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Pharmacotherapy for Stimulant Use Disorders: A Systematic Review

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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.

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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.

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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:

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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.

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