
Harms	1 Unclear-ROB RCT[82] (N=151)	No difference. There was no difference between groups in reported severe AEs. Withdrawal due to AEs: NA	No evidence: Withdrawal due to AEs Insufficient: SAEs	Single multi-site study with methodological flaws. Imprecision.
Atypical Antidepressant: Mirtazapine				
Abstinence	NA	NA	No evidence	NA
Use	1 High-ROB RCT[84] (N=60) All participants: Men who have sex with men	Favors mirtazapine. At the end of the study participants receiving mirtazapine had more negative UAs, with a larger increase in the number negative UA participants.	Insufficient	Single study with methodological flaws. Indirectness of study population. Imprecision.
Retention		No difference. There was no difference between study groups.	Insufficient	

Treatment comparison	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Harms		No difference. There was no difference in SAEs between study groups. Withdrawal due to AEs: NA	No evidence: Withdrawal due to AEs Insufficient: SAEs	
Selective Serotonin Reuptake Inhibitor: Sertraline				
Abstinence	1 Unclear-ROB RCT[83] (N=229)	No difference. For participants receiving sertraline with or without CM vs placebo with or without CM, there was a strong trend favoring placebo (P=0.052).	Insufficient	Single multi-site study with methodological flaws. Imprecision.
Use	NA	NA	No evidence	NA
Retention	1 Unclear-ROB RCT[83] (N=229)	Favors placebo. Participants receiving sertraline were retained for significantly less time than those receiving placebo. When collapsed, fewer participants receiving sertraline with or without CM were retained.	Insufficient	Single multi-site study with methodological flaws. Imprecision.
Harms	NA	NA	No evidence	NA
Atypical Antipsychotics: Aripiprazole				
Abstinence	1 Unclear-ROB RCT[85] (N=90)	No difference. One study found no difference in 2+ week abstinence.	Insufficient	Single study with methodological flaws. Imprecision.
Use	1 Unclear-ROB RCT[85] (N=90) 1 High-ROB RCT[86] (N=53)	No difference. Neither study found a positive effect of aripiprazole on reducing methamphetamine use (one study significantly favored placebo).	Low	Small body of evidence with methodological flaws. Imprecision.
Retention	1 High-ROB RCT[86] (N=53)	No difference. No difference in the number of participants who did not complete the trial.	Insufficient	Single study with methodological flaws that was ended early due to unfavorable interim results. Imprecision
Harms	Withdrawal due to AEs: 1 Unclear-ROB RCT[85] (N=90)	Favors placebo. One unclear-ROB study found significantly more withdrawals due to AEs than	Insufficient	Small body of evidence with methodological flaws.

Treatment comparison	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
	1 High-ROB RCT[86] (N=53) Severe AEs: 1 High-ROB RCT[86] (N=53)	placebo. A second small high-ROB study found no difference. No difference. One high-ROB found no difference in severe AEs.		
Psychostimulants: Modafinil, Dexamphetamine, Methylphenidate				
Abstinence	1 SR of 2 RCTs[81] (N=281)	No difference. One SR reported combined abstinence OR of 0.86 (95% CI 0.46 to 1.61).	Low	Small body of evidence with methodological flaws.
Use	1 SR of 9 RCTs[81] (N=551)	Mixed Findings. Six of 9 RCTs in a SR reported no difference in negative UAs. Three of 4 RCTs (N=278; 1 low, 3 high-ROB) reported a positive effect of methylphenidate on methamphetamine use.	Insufficient	Body of evidence with methodologic flaws. Findings in favor of methylphenidate (low SOE), but not modafinil and dexamphetamine.
Retention	1 SR of 11 RCTs[81] (N=1,027)	No difference. Number of participants who did not complete the trial, combined OR 1.11 (95% CI 0.86 to 1.44).	Low	Body of evidence with methodologic flaws. Participants receiving bupropion are included in the combined OR. Findings were similar for bupropion were similar.

Abbreviations: AE = adverse event; CI = confidence interval; MD = mean difference; NR = Not reported; OR = Odds ratio; RCT = randomized control trial; RD = risk difference; ROB = Risk of bias; RR= risk ratio; SAE = severe adverse event; SMD = standard mean difference; SR = Systematic review; SOE = strength of evidence

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table H. Summary of the evidence on anticonvulsants/muscle relaxants for amphetamine/methamphetamine use disorder

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings	Strength of Evidence[a]	Comments
Topiramate				
Abstinence	1 Low-ROB RCT[87] (N=140)	NR	No evidence	
Use	1 Low-ROB RCT[87] (N=140)	Favors topiramate. Use was significantly lower in treatment vs placebo	Low	
Retention	1 Low-ROB RCT[87] (N=140)	No difference.	Low	
Withdrawal due to AE	1 Low-ROB RCT[87] (N=140)	No difference.	Low	
Severe AE	1 Low-ROB RCT[87] (N=140)	NR	No evidence	
Baclofen vs Gabapentin				
Abstinence	1 Low-ROB RCT[88] (N=88)	No difference.	Insufficient	Only one study
Use	1 Low-ROB RCT[88] (N=88)	No difference.	Insufficient	Only one study
Retention	1 Low-ROB RCT[88] (N=88)	No difference.	Insufficient	Only one study
Withdrawal due to AE	1 Low-ROB RCT[88] (N=88)	No difference.	Insufficient	Only one study
Severe AE	1 Low-ROB RCT[88] (N=88)	NR	No evidence	

Abbreviations: AE = Adverse Event; NR = not reported; P = P-value; RCT = Randomized control trial; ROB = Risk of Bias

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table I. Summary of the evidence on pharmacotherapies used for other stimulant use disorders in studies of patients with amphetamine/methamphetamine use disorder

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Opioid Antagonists				
Naltrexone				
Abstinence	1 unclear-ROB RCT[91] (N=100)	No difference.	Insufficient	1 small RCT involving MSM participants limiting applicability to general population
Use	1 low-ROB RCTs[92] (N=80) 3 unclear-ROB RCTs[89-91] (N= 300)	Mixed findings. No consistent evidence of effect	Insufficient	Inconsistent results and methodological limitations. Higher rate of negative UA in 1 low-ROB study, but no difference in 3 unclear-ROB studies.
Retention	1 low-ROB RCTs[92] and 3 unclear-ROB RCTs were included in MA[89-91] (N= 380)	No difference. Treatment retention naltrexone vs placebo: RR =1.11, 95% CI .88-1.41 I2=61%	Low	Studies reported inconsistent results and risk of bias
Harms	1 low-ROB RCTs[92] (N=80) 3 unclear-ROB RCTs[89-91] (N= 300)	No difference. WD due to AE Only 1 of the 4 studies reported severe AE's (3)[91]	Moderate	Studies had low and unclear-ROB.

Abbreviations: AE = Adverse event; CI = Confidence interval; MSM = men who have sex with men; RCT = randomized control trial; ROB = Risk of bias; RR = risk ratio; SR = Systematic review; UA = urinalysis; wk = week

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

Conclusions Table J. Summary of the evidence on pharmacotherapies in patients with comorbid amphetamine/methamphetamine and opioid use disorders

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Summary of findings by outcome	Strength of Evidence[a]	Comments
Opioid Antagonists				
Naltrexone				
Abstinence	0 RCTs	No studies	No evidence	There were no studies that reported abstinence outcomes in opioid use disorder populations.
Use	1 unclear-ROB RCTs[90] (N=100)	No difference.	Insufficient	Only 1 study limited by unclear-ROB and imprecision due to small sample size.
Retention	1 unclear-ROB RCTs[90] (N=100)	Favors naltrexone. The study found increased retention in the treatment group at 10 weeks.	Insufficient	Only 1 study limited by unclear-ROB and imprecision due to small sample size.
Harms	1 unclear-ROB RCTs[90] (N=100)	The study reported no AEs and no withdrawals due to AE.	Insufficient	Only 1 study limited by unclear-ROB and imprecision due to small sample size.

Abbreviations: AE = Adverse event; RCT = randomized control trial; ROB = Risk of bias; SR = Systematic review; UA = urinalysis

[a] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[10]
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.

REFERENCES

1. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* 2011; http://handbook.cochrane.org/. Accessed March 24, 2017.
2. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
3. Karila L, Weinstein A, Aubin H-J, Benyamina A, Reynaud M, Batki SL. Pharmacological approaches to methamphetamine dependence: a focused review. *British journal of clinical pharmacology.* 2010;69(6):578-592.
4. Singh M, Keer D, Klimas J, Wood E, Werb D. Topiramate for cocaine dependence: a systematic review and meta-analysis of randomized controlled trials. *Addiction (Abingdon, England).* 2016;111(8):1337-1346.
5. Castells X, Cunill R, Perez-Mana C, Vidal X, Capella D. Psychostimulant drugs for cocaine dependence. *The Cochrane database of systematic reviews.* 2016;9:CD007380.
6. Elkashef A, Vocci F, Hanson G, White J, Wickes W, Tiihonen J. Pharmacotherapy of methamphetamine addiction: An update. *Substance Abuse.* 2008;29(3):31-49.
7. NIH. What are the long-term effects of cocaine use? 2016. Accessed October 10, 2017, 2017.
8. Treadwell JR, Singh S, Talati R, McPheeters ML, Reston JT. AHRQ Methods for Effective Health Care. In: *A Framework for "Best Evidence" Approaches in Systematic Reviews.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
9. Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. *Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium (IHI).* 2012:819-824.
10. Berkman N, Lohr K, Ansari M, et al. *Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update.* Rockville, MD: Agency for Healthcare Research and Quality; Methods Guide for Comparative Effectiveness Reviews (AHRQ Publication No. 13(14)-EHC130-EF);2013.
11. Castells X, Kosten TR, Capella D, Vidal X, Colom J, Casas M. Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: A systematic review and meta-analysis of controlled clinical trials. *The American journal of drug and alcohol abuse.* 2009;35(5):339-349.
12. Indave BI, Minozzi S, Pani PP, Amato L. Antipsychotic medications for cocaine dependence. *The Cochrane database of systematic reviews.* 2016;3:CD006306.
13. Minozzi S, Amato L, Pani PP, et al. Dopamine agonists for the treatment of cocaine dependence. *The Cochrane database of systematic reviews.* 2015(5):CD003352.
14. Minozzi S, Cinquini M, Amato L, et al. Anticonvulsants for cocaine dependence. *The Cochrane database of systematic reviews.* 2015(4):CD006754.
15. Pani PP, Trogu E, Vacca R, Amato L, Vecchi S, Davoli M. Disulfiram for the treatment of cocaine dependence. *The Cochrane database of systematic reviews.* 2010(1):CD007024.
16. Pani PP, Trogu E, Vecchi S, Amato L. Antidepressants for cocaine dependence and problematic cocaine use. *The Cochrane database of systematic reviews.* 2011(12):CD002950.

17. Afshar M, Knapp CM, Sarid-Segal O, et al. The efficacy of mirtazapine in the treatment of cocaine dependence with comorbid depression. *The American journal of drug and alcohol abuse.* 2012;38(2):181-186.
18. Baldacara L, Cogo-Moreira H, Parreira BL, et al. Efficacy of topiramate in the treatment of crack cocaine dependence: a double-blind, randomized, placebo-controlled trial. *The Journal of clinical psychiatry.* 2016;77(3):398-406.
19. Bisaga A, Aharonovich E, Cheng WY, et al. A placebo-controlled trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. *Drug and alcohol dependence.* 2010;111(1-2):97-104.
20. Carroll KM, Nich C, Petry NM, Eagan DA, Shi JM, Ball SA. A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence. *Drug and alcohol dependence.* 2016;160:135-142.
21. Carroll KM, Nich C, Shi JM, Eagan D, Ball SA. Efficacy of disulfiram and Twelve Step Facilitation in cocaine-dependent individuals maintained on methadone: a randomized placebo-controlled trial. *Drug and alcohol dependence.* 2012;126(1-2):224-231.
22. Gilgun-Sherki Y, Eliaz RE, McCann DJ, et al. Placebo-controlled evaluation of a bioengineered, cocaine-metabolizing fusion protein, TV-1380 (AlbuBChE), in the treatment of cocaine dependence. *Drug and alcohol dependence.* 2016;166:13-20.
23. Hersh D, Van Kirk JR, Kranzler HR. Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology.* 1998;139(1-2):44-52.
24. Johnson BA, Roache JD, Ait-Daoud N, et al. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence. *Drug and alcohol dependence.* 2006;84(3):256-263.
25. Kablinger AS, Lindner MA, Casso S, et al. Effects of the combination of metyrapone and oxazepam on cocaine craving and cocaine taking: a double-blind, randomized, placebo-controlled pilot study. *Journal of psychopharmacology (Oxford, England).* 2012;26(7):973-981.
26. Kahn R, Biswas K, Childress A-R, et al. Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug and alcohol dependence.* 2009;103(1-2):59-64.
27. Kampman K, Majewska MD, Tourian K, et al. A pilot trial of piracetam and ginkgo biloba for the treatment of cocaine dependence. *Addictive behaviors.* 2003;28(3):437-448.
28. Kampman KM, Dackis C, Pettinati HM, Lynch KG, Sparkman T, O'Brien CP. A double-blind, placebo-controlled pilot trial of acamprosate for the treatment of cocaine dependence. *Addictive behaviors.* 2011;36(3):217-221.
29. Kampman KM, Volpicelli JR, Mulvaney F, et al. Effectiveness of propranolol for cocaine dependence treatment may depend on cocaine withdrawal symptom severity. *Drug and alcohol dependence.* 2001;63(1):69-78.
30. Kennedy AP, Gross RE, Whitfield N, Drexler KPG, Kilts CD. A controlled trial of the adjunct use of D-cycloserine to facilitate cognitive behavioral therapy outcomes in a cocaine-dependent population. *Addictive behaviors.* 2012;37(8):900-907.
31. Kosten TR, Wu G, Huang W, et al. Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine beta-hydroxylase. *Biological psychiatry.* 2013;73(3):219-224.
32. LaRowe SD, Kalivas PW, Nicholas JS, Randall PK, Mardikian PN, Malcolm RJ. A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. *The American journal on addictions.* 2013;22(5):443-452.

33. Licata SC, Penetar DM, Ravichandran C, et al. Effects of daily treatment with citicoline: a double-blind, placebo-controlled study in cocaine-dependent volunteers. *Journal of addiction medicine.* 2011;5(1):57-64.
34. Ling W, Hillhouse MP, Saxon AJ, et al. Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. *Addiction (Abingdon, England).* 2016;111(8):1416-1427.
35. Malcolm R, LaRowe S, Cochran K, et al. A controlled trial of amlodipine for cocaine dependence: a negative report. *Journal of substance abuse treatment.* 2005;28(2):197-204.
36. Mancino MJ, McGaugh J, Chopra MP, et al. Clinical efficacy of sertraline alone and augmented with gabapentin in recently abstinent cocaine-dependent patients with depressive symptoms. *Journal of clinical psychopharmacology.* 2014;34(2):234-239.
37. Margolin A, Kantak K, Copenhaver M, Avants SK. A preliminary, controlled investigation of magnesium L-aspartate hydrochloride for illicit cocaine and opiate use in methadone-maintained patients. *Journal of addictive diseases.* 2003;22(2):49-61.
38. Mariani JJ, Pavlicova M, Bisaga A, Nunes EV, Brooks DJ, Levin FR. Extended-release mixed amphetamine salts and topiramate for cocaine dependence: a randomized controlled trial. *Biological psychiatry.* 2012;72(11):950-956.
39. Moran LM, Phillips KA, Kowalczyk WJ, et al. Aripiprazole for cocaine abstinence: a randomized-controlled trial with ecological momentary assessment. *Behavioural pharmacology.* 2017;28(1):63-73.
40. Oliveto A, Poling J, Mancino MJ, et al. Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients. *Drug and alcohol dependence.* 2011;113(2-3):184-191.
41. Oliveto A, Poling J, Mancino MJ, et al. Sertraline delays relapse in recently abstinent cocaine-dependent patients with depressive symptoms. *Addiction (Abingdon, England).* 2012;107(1):131-141.
42. Pettinati HM, Kampman KM, Lynch KG, et al. A pilot trial of injectable, extended-release naltrexone for the treatment of co-occurring cocaine and alcohol dependence. *The American journal on addictions.* 2014;23(6):591-597.
43. Pettinati HM, Kampman KM, Lynch KG, et al. Gender differences with high-dose naltrexone in patients with co-occurring cocaine and alcohol dependence. *Journal of substance abuse treatment.* 2008;34(4):378-390.
44. Plebani JG, Lynch KG, Yu Q, Pettinati HM, O'Brien CP, Kampman KM. Results of an initial clinical trial of varenicline for the treatment of cocaine dependence. *Drug and alcohol dependence.* 2012;121(1-2):163-166.
45. Poling J, Rounsaville B, Gonsai K, Severino K, Sofuoglu M. The safety and efficacy of varenicline in cocaine using smokers maintained on methadone: a pilot study. *The American journal on addictions.* 2010;19(5):401-408.
46. Raby WN, Rubin EA, Garawi F, et al. A randomized, double-blind, placebo-controlled trial of venlafaxine for the treatment of depressed cocaine-dependent patients. *The American journal on addictions.* 2014;23(1):68-75.
47. Reid MS, Angrist B, Baker S, et al. A placebo-controlled screening trial of celecoxib for the treatment of cocaine dependence. *Addiction (Abingdon, England).* 2005;100 Suppl 1:32-42.

48. Reid MS, Angrist B, Baker SA, et al. A placebo controlled, double-blind study of mecamylamine treatment for cocaine dependence in patients enrolled in an opiate replacement program. *Substance abuse.* 2005;26(2):5-14.
49. Schmitz JM, Green CE, Hasan KM, et al. PPAR-gamma agonist pioglitazone modifies craving intensity and brain white matter integrity in patients with primary cocaine use disorder: a double-blind randomized controlled pilot trial. *Addiction (Abingdon, England).* 2017;112(10):1861-1868.
50. Schmitz JM, Lindsay JA, Green CE, Herin DV, Stotts AL, Moeller FG. High-dose naltrexone therapy for cocaine-alcohol dependence. *The American journal on addictions.* 2009;18(5):356-362.
51. Schmitz JM, Stotts AL, Sayre SL, DeLaune KA, Grabowski J. Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. *The American journal on addictions.* 2004;13(4):333-341.
52. Schottenfeld RS, Chawarski MC, Cubells JF, George TP, Lappalainen J, Kosten TR. Randomized clinical trial of disulfiram for cocaine dependence or abuse during buprenorphine treatment. *Drug and alcohol dependence.* 2014;136:36-42.
53. Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *The American journal of psychiatry.* 2005;162(2):340-349.
54. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of general psychiatry.* 1997;54(8):713-720.
55. Shoptaw S, Majewska MD, Wilkins J, Twitchell G, Yang X, Ling W. Participants receiving dehydroepiandrosterone during treatment for cocaine dependence show high rates of cocaine use in a placebo-controlled pilot study. *Experimental and clinical psychopharmacology.* 2004;12(2):126-135.
56. Shoptaw S, Yang X, Rotheram-Fuller EJ, et al. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. *The Journal of clinical psychiatry.* 2003;64(12):1440-1448.
57. Shorter D, Lindsay JA, Kosten TR. The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: A pilot study. *Drug and alcohol dependence.* 2013;131(1-2):66-70.
58. Sofuoglu M, Carroll KM. Effects of galantamine on cocaine use in chronic cocaine users. *The American journal on addictions.* 2011;20(3):302-303.
59. Sofuoglu M, Poling J, Babuscio T, et al. Carvedilol does not reduce cocaine use in methadone-maintained cocaine users. *Journal of substance abuse treatment.* 2017;73:63-69.
60. Sofuoglu M, Poling J, Gonzalez G, Gonsai K, Oliveto A, Kosten TR. Progesterone effects on cocaine use in male cocaine users maintained on methadone: a randomized, double-blind, pilot study. *Experimental and clinical psychopharmacology.* 2007;15(5):453-460.
61. Walsh SL, Middleton LS, Wong CJ, et al. Atomoxetine does not alter cocaine use in cocaine dependent individuals: double blind randomized trial. *Drug and alcohol dependence.* 2013;130(1-3):150-157.
62. Winhusen TM, Kropp F, Lindblad R, et al. Multisite, randomized, double-blind, placebo-controlled pilot clinical trial to evaluate the efficacy of buspirone as a relapse-prevention

treatment for cocaine dependence. *The Journal of clinical psychiatry.* 2014;75(7):757-764.
63. George TP, Chawarski MC, Pakes J, Carroll KM, Kosten TR, Schottenfeld RS. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biological psychiatry.* 2000;47(12):1080-1086.
64. Petrakis IL, Carroll KM, Nich C, et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction (Abingdon, England).* 2000;95(2):219-228.
65. Poling J, Oliveto A, Petry N, et al. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Archives of general psychiatry.* 2006;63(2):219-228.
66. Kampman KM, Pettinati H, Lynch KG, et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug and alcohol dependence.* 2004;75(3):233-240.
67. Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug and alcohol dependence.* 2013;133(1):94-99.
68. Johnson BA, Ait-Daoud N, Wang X-Q, et al. Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA psychiatry.* 2013;70(12):1338-1346.
69. Nuijten M, Blanken P, van den Brink W, Hendriks V. Treatment of crack-cocaine dependence with topiramate: a randomized controlled feasibility trial in The Netherlands. *Drug and alcohol dependence.* 2014;138:177-184.
70. Umbricht A, DeFulio A, Winstanley EL, et al. Topiramate for cocaine dependence during methadone maintenance treatment: a randomized controlled trial. *Drug and alcohol dependence.* 2014;140:92-100.
71. Somoza EC, Winship D, Gorodetzky CW, et al. A multisite, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of vigabatrin for treating cocaine dependence. *JAMA psychiatry.* 2013;70(6):630-637.
72. Brodie JD, Case BG, Figueroa E, et al. Randomized, double-blind, placebo-controlled trial of vigabatrin for the treatment of cocaine dependence in Mexican parolees. *The American journal of psychiatry.* 2009;166(11):1269-1277.
73. Kolar AF, Brown BS, Weddington WW, Haertzen CC, Michaelson BS, Jaffe JH. Treatment of cocaine dependence in methadone maintenance clients: a pilot study comparing the efficacy of desipramine and amantadine. *The International journal of the addictions.* 1992;27(7):849-868.
74. Kosten TR, Rosen MI, Schottenfeld R, Ziedonis D. Buprenorphine for cocaine and opiate dependence. *Psychopharmacology bulletin.* 1992;28(1):15-19.
75. Grabowski J, Rhoades H, Stotts A, et al. Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: two double-blind randomized clinical trials. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2004;29(5):969-981.
76. Margolin A, Avants SK, Kosten TR. Mazindol for relapse prevention to cocaine abuse in methadone-maintained patients. *The American journal of drug and alcohol abuse.* 1995;21(4):469-481.
77. Margolin A ASKMRTKTR. High- and low-dose mazindol for cocaine dependence in methadone- maintained patients: A preliminary evaluation. *Substance Abuse: Substance Abuse.* 1997;18(3):125.

78. Shorter D, Nielsen DA, Huang W, Harding MJ, Hamon SC, Kosten TR. Pharmacogenetic randomized trial for cocaine abuse: disulfiram and alpha1A-adrenoceptor gene variation. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology.* 2013;23(11):1401-1407.
79. Petry NM, Barry D, Alessi SM, Rounsaville BJ, Carroll KM. A randomized trial adapting contingency management targets based on initial abstinence status of cocaine-dependent patients. *Journal of consulting and clinical psychology.* 2012;80(2):276-285.
80. Petry Nm ASMCKMHTMSRBSS. Contingency management treatments: Reinforcing abstinence versus adherence with goal-related activities. *Journal of consulting and clinical psychology.* 2006;74(3):592.
81. Bhatt M, Zielinski L, Baker-Beal L, et al. Efficacy and safety of psychostimulants for amphetamine and methamphetamine use disorders: a systematic review and meta-analysis. *Systematic reviews.* 2016;5(1):189.
82. Elkashef AM, Rawson RA, Anderson AL, et al. Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2008;33(5):1162-1170.
83. Shoptaw S, Huber A, Peck J, et al. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug and alcohol dependence.* 2006;85(1):12-18.
84. Colfax GN, Santos G-M, Das M, et al. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. *Archives of general psychiatry.* 2011;68(11):1168-1175.
85. Coffin PO, Santos G-M, Das M, et al. Aripiprazole for the treatment of methamphetamine dependence: a randomized, double-blind, placebo-controlled trial. *Addiction (Abingdon, England).* 2013;108(4):751-761.
86. Tiihonen J, Kuoppasalmi K, Fohr J, et al. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *The American journal of psychiatry.* 2007;164(1):160-162.
87. Elkashef A, Kahn R, Yu E, et al. Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. *Addiction (Abingdon, England).* 2012;107(7):1297-1306.
88. Heinzerling KG, Shoptaw S, Peck JA, et al. Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. *Drug and alcohol dependence.* 2006;85(3):177-184.
89. Runarsdottir V, Hansdottir I, Tyrfingsson T, et al. Extended-Release Injectable Naltrexone (XR-NTX) With Intensive Psychosocial Therapy for Amphetamine-Dependent Persons Seeking Treatment: A Placebo-Controlled Trial. *Journal of addiction medicine.* 2017;11(3):197-204.
90. Tiihonen J, Krupitsky E, Verbitskaya E, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. *The American journal of psychiatry.* 2012;169(5):531-536.
91. Coffin PO, Santos G-M, Hern J, et al. Extended-release naltrexone for methamphetamine dependence among men who have sex with men: a randomized placebo-controlled trial. *Addiction (Abingdon, England).* 2017.
92. Jayaram-Lindstrom N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. *The American journal of psychiatry.* 2008;165(11):1442-1448.

93. Brown ES, Gabrielson B. A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. *Journal of affective disorders.* 2012;143(1-3):257-260.
94. Johnson BA, Ait-Daoud N, Elkashef AM, et al. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. *The international journal of neuropsychopharmacology.* 2008;11(1):1-14.
95. Ling W, Shoptaw S, Hillhouse M, et al. Double-blind placebo-controlled evaluation of the PROMETATM protocol for methamphetamine dependence. *Addiction (Abingdon, England).* 2012;107(2):361-369.
96. Mancino Mj FZCMCCSOA. Randomized placebo controlled trial of sertraline and sertraline plus gabapentin in depressed, recently abstinent cocaine-dependent patients. *Proceedings of the 71th Annual Scientific Meeting of the College on Problems of Drug Dependence;.* 2009:94.
97. Ersche KD, Sahakian BJ. The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychology review.* 2007;17(3):317-336.
98. Phillips KA, Epstein DH, Preston KL. Psychostimulant addiction treatment. *Neuropharmacology.* 2014;87:150-160.
99. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry.* 2008;165(2):179-187.
100. Minozzi S, Saulle R, De Crescenzo F, Amato L. Psychosocial interventions for psychostimulant misuse. *The Cochrane database of systematic reviews.* 2016;9:CD011866.
101. Moher D, Pham B, Lawson ML, Klassen TP. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health Technol Assess.* 2003;7(41):1-90.
102. Schmitz JM, Stotts AL, Rhoades HM, Grabowski J. Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addictive behaviors.* 2001;26(2):167-180.

APPENDIX A. SEARCH STRATEGIES

Data/Websites:

- Ovid Medline/PubMed: October 18, 2017
- PsycINFO: November 16, 2017
- EBM Reviews (Cochrane Database of Systematic Reviews CDSR, DARE, HTA, Cochrane Central Register of Controlled Trials): November 16, 2017
- ClinicalTrials.gov: January 10, 2018
- WHO ICTRP: November 16, 2017

Search Strategies

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date Searched: October 18, 2017
Searched by: Robin Paynter, MLIs

	Searches	Results
1	((stimulant* or psychostimulant* or psycho-stimulant*) adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).tw,kf.	3829
2	Cocaine/ or Crack Cocaine/ or Cocaine-Related Disorders/ or ((cocaine* or crack-cocaine*) adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).tw,kf.	32735
3	Methamphetamine/ or Amphetamine-Related Disorders/ or (methamphetamine* adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).tw,kf.	10705
4	or/1-3	44607
5	Drug Therapy/ or Substance-related disorders/dt, rh, th or Substance Withdrawal Syndrome/dt, rh, th or Substance Abuse, Intravenous/dt, rh, th	58862
6	(pharmacotherap* or pharmaco-therap* or long-acting or extended-release or sustained-release or depot or implant* or ((drug or pharmacol* or medication*) adj3 (therap* or treatment* or intervention*))).tw,kf.	640277
7	(drug therapy or rehabilitation or therapy).fs.	3939558
8	exp Anticonvulsants/ or Carbamazepine/ or Phenytoin/ or Vigabatrin/ or (gabapentin or lamotrigine or tiagabine or topiramate).nm.	141535
9	(anticonvulsant* or anti-convulsant* or antiepileptic* or anti-epileptic* or carbamazepine or clorazepate or clobazam or clonazepam or chlordiazepoxide or divalproex or ethosuximide or ethotoin or felbamate or fosphenytoin or gabapentin or lamotrigine or lignocaine or levetiracetam or lidocaine or hydantoins or levetiracetam or methsuximide or oxcarbazepine or paraldehyde or phenacemide or phenytoin or pregabalin or primidone or succinimide or tiagabine or topiramate or valproate or valproic-acid or vigabatrin or zonisamide).tw,kf.	113093
10	(A-poxide or Absenor or Akten or Anecream or Carbatrol or Celontin or Cerebyx or Chlordiazachel or Convulex or Depakene or Depakine or Depakote* or Depalept or Deprakine or Dilantin or Eha or Encorate or Endoxcin or Epilim or Epitol or Epival or Equetro or Felbatol or Gabitril or Gralise or H-tran or Horizant or Keppra* or Klonopin or Lidocaine* or Lamictal or Librax or Lidoderm or Librelease or Libritabs or Librium or Lygen or Lyrica or Mitran or Mysoline or Neuraptine or Neurontin or Onfi or Oxtellar* or Paral or Peganone or Phenurone or Phenytek or Poxi or Qudexy* or Recticare or Roweepra or "SmartRx Gaba-V	24697

	Kit" or Spritam or Stavzor orTegretol or Topicaine or Tranxene T-Tab or Trileptal or Topamax or Trokendi* or valcote or Valdoxan or valpakine or sabril or Xylocaine* or Zarontin or zonegran).tw,kf.	
11	Antidepressive Agents/ or Antidepressive Agents, Second-Generation/ or Antidepressive Agents, Tricyclic/ or Serotonin Uptake Inhibitors/ or Monoamine Oxidase Inhibitors/ or Amitriptyline/ or Amoxapine/ or Bupropion/ or Citalopram/ or Clomipramine/ or Desipramine/ or Doxepin/ or Duloxetine Hydrochloride/ or Fluoxetine/ or Fluvoxamine/ or Imipramine/ or Isocarboxazid/ or Maprotiline/ or Nortriptyline/ or Paroxetine/ or Perphenazine/ or Phenelzine/ or Protriptyline/ or Quetiapine Fumarate/ or Selegiline/ or Sertraline/ or Tranylcypromine/ or Trazodone/ or Trimipramine/ or Venlafaxine Hydrochloride/ or ("amitriptyline, chlordiazepoxide drug combination" or "amitriptyline, perphenazine drug combination" or duloxetine or nefazodone or mirtazapine or "olanzapine-fluoxetine combination" or venlafaxine).nm.	109361
12	(Antidepress* or anti-depress* or "Monoamine-oxidase inhibitor*" or MAOIs or "Serotonin and norepinephrine reuptake inhibitor*" or SNRI* or "selective serotonin reuptake inhibitor*" or SSRI* or amitriptyline or amoxapine or bupropion or citalopram or chlordiazepoxide-amitriptyline or clomipramine or desipramine or doxepin or duloxetine or escitalopram or fluoxetine or fluvoxamine-maleate or imipramine or isocarboxazid or maprotiline or mirtazapine or nefazodone or nortriptyline or olanzapine-fluoxetine or paroxetine* or perphenazine-amitriptyline or phenelzine-sulfate or protriptyline or quetiapine or selegiline or sertraline or tranylcypromine-sulfate or trazodone or trimipramine or venlafaxine).tw,kf.	110616
13	(Anafranil or Asendin or Aventyl or Celexa or Cymbalta or Desyrel or Elavil or Effexor or Emsam or Etrafon or fluvoxamine maleate or Lexapro or Limbitrol or Ludiomil or Luvox or Marplan or Nardil or Nefadar or Norpramin or Pamelor or Parnate or Paxil or Pexeva or Prozac or Remeron or Sarafem or Seroquel or Serzone or Sinequan or Surmontil or Symbyax or Tofranil* or Triavil or Vivactil or Wellbutrin or Zoloft or Zyban).tw,kf.	1993
14	exp antipsychotic/ or exp serotonin antagonists/ or Chlorpromazine/ or Clozapine/ or Droperidol/ or Fluphenazine/ or Haloperidol/ or Loxapine/ or Perphenazine/ or Pimozide/ or Prochlorperazine/ or Risperidone/ or Tetrabenazine/ or Thioridazine/ or Thiothixene/ or Trifluoperazine/	94870
15	(antipsychotic* or anti-psychotic* or aripiprazole or chlorpromazine or clozapine or droperidol or fluphenazine or haloperidol or lamotrigine or olanzapine or perphenazine or prochlorperazine or pimozide or quetiapine or reserpine or risperidone or ritanserin or ropinirol or symbax or tetrabenazine or thioridazine or trifluoperazine or ziprasidone).tw,kf.	104222
16	(Abilify or Aristada or Clozaril or Compro or Eskazine or Eskazinyl or FazaClo or Geodon or Haldol-Decanoate or Hibernal or Inapsine or Jatroneural or Lamictal or Largactil or Megaphen or Modalina or Modecate or Moditen or Orap or Prolixin or Raudixin or Risperdal or Seroquel or Serpalan or Serpasil or Stelazine or Symbyax or Terfluzine or Thorazine or Trifluoperaz or Triftazin or Trilafon or USAN or Versacloz or Xenazine or Zeldox or Zipwell or Zyprexa).tw,kf.	2118
17	Central nervous system stimulants/ or Dextroamphetamine/	25685
18	("central nervous system stimulant*" or CNS-stimulant* or dextroamphetamine or lisdexamfetamine or methadone or methylphenidate or modafinil or mazindol or "mixed amphetamine salts" or selegiline).tw,kf.	24702
19	Disulfiram/	3480
20	(disulfiram or antabuse).tw,kf.	3513
21	Dopamine agonists/ or Amantadine/ or Apomorphine/ or Bromocriptine/ or Carbidopa/ or Levodopa/ or Pergolide/ or Piribedil/ or (cabergoline or ciladopa or dihydrexidine or dinapsoline or lisuride or pramipexole or quinagolide or ropinirole or rotigotine or roxindole or "U 95666E").nm.	43732

22	("dopamine agonist*" or amantadine or apomorphine or bromocriptine or cabergoline or carbidopa or ciladopa or dihydrexidine or dinapsoline or doxanthrine or levodopa or L-Dopa or lisuride or pergolide or piribedil or pramipexole or quinagolide or ropinirole or rotigotine or roxindole or sumanirole).tw,kf.	47046
23	(Apokyn or Cabaser or Cycloset or Doperigin or Dostinex or Duopa or Lodosyn or Mirapex or Neupro or Norprolac or Parlodel or Permax or Prascend or Proclacam or Pronoran or Requip or Revanil or Rytary or Sinemet or Symmetrel or Trastal or Trivastal or Trivastan).tw,kf.	838
24	Narcotic antagonists/ or Buprenorphine/ or Naloxone/ or Naltrexone/ or Buprenorphine, Naloxone Drug Combination/	32558
25	(narcotic-antagonist* or opiate-antagonist* or naltrexone or naloxone or buprenorphine).tw,kf.	34250
26	(Belbuca or Buprenex or Butrans or Evzio or Narcan or Probuphine or Revia or Subutex or Vivitrol).tw,kf.	273
27	Baclofen/ or Buprenorphine/ or Butyrylcholinesterase/ or Dopamine Uptake Inhibitors/ or Guanfacine/ or Lisdexamfetamine Dimesylate/	20410
28	(baclofen or Biperiden or Buspirone or Butyrylcholinesterase or BChE or Cholinergic-antagonist or Citicoline or D-cycloserine or Dexamphetamine or Disulfiram or Guanfacine or Huperzine-A or Acetylcholinesterase-inhibitors or Ibudilast or Levodopa-carbidopa or Lisdexamfetamine or LDX or Mazindol or Methadone or Methylphenidate or "Mixed amphetamine salts" or Modafinil or Naltrexone or N-acetylcysteine or Nepicastat or DbetaH or Dopamine-beta-hydroxylase or Oxytocin or Phendimetrazine or Selegiline or Seroquel-XRTM or Topiramate or varenicline or venlafaxine or Yohimbine).tw,kf.	106743
29	(Acetadote or Adipost or Akineton or Anorex-SR or Appecon or Aptensio-XR or Bontril or Buspar or Cerebra or Cetylev or Chantix or Concerta or "Cotempla XR-ODT" or Daytrana or Dexedrine-Spansule or Diskets or Dolophine or Effexor-XR or Eyevinal or Gablofen or Intuniv or Ketas or Lioresal or Mazanor or Melfiat or Metadate-ER or Methadose or Methylin or Neurocoline or Obezine or Phendiet or Pinatos or Pitocin or Plegine or Prelu-2 or ProCentra or Provigil or QuilliChew-ER or Quillivant-XR or Ritalin or Sanorex or Statobex or Vyvanse or Zenzedi).tw,kf.	1746
30	or/5-29	4748040
31	and/4,30	20963
32	randomized controlled trial.pt.	497191
33	controlled clinical trial.pt.	99259
34	randomized.ab.	434049
35	placebo.ab.	202943
36	drug therapy.fs.	2115665
37	randomly.ab.	299103
38	trial.ti,ab.	535945
39	groups.ab.	1847636
40	or/32-39	4396867
41	and/31,40	6818
42	((exp child/ or adolescent/ or exp infant/) not exp adult/) or ((infant or infants or neonatal* or newborn* or toddler* or pre-school or preschool or children or girl or girls or boy or boys or pediatric or paediatric or adolesc* or pre-teen* or teenager or teenagers or juvenile or juveniles or youth or youths) not (adult or adults or middle-aged or aged)).ti.	2106853
43	41 not 42	6343
44	(exp animals/ not humans/) or (bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or ewe or ewes or feline or goat or goats or horse or horses or invertebrate or invertebrates or macaque or macaques or mare or mares or mice or monkey	5015863

	or monkeys or mouse or ovine or pig or pigs or porcine or primate or primates or rabbit or rabbits or rat or rats or rattus or rhesus or sheep or simian or sow or sows or vertebrate or vertebrates).ti.	
45	43 not 44	4523
46	((opioid or opiate) adj2 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).ti.	4789
47	45 not 46	4442
48	limit 47 to english language	4248
49	remove duplicates from 48	3872

Ovid PsycINFO 1806 to November Week 1 2017
Date Searched: November 16, 2017
Searched by: Robin Paynter, MLIS

#	Searches	Results
1	((stimulant* or psychostimulant* or psycho-stimulant*) adj5 (abstain* or abstinence or abstinent or abuse* or addict* or chronic* or detox* or disorder* or depend* or habitual* or misuse* or overuse or reduce* or reducing or reduction or retain* or retention or users or withdrawal)).tw,hw,id.	3021
2	cocaine/ or crack cocaine/ or ((cocaine* or crack-cocaine*) adj5 (abstain* or abstinence or abstinent or abuse* or addict* or chronic* or detox* or disorder* or depend* or habitual* or misuse* or overuse or reduce* or reducing or reduction or retain* or retention or users or withdrawal)).tw,hw,id.	15144
3	methamphetamine/ or ((methamphetamine or metamfetamine) adj5 (abstain* or abstinence or abstinent or abuse* or addict* or chronic* or detox* or disorder* or depend* or habitual* or misuse* or overuse or reduce* or reducing or reduction or retain* or retention or users or withdrawal)).tw,hw,id.	3901
4	or/1-3	20687
5	drug therapy/ or craving/ or detoxification/ or drug abstinence/ or drug rehabilitation/ or drug withdrawal/ or exp "recovery (disorders)"/ or sobriety/	165337
6	(pharmacotherap* or pharmaco-therap* or psychopharmacol* or psycho-pharmacol* or controlled-release or delayed-action or depot or extended-release or implant* or long-acting or prolonged-action or sustained-release or timed-release or ((drug or pharmacol* or medication*) adj3 (therap* or treatment* or intervention*))).tw,hw,id.	186235
7	drugs/ or anticonvulsive drugs/ or antidepressant drugs/ or cns affecting drugs/ or dopamine agonists/ or narcotic antagonists/ or serotonin agonists/ or serotonin antagonists/	58893
8	anticonvulsive drugs/ or carbamazepine/ or chloral hydrate/ or clonazepam/ or diphenylhydantoin/ or gabapentin/ or nitrazepam/ or oxazepam/ or pentobarbital/ or phenobarbital/ or pregabalin/ or primidone/ or valproic acid/	11044
9	(anticonvuls* or anti-convuls* or antiepileptic* or anti-epileptic* or carbamazepine or clorazepate or clobazam or clonazepam or chlordiazepoxide or divalproex or ethosuximide or ethotoin or felbamate or fosphenytoin or gabapentin or hydantoin? or lamotrigine or lignocaine or levetiracetam or lidocaine or lignocaine or methsuximide or oxcarbazepine or paraldehyde or phenacemide or phenytoin or pregabalin or primidone or succinimide or tiagabine or topiramate or valproate or valproic-acid or vigabatrin or xylocaine or zonisamide).tw,hw,id.	22792
10	(A-poxide or Absenor or Akten or Anecream or Carbatrol or Celontin or Cerebyx or Chlordiazachel or Convulex or Depakene or Depakine or Depakote* or Depalept or Deprakine or Dilantin or Eha or Encorate or Endoxcin or Epilim or Epitol or Epival or Equetro or Felbatol or Frisium or Gabitril or Gralise or H-tran or Horizant or Keppra* or Klonopin or Lidocaine* or	4442

	Lamictal or Librax or Lidoderm or Librelease or Libritabs or Librium or Lygen or Lyrica or Mesantoin or Mitran or Mysoline or Neuraptine or Neurontin or Onfi or Oxtellar* or Paral or Peganone or Phenurone or Phenytek or Poxi or Qudexy* or Recticare or Roweepra or Sabril or "SmartRx Gaba-V Kit" or Spritam or Stavzor or Tegretol or Topicaine or Tranxene or Trileptal or Topamax or Topicaine or Trokendi* or Valcote or Valdoxan or Valpakine or Valproate or Xylocaine* or Zarontin or Zonegran).tw,hw,id.	
11	antidepressant drugs/ or monoamine oxidase inhibitors/ or serotonin norepinephrine reuptake inhibitors/ or serotonin reuptake inhibitors/ or tricyclic antidepressant drugs/ or amitriptyline/ or bupropion/ or chlorimipramine/ or citalopram/ or desipramine/ or doxepin/ or fluoxetine/ or fluvoxamine/ or imipramine/ or iproniazid/ or isocarboxazid/ or lithium carbonate/ or maprotiline/ or methylphenidate/ or mianserin/ or moclobemide/ or molindone/ or monoamine oxidase inhibitors/ or nefazodone/ or nialamide/ or nomifensine/ or nortriptyline/ or pargyline/ or paroxetine/ or phenelzine/ or pheniprazine/ or pipradrol/ or sertraline/ or sulpiride/ or tranylcypromine/ or trazodone/ or venlafaxine/ or zimeldine/	39238
12	(Antidepress* or anti-depress* or "Monoamine-oxidase inhibit*" or MAOIs or "Norepinephrine-dopamine reuptake inhibit*" or "Serotonin antagonist and reuptake inhibit*" or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Tricyclic uptake inhibit*" or amitriptyline or amoxapine or bupropion or citalopram or chlordiazepoxide-amitriptyline or clomipramine or desipramine or desvenlafaxine or doxepin or duloxetine or escitalopram or fluoxetine or fluvoxamine or imipramine or isocarboxazid or levomilnacipran or maprotiline or mirtazapine or nefazodone or nortriptyline or olanzapine-fluoxetine or paroxetine* or perphenazine or phenelzine or piperazinyl-phenothiazine or protriptyline or quetiapine or selegiline or sertraline or tranylcypromine or trazodone or trimipramine or venlafaxine).tw,hw,id.	59349
13	(Anafranil or Asendin or Aventyl or Celexa or Cymbalta or Desyrel or Effexor or Elavil or Elontril or Emsam or Enerzer or Etrafon or Fetzima or Fluvoxamine-maleate or Khedezla or Lexapro or Limbitrol or Ludiomil or Luvox or Marplan or Nardelzine or Nardil or Nefadar or Norpramin or Oleptro or Pamelor or Parnate or Paxil or Pexeva or Pristiq or Prozac or Remeron or Sarafem or Seroquel or Serzone or Sinequan or Surmontil or Symbyax or Tofranil* or Triavil or Vanatrip or Vivactil or Wellbutrin or Zoloft or Zyban).tw,hw,id.	891
14	neuroleptic drugs/ or serotonin antagonists/ or piperazines/ or aripiprazole/ or clozapine/ or dihydroxytryptamine/ or lysergic acid diethylamide/ or mianserin/ or molindone/ or nialamide/ or olanzapine/ or parachlorophenylalanine/ or quetiapine/ or reserpine/ or risperidone/ or ritanserin/ or spiroperidol/ or sulpiride/ or tetrabenazine/ or trazodone/	33526
15	(antipsychotic* or anti-psychotic* or aripiprazole or chlorpromazine or clozapine or droperidol or fluphenazine or haloperidol or lamotrigine or olanzapine or perphenazine or prochlorperazine or pimozide or reserpine or risperidone or ritanserin or ropinirol or symbax or tetrabenazine or thioridazine or trifluoperazine or ziprasidone).tw,hw.	45882
16	(Abilify or Aristada or Clozaril or Compro or Eskazine or Eskazinyl or FazaClo or Geodon or Haldol-Decanoate or Hibernal or Inapsine or Jatroneural or Lamictal or Largactil or Megaphen or Modalina or Modecate or Moditen or Navane or Orap or Prolixin or Raudixin or Risperdal or Seroquel or Serpalan or Serpasil or Stelazine or Symbyax or Terfluzine or Thorazine or Trifluoperaz or Triftazin or Trilafon or Versacloz or Xenazine or Zeldox or Zipwell or Zyprexa).tw,hw,id.	577
17	cns stimulating drugs/ or cns affecting drugs/ or caffeine/ or dextroamphetamine/ or ephedrine/ or methylphenidate/ or pemoline/ or pentylenetetrazol/ or pipradrol/ or piracetam/	11460
18	("central nervous system stimulant*" or CNS-stimulant* or dextroamphetamine or lisdexamfetamine or methadone or methylphenidate or modafinil or mazindol or amphetamine-salts).tw,hw,id.	15298
19	disulfiram/	339
20	(disulfiram or antabuse).tw,hw,id.	780

21	dopamine agonists/ or amantadine/ or apomorphine/ or bromocriptine/ or cabergoline/ or carbidopa/ or levodopa/ or quinpirole/	6922
22	("dopamine agonist*" or amantadine or apomorphine or bromocriptine or cabergoline or carbidopa or ciladopa or dihydrexidine or dinapsoline or doxanthrine or levodopa or L-Dopa or lisuride or pergolide or piribedil or pramipexole or quinagolide or ropinirole or rotigotine or roxindole or sumanirole).tw,hw,id.	11673
23	(Apokyn or Cabaser or Cycloset or Doperigin or Dostinex or Duopa or Lodosyn or Mirapex or Neupro or Norprolac or Parlodel or Permax or Prascend or Proclacam or Pronoran or Requip or Revanil or Rytary or Sinemet or Symmetrel or Trastal or Trivastal or Trivastan).tw,hw,id.	75
24	narcotic antagonists/ or nalorphine/ or naloxone/ or naltrexone/ or buprenorphine/	6649
25	(narcotic-antagonist* or opiate-antagonist* or naltrexone or nalorphine or naloxone or buprenorphine).tw,hw,id.	10481
26	(Belbuca or Buprenex or Butrans or Evzio or Lethidrone or Nalline or Narcan or Probuphine or Revia or Subutex or Vivitrol).tw,hw,id.	116
27	acetylcholine/ or adrenergic drugs/ or dextroamphetamine/ or ephedrine/ or epinephrine/ or methoxamine/ or tyramine/ or adrenergic blocking drugs/ or alpha methylparatyrosine/ or dihydroergotamine/ or "hydroxydopamine (6-)"/ or phenoxybenzamine/ or propranolol/ or yohimbine/ or exp baclofen/ or benzodiazepines/ or alprazolam/ or chlordiazepoxide/ or clonazepam/ or diazepam/ or flunitrazepam/ or flurazepam/ or lorazepam/ or midazolam/ or nitrazepam/ or oxazepam/ or cholinesterase inhibitors/ or galanthamine/ or neostigmine/ or physostigmine/ or dopamine antagonists/ or sulpiride/ or gamma aminobutyric acid/ or gamma aminobutyric acid agonists/ or acamprosate/ or muscimol/ or hydroxyzine/	32505
28	(Acamprosate or Acetylcholinesterase-inhibitors or Adderall or Baclofen or Biperiden or Buspirone or Butyrylcholinesterase or BChE or CDP-choline or Cholinergic-antagonist or Citicoline or D-amphetamine or D-cycloserine or D-serine or DbetaH or Dexamphetamine or Diazepam or Disulfiram or Dopamine-beta-hydroxylase or Doxazosin or Flumazenil or Flupenthixol or GABA or Guanfacine or Huperzine-A or Hydroxyzine or Ibudilast or Labetalol or Levodopa-carbidopa or Lisdexamfetamine or LDX or Mifepristone or N-acetylcysteine or Nepicastat or Nimodipine or Ondansetron or Oxytocin or Pemoline or Phendimetrazine or Piracetam or Prazosin or Progesterone or Propranolol or Seroquel-XRTM or Varenicline or Yohimbine).tw,hw,id.	38665
29	(Acetadote or Adipost or Akineton or Anorex-SR or Appecon or Aptensio-XR or Bontril or Buspar or Cardura or Cerebra or Cetylev or Chantix or Concerta or "Cotempla XR-ODT" or Daytrana or Dexedrine-Spansule or Diskets or Dolophine or Effexor-XR or Eyevinal or Gablofen or Intuniv or Ketas or Lioresal or Mazanor or Melfiat or Metadate-ER or Methadose or Methylin or Neurocoline or Obezine or Phendiet or Pinatos or Pitocin or Plegine or Prelu-2 or ProCentra or Prometa or Provigil or QuilliChew-ER or Quillivant-XR or Ritalin or Sanorex or Statobex or Vyvanse or Zenzedi).tw,hw,id.	791
30	or/5-29	331603
31	and/4,30	10058
32	limit 31 to "0300 clinical trial"	264
33	random sampling/	767
34	placebo/	5003
35	(trial* or RCT*).tw,id.	160183
36	(random* or sham or placebo*).ab,id.	199886
37	((singl* or doubl* or tripl* or trebl*) adj (blind* or dumm* or mask*)).tw,hw,id.	23708
38	or/32-37	301662
39	and/31,38	1971

40	((animal model* or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or ewe or ewes or feline or goat or goats or horse or hamster* or horses or invertebrate or invertebrates or macaque or macaques or mare or mares or mice or monkey or monkeys or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate or primates or rabbit or rabbits or rat or rats or rattus or rhesus or rodent* or sheep or simian or sow or sows or vertebrate or vertebrates or zebrafish) not (aged or adolescen* or adults or boy or boys or case or child or children or childhood or clinical* or fraternal* or geriatric* or girl or girls or human* or juvenile* or man or maternal* or men or middle-aged or paternal* or patient* or sororal* or subjects or woman or women or youth)).ti,id. not (adults or boy or boys or child or children or childhood or clinical* or geriatric* or girl or girls or human* or man or men or patient* or woman or women).ab,id.	192341
41	39 not 40	1788
42	limit 41 to english language	1751
43	remove duplicates from 42	1749
44	limit 31 to ("0830 systematic review" or 1200 meta analysis)	87
45	limit 44 to english language	82
46	remove duplicates from 45	82

WHO ICTRP (http://apps.who.int/trialsearch/AdvSearch.aspx**)**
Date Searched: November 16, 2017
Searched by: Robin Paynter, MLIS

Methamphetamine OR metamfetamine OR cocaine OR crack [Title] ALL [Recruitment status] Phase 3 OR Phase 4 [Phases] 77 result records

APPENDIX B. TECHNICAL EXPERT PANEL

Adam Gordon, MD, MPH, FACP
Professor of Medicine, University of Pittsburgh
Co-Director, Interdisciplinary Addictions Program for Education and Research, Pittsburgh VAMC
Core Investigator, CHERP

Steven Batki, MD
Professor of Psychiatry, University of California, San Francisco
Director, Addiction Psychiatry Research Program, San Francisco VAMC

Bryon Adinoff, MD
Professor and Distinguished Professor of Alcohol and Drug Abuse Research, University of Texas Southwestern Medical Center (Dallas)
Director of Research for Mental Health, VA North Texas Health Care System

Larissa Mooney, MD
Director, Addiction Medicine Clinic, University of California – Los Angeles
Physician, Mental Health, VA Greater Los Angeles Health Care System

Kyle Kampman, MD
Professor of Psychiatry at the Hospital of the University of Pennsylvania and the Presbyterian Medical Center of Philadelphia
Medical Director, The Charles O'Brien Center for the Treatment of Addictions

Richard De La Garza, Ph.D.
Professor of Psychiatry Research, Baylor College of Medicine, Houston, TX, US
Professor and Director of Research, Department of Psychiatry, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Peter Hauser, MD
Mental Health Program Coordinator, VA Long Beach Healthcare System

APPENDIX C. STUDY SELECTION

Inclusion codes, code definitions, and criteria

1. Is the population made up of non-pregnant/non-postpartum adults with cocaine or amphetamine use disorder?

   Yes " Proceed to 2.
   No " STOP. **Code X1** *(Excluded population)*

2. Does the intervention include pharmacotherapy to treat stimulant use disorder?
   Exclude: Pharmacotherapies intended to treat comorbid substance dependence (eg, alcohol or heroin) rather than stimulant use.

   Yes " Proceed to 3.
   No " STOP. **Code X2** *(Not relevant to topic)*

3. Is the study design a randomized controlled trial with followup of 4 weeks or longer?

   Yes " Proceed to 4.
   No " STOP. **Code X3** (*Excluded study design or publication type)*

   Exclude: Narrative or non-systematic review; opinion/editorial; cross-sectional study; case report/case series; case-control; cohort study; conference proceeding published before 2015.
   Also exclude RCTs that compare dosage levels of the same drug, without a placebo group or other active comparator.

   . **Note:** Systematic reviews, meta-analyses, and other important background/discussion papers should be coded **B-X3**, followed by notes/keywords**.**

   Examples:
   B-X3 – SR, pearl references
   B-X3 – narrative review with good background
   B-X3 – useful for discussion
   B-X3 – discusses timing and frequency of UA in trials

4. Does the study measure substance use by urinalysis at least once per week?

   Yes " Proceed to 5.
   No " STOP. **Code X4** *(No outcomes of interest)*

   Note: We will not analyze the following outcomes:

   - Craving or withdrawal symptoms
   - Mental health outcomes (anxiety/depression)
   - Medication adherence via pill count or biomarkers

- Lab values other than UA for measuring abstinence

5. Do all study arms receive identical treatment with the exception of the medication being tested? For example, if the active arm receives psychotherapy, the comparator arm should receive an identical form of psychotherapy with the same frequency and level of intensity as the primary arm.
   Yes " Proceed to 6.
   No " STOP. **Code X5** (*Unbalanced study design*)

6. Does the comparator arm consist of another active medication for treating stimulant use disorder?
   Yes " **Code H2H.** Go to 7.
   No " **Code RCT.** Go to 7.

7. Indicate which stimulant disorder is the primary target of the intervention (cocaine, methamphetamine, or either/both).

8. Enter the medication(s) being tested.

9. Enter any applicable subgroups. Examples:

   Opioid: Methadone/buprenorphine-maintained or comorbid opioid-dependent

   ADHD: Attention-deficit hyperactive disorder

   Alcohol: comorbid alcohol abuse

   Depression/anxiety: identified at study entry

   PTSD: identified at study entry

   MSM

   HIV, HCV

APPENDIX D. QUALITY ASSESSMENT CRITERIA

Domain	Criteria[1]
Sequence generation	Was the allocation sequence adequately generated?
Allocation concealment	Was allocation adequately concealed?
Blinding	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data	Were incomplete and missing outcome data adequately addressed?
Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	Was the study apparently free of other problems that could put it at a high risk of bias?
Overall assessment of potential for bias	Low/Unclear/High

Quality Assessment of Included Studies

Author, year	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Risk of Bias
Afshar, 2012[17]	NR	NR	Yes	No	Yes	No	High
Baldacara, 2016[18]	Yes	Unclear	Yes	Yes	Yes	Yes	Low
Bisaga, 2010[19]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Carroll, 2012[21]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Carroll, 2016[20]	Yes	Yes	Yes	NR	Yes	Yes	Low
Coffin, 2013[85]	Yes	Yes	Yes	Yes	Yes	No	Unclear
Coffin, 2017[91]	Yes	Yes	Yes	Yes	Yes	No	Unclear
Colfax, 2011[84]	Yes.	Yes	Yes	Yes	Yes	No	Unclear
Elkashef, 2008[82]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear
Elkashef, 2012[87]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Heinzerling, 2006[88]	Unclear	Unclear	Yes	Yes	Yes	Yes	Low
Hersh, 1998[23]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Jayaram-Lindstrom, 2008[92]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Kahn, 2009[26]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Kampman, 2011[28]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Kosten, 2013[31]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Ling, 2016[34]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Mancino, 2014[36]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Moran, 2017[39]	Yes	Yes	Yes	Yes	Yes	No	High
Oliveto, 2011[40]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Oliveto, 2012[41]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Pettinati, 2008[43]	Yes	Yes	Yes	Yes	Yes	No	Unclear
Pettinati, 2014[42]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Plebani, 2012[44]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Poling, 2010[45]	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear

Author, year	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Risk of Bias
Raby, 2014[46]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Runarsdottir, 2017[89]	Yes	Unclear	Yes	Yes	Yes	No	Unclear
Schmitz, 2004[51]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Schmitz, 2009[50]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Schottenfeld, 1997[54]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Schottenfeld, 2005[53]	Yes	Yes	Yes	No	Yes	Yes	Unclear
Schottenfeld, 2014[52]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Shoptaw, 2003[56]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear
Shoptaw, 2006[83]	Yes	Yes	Yes	Unclear	Yes	No	Unclear
Tiihonen, 2007[86]	No	Unclear	No	Yes	Yes	No	High
Tiihonen, 2012[90]	Yes	Yes	Yes	Yes	Yes	No	High
Walsh, 2013[61]	Yes	Yes	Yes	Yes	Yes	No	Unclear
Winhusen, 2014[62]	Yes	NR	Yes	Yes	Yes	No	High

APPENDIX E. PEER REVIEWER COMMENTS AND AUTHOR RESPONSES

Reviewer Number	Comment	Author response
Are the objectives, scope, and methods for this review clearly described?		
1	Yes	Noted.
3	Yes	Noted.
5	Yes	Noted.
6	Yes	Noted.
7	Yes	Noted.
Is there any indication of bias in our synthesis of the evidence?		
1	No	Noted.
3	Yes - I am concerned that relying on review papers may have biased the results slightly see below	By necessity this review was broadly scoped. There is good precedent for using systematic reviews for this process.
5	No	Noted.
6	No	Noted.
7	No	Noted.
Are there any published or unpublished studies that we may have overlooked?		
1	Yes - 3 papers: Kampman paper on propranolol; Carroll paper on psychotherapy and disulfiram; Kosten paper on disulfiram and genetics. The latter 2 are provided in the attachment.	We had identified and included the Kampman 2001 study of propranolol, but inadvertently omitted it from the draft report; we have made this correction and added it to the section on Other Pharmacotherapies. We examined the Carroll 2004 study, which was identified in an included systematic review (Pani 2010), but we were not able to combine the outcomes with other studies in meta-analysis. The Kosten paper on disulfiram and genetics has been incorporated in KQ2.
3	Yes - The use of reviews may have led to insufficient weight being given to the evidence supporting some medications, for instance topiramate	As mentioned above there is good precedent for the use of reviews. However, one of the SRs (Minozzi 2015) did not examine continuous abstinence as an outcome. Subsequently, we abstracted data on continuous abstinence from the included RCTs and this did reveal positive findings on topiramate which are now included in this report.
5	Yes - See Comments from Reviewer 5 below	Noted.
6	No	Noted.
7	No	Noted.
Additional suggestions or comments can be provided below.		

Reviewer Number	Comment	Author response
1	There are multiple wording issues. The provision of data from the ASI makes no sense throughout the synthesis and needs to be corrected. Many other specific suggestions are included below.	Wording issues have been addressed. We agree that the ASI drug composite metric may not be meaningful since the ASI score is not specific to stimulant use. While our initial aim was to abstract addiction severity as a population characteristic, we agree that there is no clear way to present severity for comparison across studies due to variability in reporting and metrics used. We have therefore removed addiction severity from the tables altogether.
3	The use of red and green as highlighting color for the tables is difficult for those who are red green colorblind.	We considered this limitation of the color choices, and selected hues with varying levels of saturation that were distinguishable on hardcopy when printed in greyscale.
3	There are now two positive trials of the combination of Adderall and topiramate for the treatment of cocaine use disorder. One is referenced, the second is being presented at CPDD 13 June.	We included a study published in 2012 among the section of “Other Pharmacotherapies” in KQ1, and noted a positive effect of topiramate combined with mixed amphetamine salts. We looked into the recently completed trial of Adderall-ER combined with topiramate for cocaine dependence (NCT01811940) as suggested, but the findings of this study were not yet available at the time of this writing.
6	Nice job! No further comments.	Noted, thank you.
1	Page 2; line 12: Not clear if "withdrawals" here means a physiologic withdrawal syndrome or dropout from treatment.	We have clarified the wording to mean dropout from treatment.
1	Page 2; line 45: We may have missed propranolol and doxazosin.	The Shorter, 2013 study in the “Other Pharmacotherapies” section examined the effects of doxazosin. We had included a study on propranolol (Kampman 2001) but had mistakenly omitted it from the narrative; we have corrected this error.
1	Page 6; line 20: These medications all work in the brain, so why would they not be considered psychopharmacotherapies. The distinction is unclear.	We agree, and have changed the category of “psychopharmacotherapies” to “mental health pharmacotherapies”.
1	Page 11; line 9: Change to "stimulant use disorder."	Done.
1	Page 11; line 44: It is not alternative or concurrent, it is offered as the primary treatment modality.	We have revised the sentence accordingly.
1	Page 11; line 46: Add "treatment" before "retention."	Done.

Reviewer Number	Comment	Author response
1	Page 13; line 43: Treatment retention and dropout are really the same outcome, and both probably do not need to be mentioned.	We have made the suggested change.
1	Page 20; line 15: Do not capitalize acamprosate	Done.
1	Page 22; line 28: specify treatment dropout or study withdrawal here so as not to confuse with physiologic cocaine withdrawal.	Done.
1	Page 24; line 49: Hard to grasp this row when it breaks across pages.	We have adjusted the rows as suggested.
1	Page 28; line 52: Resperpine is not really an antipsychotic.	We understand that this isn't a perfect characterization, however we are using the classification that Cochrane used. Additionally, changing the class would not change the conclusions.
1	Page 30; line 20: selegeline in an MAO inhibitor, not a stimulant, although l-amphetamine is a metabolite.	We understand that this isn't a perfect characterization, however we are using the classification that Cochrane used. Additionally, changing the class would not change the conclusions.
1	Page 37; line 8: Not sure why Carroll, K. M., L. R. Fenton, S. A. Ball, C. Nich, T. L. Frankforter, J. Shi and B. J. Rounsaville (2004). "Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial." Archives of General Psychiatry 61(3): 264-272. is not included.	The Carroll 2004 paper was identified in an included systematic review (Pani, 2010). We examined the Carroll 2004 study for inclusion in our meta-analyses, but the reported outcomes were not combinable with other studies.
1	Page 39; line 39: Injectable should be sublingual.	We have made the correction as suggested.
1	Page 45; line 42: change 280 to 380	We corrected this error.
1	Page 60; line 22: What about, Kosten et al., Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β-hydroxylase. Biol Psychiatry. 2013 Feb 1;73(3):219-24. doi: 10.1016/j.biopsych.2012.07.011.	We have added this study as suggested.
1	Page 68; line 43: Don't understand "study duration use."	We have clarified the wording to convey use during the study period.
1	Page 69; line 5: treatment withdrawals	Noted.
1	Page 76; line 22: This sentence is in contradiction to one two paragraphs below (Line 41)	We have corrected the inconsistency.
1	Page 92; line 6: You may be lumping cocaine studies and methamphetamine studies together here. If so, you need to explain that point.	We have separated the cocaine and methamphetamine studies in the analysis of contingency management, and included them with the respective sections on subgroup analyses (KQ2 and KQ4).
1	Page 93; line 23: treatment withdrawal or dropout.	We have made this change throughout the review.

5	Page 92: The Contingency Management (CM) section of the review reports "there was no significant difference between studies that did vs. did not use contingency management in proportion of subjects who completed treatment." This can easily be misinterpreted to mean that CM has no effect on treatment retention in general, not just in pharmacotherapy trials. In fact, several studies have demonstrated a treatment retention benefit associated with CM. The attendance rates for prize CM in the published literature range from as high as 70.5% (Petry, Alessi, Carroll, et al., 2006) to as low as 45% (Petry, Weinstock, Alessi, et al., 2010). In the VA's national implementation of CM, patients attended 55.9% of sessions delivered twice-weekly over 12 weeks (DePhilippis et al., 2018). Because patients in the VA initiative included those who were initially-abstinent and those who were not, the study by Petry and colleagues (2012) that examined differential outcomes by initial abstinence status provides the most appropriate comparison. That study found an attendance rate of 67.1% for patients initially abstinent and 46.7% for patients who began treatment with a positive sample (Petry, Barry, Alessi, et al., 2012). The attendance rate (55.9%) observed among VA's CM patients is about the average of these two rates. Furthermore, in the VA's CM implementation, fifty percent of CM patients completed 14 or more CM sessions within the designated treatment period (typically 12 weeks) (DePhilippis et al., 2018). In comparison, Oliva et al. (2013) found that only 42% of VA patients with an outpatient SUD treatment episode completed more than two sessions of care in a one year period. Petry, N.M., Alessi, S.M., Carroll, K.M., Hanson, T., MacKinnon, S., Rounsaville, B., Sierra, S., 2006. Contingency management treatments: Reinforcing abstinence versus adherence with goal-related activities. J. Consult. Clin. Psychol., 74(3), 592–601. doi:10.1037/0022-006X.74.3.592 Petry, N.M., Weinstock, J., Alessi, S.M., Lewis, M.W., Dieckhaus, K., 2010b. Group-based randomized trial of contingencies for health and abstinence in HIV patients. J. Consult. Clin. Psychol., 78(1), 89–97. doi:10.1037/a0016778. Oliva, E.M., Bowe, T., Sox-Harris, A.H., Trafton, J.A., 2013. False Starts in Psychotherapy for Substance Use Disorders and PTSD in the VHA.	Noted. We have added clarification on the efficacy of CM, specifically that the efficacy of the pharmacotherapy didn't change based on CM, but that this observation is limited by very few studies that directly compared the use of CM.

Reviewer Number	Comment	Author response
	Psychiatric Services, 64(8), 722. doi:10.1176/appi.ps.201300145. DePhilippis, D., Petry, N.M., Bonn-Miller, M.O., Rosenbach, S.B., McKay, J.R. (2018). The national implementation of Contingency Management (CM) in the Department of Veterans Affairs: Attendance at CM sessions and substance use outcomes. Drug and Alcohol Dependence, 185, 367-373. doi: 10.1016/j.drugalcdep.2017.12.020	
5	Page 1, Line 8: change 'Stimulant abuse and dependence' to the new, DSM-V nomenclature of 'Stimulant use disorder.'	We have made the suggested change.
5	Page 11, Line 16: change 'dependence or abuse' to 'substance use disorder.'	We have made the suggested change.
5	Page 11, Lines 39-48: The review should note that contingency management among the treatments available for 'stimulant addiction.'	We have made this change.
5	Page 48, Section on Anticonvulsants: The review appears to have excluded a RCT by Kampman and colleagues (2004) that found "topiramate-treated subjects were more likely to be abstinent from cocaine compared to placebo-treated subjects (Z=2.67, P=0.01). Topiramate-treated subjects were also more likely to attain 3 weeks of continuous abstinence from cocaine ($\chi 2$=3.9, d.f.=1, P=0.05)." Kampman, K.M., Pettinati, H., Lynch, K.G., Dackis, C., Sparkman, T., Weigley, C., O'Brien, C.P., Kampman, K.M., Pettinati, H., Lynch, K.G., Dackis, C., Sparkman, T., Weigley, C., O'Brien, C.P., 2004. A pilot trial of topiramate for the treatment of cocaine dependence. Drug Alcohol Depend. 75, 233–240.	This RCT was included in the Minozzi 2015 systematic review. Per our protocol, we did not write up the results of the individual trials in the SR, and relied on the conclusions of the SR authors. Upon review, it seems that because continuous abstinence was not an outcome of interest in the Minozzi 2015 review, we did not abstract that information, and hence the findings of that study were overlooked. We have now analyzed the RCTs from the review that reported continuous abstinence, including the 2004 Kampman study and incorporated these findings in the report.
5	Page 59, Section entitled "Comorbid or Lifetime Alcohol Use Disorder": The review neglected to include the Kampman et al. 2013 RCT examining topiramate among patients with co-morbid cocaine and alcohol dependence. The study is cited elsewhere in the review and is reference 42 in the Reference section of the review.	This study was not included in this section because we were only looking at studies that had a comparison group. All patients in this trial had comorbid cocaine and alcohol dependence.
5	Page 80, Section on 'Pharmacotherapies for other SUDs': In subsection including naltrexone is mistakenly named 'Opioid Agonists.' Naltrexone is a full opioid antagonist.	We have made this correction.