Pharmacotherapy for the Treatment of Cannabis Use Disorder: A Systematic Review

February 2019

Authors:

Principal Investigator:
Karli Kondo, PhD, MA

Co-Investigators:
Benjamin J. Morasco, PhD
Shannon Nugent, PhD
Chelsea Ayers, BA
Maya E. O'Neil, PhD
Michele Freeman, MPH
Robin Paynter, MLIS
Devan Kansagara, MD, MCR

U.S. Department of Veterans Affairs

Veterans Health Administration
Health Services Research & Development Service

PREFACE

The VA Evidence 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. 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 program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center, at Nicole.Floyd@va.gov.

ACKNOWLEDGMENTS

Eric Hawkins, PhD
Associate Professor, Department of Psychiatry & Behavioral Sciences, University of Washington
Associate Director Seattle CESATE
VA Puget Sound Health Care System

Andrew Saxon, MD
Professor and Director, Addiction Psychiatry Residency Program, Department of Psychiatry & Behavioral Sciences, University of Washington
Director, Seattle CESATE
VA Puget Sound Health Care System

Kendall Browne, PhD
Core Investigator, Center of Excellence in Substance Addiction Treatment and Education (CESATE), Corporal Michael J. Crescenz VA Medical Center; Philadelphia, PA
Associate Director for Training and Education, Center of Excellence in Substance Addiction Treatment and Education (CESATE), VA Puget Sound Health Care System; Seattle, WA
Acting Assistant Professor, Department of Psychiatry & Behavioral Health, University of Washington

Kipling Bohnert, PhD
Assistant Professor of Psychiatry, University of Michigan Medical School
Core Investigator, VA Ann Arbor HSR&D Center for Clinical Management Research (CCMR)

Tony P. George, MD
Professor and Chair of Addiction Psychiatry, University of Toronto
Clinical Director, Schizophrenia program at the U of T Centre for Addiction and Mental Health

Kevin M. Gray, MD
Professor of Addiction Sciences, Medical University of South Carolina

Mark A. Ilgen, PhD
Professor, Department of Psychiatry
Director, University of Michigan Addiction Treatment Services
Associate Director for Adult Research, Addiction Center
Research Investigator, Center for Clinical Management Research, Ann Arbor VA Healthcare System

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

FIGURES

TABLES

EXECUTIVE SUMMARY

<u>Aim:</u> We conducted a systematic review and meta-analysis of the benefits and risks associated with the use of various pharmacotherapies for the achievement of abstinence, the promotion of cessation or reduction of cannabis use, and retention among individuals with cannabis use disorder (CUD).

<u>Methods:</u> We searched electronic databases, clinical trial registries, and reference lists through July 2018 for randomized controlled trials (RCTs) directly comparing pharmacological interventions against each other, placebo, usual care, or psychotherapy in individuals with CUD. We abstracted data on study design, interventions, and outcomes. Dual assessment of study's full text, quality, and strength of evidence (SOE) was agreed upon by consensus using published criteria.

<u>Results:</u> We included 23 primary studies. Antidepressants were the most widely studied drug class. We found moderate SOE that subjects receiving antidepressants are less likely to achieve abstinence than those randomized to placebo, that antidepressants are not beneficial in reducing overall cannabis use, and that there is no difference from placebo in study retention (combined RR=0.95, 95% CI: 0.85-1.07). We found no difference between antidepressants and placebo in dropouts due to serious adverse events (low SOE). In addition, we found no difference between cannabinoids and placebo in the achievement of abstinence (low SOE), treatment retention (combined RR=1.06, 95% CI: 0.89 to 1.25; moderate SOE), and reduction in cannabis use (low SOE). We did find low strength evidence that cannabinoids may result in a greater reduction in cannabis withdrawal symptoms. Anticonvulsants may improve study retention (low SOE); the evidence for anticonvulsants on other outcomes is insufficient. We found low to moderate strength evidence that buspirone and N-acetylcysteine do not improve outcomes. There was insufficient evidence for most other drug classes examined.

<u>Conclusion:</u> There is limited research examining the effectiveness of pharmacotherapies for CUD, and many of the existing studies are hampered by poor methodological quality or reporting. There is moderate strength evidence that antidepressants do not reduce cannabis use or improve treatment retention, and may be associated with lower rates of abstinence. There is low to moderate strength evidence that buspirone, and N-acetylcysteine do not improve outcomes. Although we found that cannabinoids do not improve retention, increase rate of abstinence, or reduce cannabis use, we did find low strength evidence that they may reduce withdrawal symptoms. We found insufficient evidence to comment on effects of all other drug classes. Given the increasing access to, and use of, cannabis in both the general and Veteran populations, along with the high prevalence of CUD among current cannabis users, there is an urgent need to identify novel interventions and effective pharmacologic treatments.

ABBREVIATIONS TABLE

Abbreviation	Term
AA	African American
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
AU	Australian
BAI	Beck Anxiety Inventory
BBCET	Brief Behavioral Compliance Enhancement Treatment
C	Control group
Can	Canadian
CBD	Cannabidiol
CBT	Cognitive behavioral therapy
CGI	Clinical Global Impressions
CI	Confidence interval
CM	Contingency management
CN-THCCOOH	creatinine normalized 11-nor-9-carboxy-Δ9-tetrahydrocannnabinol
CUD	Cannabis use disorder
DRO	Dronabinol
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBM	Evidence-based Medicine
EPC	Evidence-based Practice Center
ESP	Evidence Synthesis Program
FDA	Food and Drug Administration
FT	Full time
GAB	gabapentin
HAM-D	Hamilton Depression Rating Scale
hr	Hour
HR	Hazard ratio
HSR&D	Health Services Research and Development Service
ITT	Intention-to-treat
IU	International unit
KQ	Key question
Ln	Natural logarithm
MA	Meta-analysis
MCQ	Marijuana Craving Questionnaire
MD	Mean difference
MDD	Major depressive disorder
MET	Motivation Enhancement Therapy
mg	Milligram
min	Minutes
MM	Medication management

Abbreviation	Term
MTD	Maximum tolerated dose
NA	Not applicable
NIH	National Institutes of Health
NR	Not reported
NS	Not significant
OR	Odds ratio
P	P-value
PBO	Placebo
PICOTS	Population, interventions, comparators, outcomes, timing, and setting
PRN	As needed
QUERI	Quality Enhancement Research Initiative
RCT	Randomized controlled trial
RD	Risk difference
ROB	Risk of bias
RPT	Relapse prevention therapy
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SERT	Sertraline
SES	Socioeconomic status
Sig	Statistically significant
SMD	standard mean difference
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SOE	Strength of evidence
SR	Systematic review
SSRI	Selective Serotonin Reuptake Inhibitors
SUD	Substance use disorder
TEP	Technical expert panel
THC	Tetrahydrocannabinol
TLFB	Timeline Follow-back Interview
T	Treatment group
UA	Urinalysis
US	United States
VHA	Veterans' Health Administration
wk	Week
yr	Year

EVIDENCE REPORT

INTRODUCTION

Social, medical, and legal acceptance of cannabis has grown dramatically over the last 15 years, and cannabis use – for medical and recreational purposes – has also increased. From 2002 to 2012, the prevalence of daily cannabis use in the United States increased from 1.3 to 2.1%.[2] Along with an increase in the acceptance and use of cannabis, the potency of cannabis available on the market has dramatically increased.[1,3] Meanwhile, the proportion of the public that perceives important harms from cannabis use has decreased.[1,2] A recent national survey found that only about 1 in 5 individuals reporting any past-year cannabis use perceived addiction to be a risk associated with cannabis.[4]

In fact, a growing body of evidence shows addiction is a concern. Among regular users, cannabis use can lead to physiologic dependence, with withdrawal symptoms similar to that of other substance use disorders.[5,6] Cannabis withdrawal symptoms include dysphoric mood, disturbed sleep, gastrointestinal symptoms, and decreased appetite. Between 2.5% and 6.3% of adults are estimated to have cannabis use disorder (CUD)[7] – the diagnosis that, according to DSM V criteria, necessitates clinically significant impairment or distress in more than one realm (*eg,* tolerance, social, interpersonal, or occupational challenges, or continued use despite adverse consequences).[8] Furthermore, among those reporting any past-year cannabis use, 36% met criteria for CUD over the prior year.[9] Nearly half those with CUD have moderate or severe CUD, and the risk is greatest in young adults and socioeconomically disadvantaged groups.[7] Cannabis use disorder is also a growing concern among Veterans.[10]

While CUD is much more prevalent and of greater severity than many recognize, the vast majority of patients do not seek treatment. The lifetime prevalence of CUD in the general population is 6.3%, but only 5% of those with CUD have sought treatment from a health care provider.[7] Standard treatment of CUD includes psychotherapy, such as cognitive behavior therapy (CBT), motivation enhancement therapy (MET), or contingency management (CM). However, these treatments may be inaccessible to many and are time-intensive. Pharmacotherapy could offer additional treatment options for the growing number of patients with CUD. Currently, there are no FDA-approved pharmacotherapies available for CUD, though a number (*eg*, cannabinoids, antidepressants, anxiolytics, and glutamatergic modulators) have been proposed for off-label use.[1] The purpose of this systematic review and meta-analysis is to examine the benefits and harms associated with the use of off-label pharmacotherapies to promote the cessation/reduction of cannabis use and to mitigate withdrawal symptoms.

METHODS

TOPIC DEVELOPMENT

The research questions for this systematic review were nominated by Dr. Dominick DePhilippis, Education Coordinator at the Philadelphia CESATE, in conjunction with Dr. Karen Drexler, National Mental Health Program Director, Substance Use Disorders for the Office of Mental Health Services, 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 cannabis use disorder?

KQ2: Are there known subpopulations for whom currently used pharmacotherapy is most/least effective for cannabis 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.[11]

SEARCH STRATEGY

To identify evidence examining pharmacotherapy for cannabis use disorder, we independently evaluated and abstracted studies included in a 2014 systematic review of pharmacotherapies for cannabis dependence.[1] In addition, we conducted a search of Ovid MEDLINE, OvidPsycINFO, and Ovid EBM Reviews Cochrane Database of Systematic Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*) for studies published after the prior review[1] (January 2014 to July 2018) as well as ClinicalTrials.gov, OpenTrials, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). 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).[12]

STUDY SELECTION

We included studies that directly compared pharmacological interventions against each other, placebo, usual care, or psychotherapy in adults and adolescents with cannabis use disorders. We examined only randomized controlled trials (RCTs). We used a "best evidence" approach to guide additional study design criteria depending on the question under consideration and the literature available.[13] To address concerns related to the detection window for THC, we limited inclusion to studies of 4 weeks or longer for all outcomes except withdrawal symptoms (see Appendices B and C and Table 1).

Two independent reviewers evaluated titles, abstracts, and relevant full-text articles for inclusion. All discordant results were resolved through consensus or consultation with a third reviewer.

DATA ABSTRACTION AND QUALITY ASSESSMENT

Data from studies meeting inclusion criteria were abstracted by 1 investigator and were confirmed by a second. Two reviewers independently assessed the risk of bias (ROB) of each study using a tool developed by the Cochrane Collaboration (Appendix C).[14,15] Disagreements were resolved by consensus or a third reviewer.

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. When meta-analysis was performed, we used a random effects model of analysis. Meta-analyses were performed using RevMan 5.3 software.[16] For trials reporting both intent-to-treat (ITT) analyses and modified ITT analyses (*eg*, subjects who received the study drug/placebo, or for whom at least 1 outcome was assessed), we examined both. Our synthesis is based on ITT analyses when provided, and we report differences between the 2 methods only when they impacted our conclusions. We assessed the overall strength of evidence (SOE) for each outcome using an established method that takes into consideration a range of factors (*eg*, study quality, consistency of findings, directness of the comparisons, applicability), and classified SOE as high, moderate, low, or insufficient.[17] For findings for which the SOE was not insufficient, we classified the direction of effects as evidence of benefit, no benefit (*ie*, no difference from placebo or mixed findings of no difference from placebo and favors placebo), and favors placebo.

Figure 1. Analytic Framework
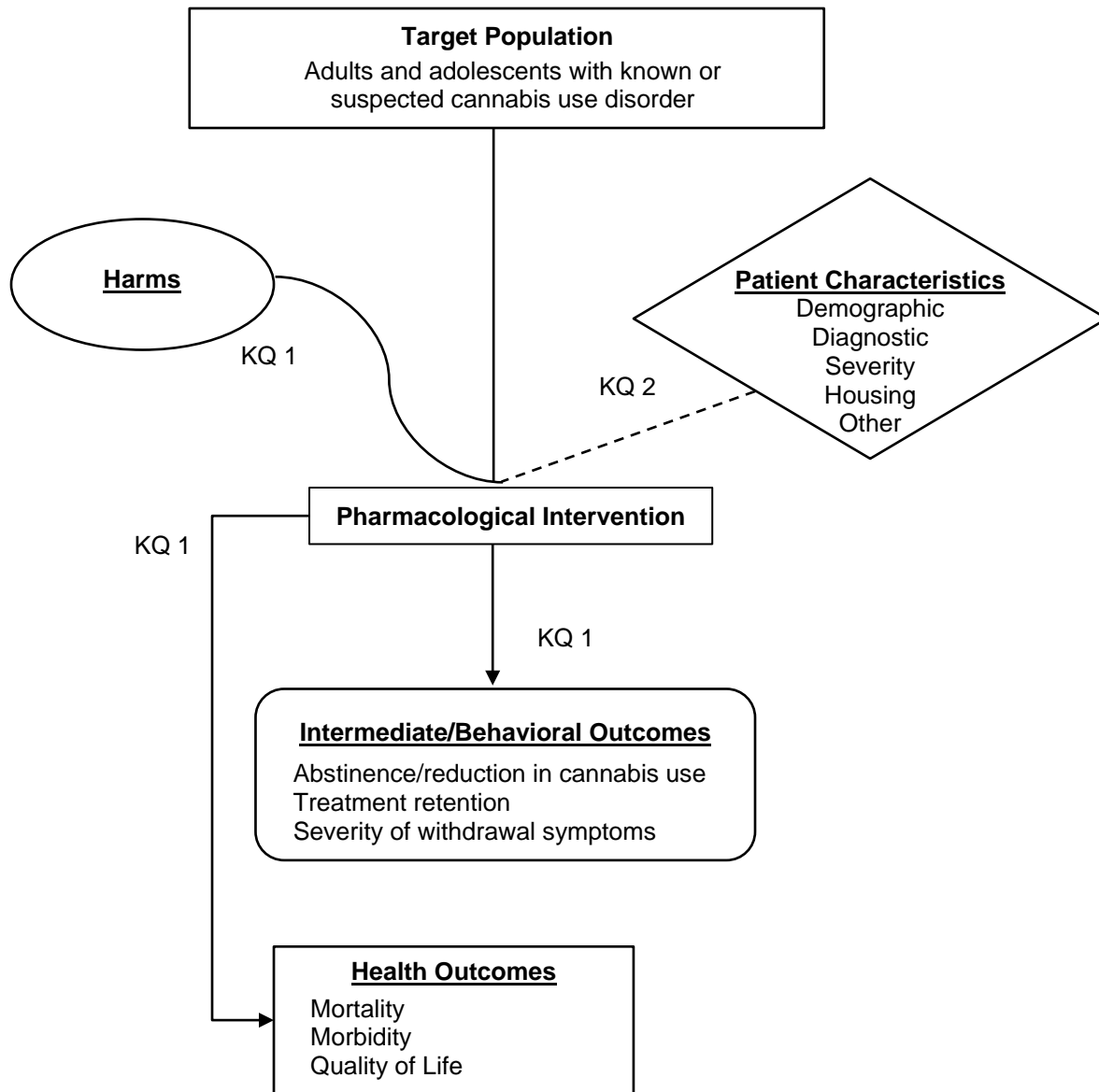
Table 1. PICOTS by Key Question

Key Question:	KQ1: What are the effectiveness and harms of pharmacotherapies (with or without concurrent psychosocial treatment) for cannabis use disorder?	KQ2: Are there known subpopulations for whom currently used pharmacotherapy is most/least effective?
Population	Included: Non-pregnant adults and adolescents with known or suspected cannabis use disorder. Excluded: Children and pregnant adults.	Subpopulations may include: - Demographic factors - Addiction severity - Comorbid mental and substance use disorders (*eg*, HIV, mood and anxiety disorders, psychotic disorders, ADHD, alcohol use, stimulant use, opioid use/methadone maintained) - Other clinical conditions (*eg,* pain, sleep disorders)
Intervention	Included: Pharmacotherapies identified as a potential treatment for cannabis use disorder with or without adjunctive treatment (*eg,* medication management; interpersonal therapy; contingency management [or motivational incentives]; CBT [including matrix therapy, relapse prevention]). Excluded: Pharmacotherapies intended to treat other conditions.	
Comparators	Usual care, placebo, or other interventions (comparison groups must receive the same adjunctive treatments)	

Outcomes	· Intermediate/Behavioral outcomes
	   - Abstinence/Reduction of cannabis use (*eg,* quantitative urine levels; validated self-report measures [*ie,* TimeLine Follow Back, ASI, diagnostic interviews])
	   - Severity of withdrawal symptoms
	   - Retention in treatment
	· Health outcomes
	   - Morbidity/mortality
	   - Quality of life
	· Harms
	   - Dropout due to AE, and serious AE (as reported)	

Timing	Minimum study duration (including follow-up) 4 weeks. Except for studies of withdrawal	
Settings	· Outpatient · Inpatient · Incarceration/detention centers, correctional facilities	
Study design	· Randomized controlled trials.	

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; AE = adverse event; ASI = Addiction Severity Index; CBT = cognitive behavioral therapy; HIV = Human immunodeficiency virus

RESULTS

We reviewed a total of 983 studies. After title and abstract review, 59 met inclusion criteria. Upon full-text review, we included a total of 11 RCTs, plus an additional 12 from a previous systematic review,[1] for a total of 23 RCTs. The 7 RCTs examined in Key Question 2 were also included in Key Question 1 (see Figure 2; Quality assessment is presented in Appendix D).

Figure 2. Literature Flow Diagram

983 Citations identified from electronic database searches:
    627 from PubMed/Ovid MEDLINE (DATE)
    103 from PsycINFO (DATE)
    126 from Ovid EBM Reviews (CDSR, DARE, HTA, Cochrane CENTRAL; DATE)
    37 from WHO ICTRP (DATE)
    90 from ClinicalTrials.gov

23 Citations identified from reference lists of relevant articles and reviews, key experts, and other sources

1,006 Citations compiled for review of titles and abstracts

947 Titles and abstracts excluded for lack of relevance

59 Potentially relevant articles for full-text review

36 Excluded publications:
    2 Excluded population
    5 Not relevant to topic
    27 Excluded study design or publication type
    2 No outcomes of interest

11 Studies included from search

12 Studies from Marshall SR1

23 Total included studies

KQ 1:
23 Studies*

KQ 2:
7 Studies*

*All 7 KQ 2 studies were also included in KQ 1.

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

We identified 23 RCTs that addressed Key Question 1. Twelve trials examined psychopharmacological interventions, 5 trials examined cannabinoids, 2 trials examined anticonvulsants, 2 trials examined N-acetylcysteine, 1 trial examined aprepitant, and 1 trial examined oxytocin.

Psychopharmacology

We identified 12 trials examining psychopharmacological interventions for the treatment of cannabis use disorder. Trials examined antidepressants (*ie*, escitalopram, fluoxetine, bupropion, nefazodone, venlafaxine, vilazodone), antipsychotics (*ie*, clozapine, ziprasidone), buspirone, mood stabilizers (*ie*, divalproex, lithium), and atomoxetine. Overall, studies found that antidepressants as a class were less effective than placebo for the achievement of abstinence (moderate SOE). There was no difference between antidepressants (moderate SOE) or buspirone (low SOE) and placebo in reducing overall cannabis use or retention in treatment. We found low strength evidence of no difference from placebo for antidepressants or buspirone on harms. Antidepressant medications did not impact secondary outcomes (low SOE). Findings for all other psychopharmacotherapies and drug/outcome combinations were either insufficient or were not identified in the current literature.

Antidepressants: Escitalopram, Fluoxetine, Bupropion, Nefazodone, Venlafaxine, Vilazodone

We identified 4 low-ROB RCTs[18-21] and 2 high-ROB RCTs[22,23] examining the use of antidepressants for the treatment of cannabis use disorder. Trials comparing escitalopram[22] and bupropion and nefazodone[21] to placebo found no difference for the achievement of abstinence. However, 1 trial found that significantly fewer subjects who received venlafaxine achieved abstinence.[19]

Two RCTs found no difference from placebo in reduction of cannabis use associated with fluoxetine[20] or vilazodone.[18] However, 1 RCT found significantly higher urinary THC levels in the second half of the study among subjects randomized to venlafaxine compared to those receiving placebo.[19]

No trial examining antidepressants found a significant difference in study retention, harms, or withdrawal symptoms compared to placebo. Studies generally had high rates of attrition, with the exception of a trial comparing fluoxetine to placebo[20] in subjects aged 14-25, which was provided in combination with contingency management, cognitive behavioral therapy (CBT), and motivational enhancement therapy (MET). This trial had improved retention relative to other trials.

The secondary outcomes that were assessed varied widely by study. Findings were largely not significantly different between antidepressants and placebo. The exceptions were more missed medication doses of nefazodone compared to bupropion and placebo,[21] and greater reduction on a single subscale of cannabis craving (purposefulness) associated with vilazodone.[18]

Interestingly, in the 3 trials examining the effect on depressive symptomology, none identified a benefit of antidepressant medication from placebo (see below for more detail).[19,20,22]

Across all antidepressants studied, we found moderate strength evidence that the achievement of abstinence is less likely in subjects receiving antidepressants than placebo (3 RCTs, N=291; combined RR=0.49, 95% CI [0.30-0.83]; see Figure 3). Because 1 RCT had 2 active treatment arms (nefazodone and bupropion),[21] we combined the active arms in a sensitivity analysis to examine the effect of using the same control group twice when each drug was compared separately with placebo in meta-analysis. Upon combining the active treatment arms, findings were consistent (combined RR=0.46, 95% CI [0.27-0.78]). In addition, we found moderate strength evidence that antidepressants have no benefit for reducing cannabis use (2 RCTs found no difference from placebo, 1 RCT found greater reduction with placebo)[18-20], and that antidepressants are no different from placebo for retaining participants in treatment (6 RCTs, N=429, combined RR=0.95, 95% CI [0.85-1.07]; see Figure 4). One trial reporting retention outcomes was only 4 weeks in duration.[23] We performed a sensitivity analysis without the trial and found no difference in overall findings (combined RR=0.93, 95% CI [0.81 to 1.07]).

There is low strength evidence that antidepressant medications did not impact study dropout due to adverse events, and that randomization to antidepressant medications did not result in improvement on secondary outcome measures. Although the RCTs assessed different secondary outcomes, we found no consistent impact of antidepressant medications on measures of craving for cannabis, time to first THC-negative urinalysis (UA), symptoms of depression or anxiety, cognitive effects, or medication adherence (see Tables 2, 3, and 5 and the Conclusions Table for more detail).

Of the 6 RCTs that evaluated an antidepressant medication among those with comorbid major depressive disorder (MDD), 4 also assessed differences in depressive symptom reduction by treatment.[19,20,22,23] At baseline, subjects in 2 RCTs fell in the severe range,[19,22] subjects in 1 RCT fell in the mild to moderate range,[20] and in 1 RCT subjects were within non-clinical ranges.[23] Among subjects with severe depression at baseline, randomization to escitalopram[22] or venlafaxine[19] did not result in clinically significant reductions in depressive symptoms and there were no statistically significant reductions relative to those randomized to placebo.[19,22] Among subjects in the mild to moderate range at baseline, subjects randomized to both fluoxetine and placebo experienced significant reductions in depressive symptoms over the course of the study, though there were no between-group differences detected.[20] In the RCT which included participants with subclinical depressive symptoms at baseline, neither participants randomized to bupropion or placebo had significant changes in symptom severity, nor was there a difference in symptom reduction when comparing the 2 groups.[23]

Figure 3. Number of patients who achieve 2+ week abstinence in trials comparing antidepressants versus placebo for cannabis use disorder

Study or Subgroup	Antidepressants Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bupropion, 13 wk (Carpenter, 2009)	4	40	7	30	19.3%	0.43 [0.14, 1.33]	
Escitalopram, 23 wk (Weinstein, 2014)	3	26	7	26	16.3%	0.43 [0.12, 1.48]	
Nefazodone, 13 wk (Carpenter, 2009)	8	36	7	30	30.2%	0.95 [0.39, 2.32]	
Venlafaxine, 12 wk (Levin, 2013)	6	51	19	52	34.2%	0.32 [0.14, 0.74]	
Total (95% CI)		**153**		**138**	**100.0%**	**0.49 [0.30, 0.83]**	
Total events	21		40				

Heterogeneity: Tau² = 0.02; Chi² = 3.23, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 2.69 (P = 0.007)

0.1 0.2 0.5 1 2 5 10
Favors placebo   Favors antidepressants

Figure 4. Number of patients who completed treatment in trials comparing antidepressants versus placebo for cannabis use disorder

Study or Subgroup	SSRIs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bupropion							
Bupropion, 13 wk (Carpenter, 2009)	18	40	14	30		0.96 [0.58, 1.61]	
Bupropion, 4 wk (Penetar, 2012)	5	10	4	12		1.50 [0.55, 4.13]	
Subtotal (95% CI)						1.06 [0.67, 1.67]	

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

SNRI							
Venlafaxine, 12 wk (Levin, 2013)	31	51	33	52		0.96 [0.71, 1.30]	
SSRIs							
Escitalopram, 23 wk (Weinstein, 2014)	10	26	16	26		0.63 [0.35, 1.11]	
Fluoxetine, 12 wk (Cornelius, 2010)	31	34	33	36		0.99 [0.86, 1.15]	
Subtotal (95% CI)						0.82 [0.44, 1.53]	

Heterogeneity: Tau² = 0.16; Chi² = 4.54, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.61 (P = 0.54)

Other antidepressants							
Nefazodone, 13 wk (Carpenter, 2009)	14	36	14	30		0.83 [0.48, 1.46]	
Vilazodone, 8 wk (McRae-Clark, 2016)	14	41	17	35		0.70 [0.41, 1.21]	
All antidepressants combined							
Total (95% CI)		**238**		**221**		**0.95 [0.85, 1.07]**	
Total events	123		131				

Heterogeneity: Tau² = 0.00; Chi² = 5.74, df = 6 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)

0.2 0.5 1 2 5
Favors placebo   Favors antidepressants

Antipsychotics: Clozapine, Ziprasidone

There is insufficient evidence examining the effectiveness of antipsychotic medications to treat cannabis use disorder. We identified 1 high-ROB head-to-head RCT[24] comparing ziprasidone and clozapine (N=30) in adults with both cannabis use disorder and a psychotic spectrum disorder. Findings indicated no difference between groups on cannabis use or study retention. Results suggest that clozapine may be associated with more adverse events (specifically hypersalivation), and that ziprasidone may be associated with better drug tolerance and psychotherapy compliance. Positive (psychotic) symptoms decreased significantly for both groups, with a stronger decline in clozapine (P=0.05). Ziprasidone was associated with more emergency therapy sessions (P=0.022), and higher group therapy attendance (P=0.024; see Tables 2, 3 and 5, and the Conclusions Table for more detail).

Anxiolytics: Buspirone

One low-ROB RCT[25] and 1 unclear-ROB RCT[26] provide data about the efficacy of buspirone for the treatment of CUD. We found low strength evidence that buspirone is no better than placebo for study retention (2 RCTs, N=268, RR=0.92, 95% CI [0.71-1.19]; Figure 5). In intent-to-treat analyses, neither study identified statistically significant differences in the likelihood of negative UA results over the course of the study (low SOE). There is low strength evidence that buspirone treatment does not increase adverse events. Findings were insufficient to form conclusions about any differences between buspirone and placebo on secondary outcomes (see Tables 2, 3, and 5, and the Conclusions Table).

Figure 5. Number of patients who completed treatment in trials comparing buspirone versus placebo for cannabis use disorder
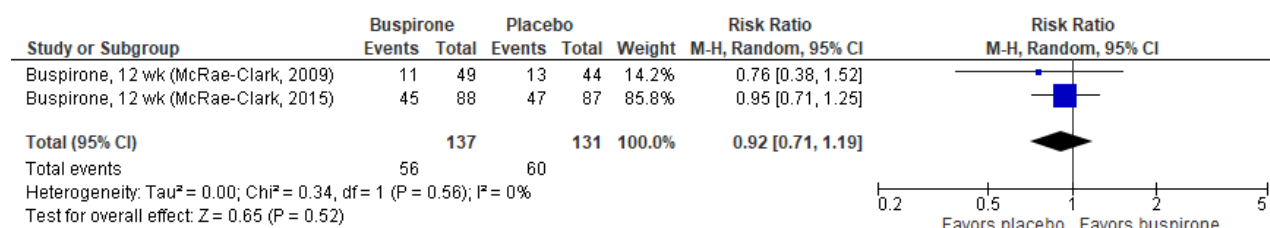
Mood Stabilizers: Divalproex, Lithium

One low-ROB RCT[27] (lithium) and 1 high-ROB RCT[28] (divalproex) provide insufficient evidence from which to form conclusions about the use of mood stabilizers for the treatment of cannabis use disorder. Trials found no difference between divalproex or lithium versus placebo for abstinence or the frequency or quantity of cannabis use. We performed a meta-analysis to examine the effect of mood stabilizers on study retention and found no difference from placebo (RR=1.07, 95% CI [0.79 – 1.44]; see Figure 6). Related to withdrawal symptoms, divalproex did not differ from placebo for craving or irritability.[28] Lithium was similar to placebo in reported withdrawal severity. However, lithium was more effective for attenuating nightmares, loss of appetite, and stomachaches.[27] Neither RCT found a difference in study retention as compared to placebo. Findings also suggested better rates of medication compliance with placebo versus divalproex, and no difference between lithium and placebo for severity of dependence or cannabis-related problems (see Tables 2, 3, and 5, and the Conclusions Table).[28]

Figure 6. Number of patients who completed treatment in trials comparing mood stabilizers versus placebo for cannabis use disorder
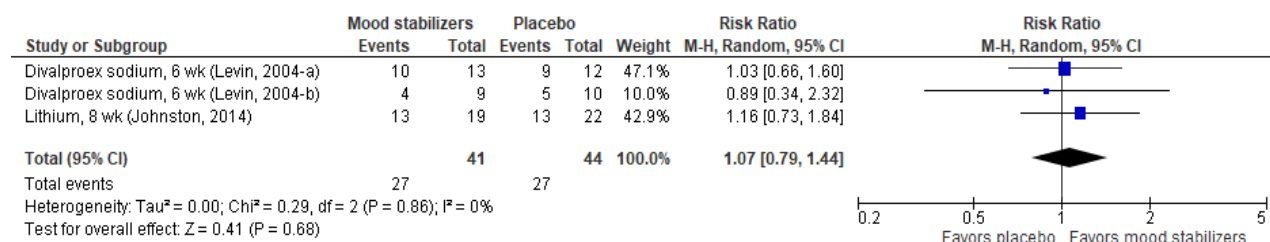
Cognitive-enhancing: Atomoxetine

One unclear-ROB RCT[29] provides insufficient evidence for the use of atomoxetine for the treatment of cannabis use disorder. The trial compared 100 mg of atomoxetine to placebo, along with contingency management (CM) and motivational enhancement therapy (MET) in subjects with comorbid attention deficit hyperactivity disorder (ADHD). Findings indicated no difference between atomoxetine and placebo on cannabis use, treatment retention, or dropout from treatment due to adverse events. Subjects who received atomoxetine experienced greater ADHD improvement on the Clinical Global Impressions improvement scale (CGI-I; P=0.022) and a greater decline in ADHD symptoms in weeks 1-4. There was no difference from placebo on the CGI severity scale (CGI-S), and no difference in ADHD symptom improvement after week 4 (see Tables 2, 3, and 5, and the Conclusions Table).

Cannabinoids: *Dronabinol, Nabilone, Nabiximols*

Included studies examined dronabinol, a pharmaceutically prepared synthetic THC,[30,31] nabilone, an FDA-approved synthetic cannabinoid,[32] and nabiximols, a pharmaceutically prepared nasal spray of 27mg/ml of THC and 25mg of cannabidiol (CBD).[33,34]

Two low-ROB RCTs[30,34] and 3 unclear-ROB RCTs[31-33] examined the use of cannabinoids for the treatment of cannabis use disorder. A small RCT (N=18) compared nabilone to placebo and found no difference on any outcome of interest.[32] Two trials compared dronabinol to placebo and found no difference for the achievement of abstinence (RR=1.07, 95% CI [0.65-1.76]; see Figure 7), reduction in cannabis use, cannabis craving, or harms. Findings were mixed for the effect of dronabinol on withdrawal symptoms and study retention. Two trials compared nabiximols to placebo. Findings on the effect of nabiximols on withdrawal symptoms were mixed, with 1 of 2 RCTs reporting better outcomes with treatment than placebo (see Tables 2 and 3).[33,34]

Across cannabinoids as a class, we found low strength evidence that dronabinol specifically has no effect on the achievement of abstinence, low strength evidence that cannabinoids are no different than placebo for reducing cannabis use, and moderate strength evidence that they are similar to placebo for study retention (5 RCTs, N=387; combined RR=1.06, 95% CI [0.89-1.25]; see Figure 8). One trial reporting retention outcomes was only 4 weeks in duration;[34] we performed a sensitivity analysis without this trial and found no difference in overall findings (4 RCTs, N=336; combined RR=1.04, 95% CI [0.87-1.24]). There is low strength evidence that cannabinoids may reduce withdrawal symptoms, and that they do not increase harms. Although findings were consistent across studies regarding treatment dropout s due to adverse events, we downgraded strength of evidence due to high attrition and lack of clarity related to reasons for dropout. Findings for secondary outcomes are insufficient to draw conclusions (see Table 5 and the Conclusions Table).

Figure 7. Number of patients who achieved abstinence in trials of cannabinoids versus placebo for cannabis use disorder

Study or Subgroup	Dronabinol Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dronabinol + lofexidine, 11 wk (Levin, 2016)	12	61	12	61	49.1%	1.00 [0.49, 2.05]
Dronabinol, 11 wk (Levin, 2011)	14	79	12	77	50.9%	1.14 [0.56, 2.30]
Total (95% CI)		140		138	100.0%	1.07 [0.65, 1.76]
Total events	26		24			

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

Risk Ratio M-H, Random, 95% CI — 0.2   0.5   1   2   5 — Favors placebo   Favors dronabinol

Figure 8. Number of patients who completed treatment in trials comparing cannabinoids versus placebo for cannabis use disorder

Study or Subgroup	Cannabinoids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dronabinol + lofexidine, 11 wk (Levin, 2016)	32	61	35	61	26.5%	0.91 [0.66, 1.26]
Dronabinol, 11 wk (Levin, 2011)	55	79	44	77	46.9%	1.22 [0.96, 1.55]
Nabilone, 10 wk (Hill, 2017)	6	10	6	8	6.6%	0.80 [0.42, 1.52]
Nabiximols, 12 wk (Trigo, 2018)	13	20	14	20	14.8%	0.93 [0.60, 1.43]
Nabiximols, 4 wk (Allsop, 2014)	11	27	8	24	5.2%	1.22 [0.59, 2.53]
Total (95% CI)		197		190	100.0%	1.06 [0.89, 1.25]
Total events	117		107			

Heterogeneity: Tau² = 0.00; Chi² = 3.32, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

Risk Ratio M-H, Random, 95% CI — 0.5   0.7   1   1.5   2 — Favors placebo   Favors cannabinoids

Anticonvulsants: *Gabapentin, Topiramate*

Two small, unclear-ROB RCTs[35,36] provide evidence for the use of gabapentin[36] and topiramate[35] for the treatment of cannabis use disorder. Findings indicated better retention associated with both gabapentin and topiramate. Subjects receiving gabapentin (N=50), but not topiramate, significantly decreased their cannabis use as compared to those receiving placebo. In addition, gabapentin was associated with a decrease in depressive symptoms and better neurocognitive performance, whereas subjects receiving topiramate experienced poorer depressive and neurocognitive outcomes than those receiving placebo. Gabapentin also performed better than placebo for cannabis withdrawal symptoms and a range of secondary outcomes (see Tables 2 and 3). Across anticonvulsants as a class, we found low strength evidence for improved treatment retention over placebo, and insufficient evidence for all other outcomes of interest (see Table 5 and the Conclusions Table).

Glutamatergic Modulator: *N-acetylcysteine*

Two low-ROB RCTs[37,38] examine the effectiveness of the glutamatergic modulating dietary supplement N-acetylcysteine (NAC) versus placebo for the treatment of cannabis use disorder. One RCT examined adults,[37] and the other examined adolescents and young adults (ages 13-21).[38] Neither trial found a difference in the reduction of cannabis use versus placebo (see Figure 9), study retention (see Figure 10), harms, or medication adherence. The RCT examining adolescents and young adults found a non-significant trend towards 2-week end of trial abstinence favoring NAC (see Tables 2 and 3).[38]

Across trials examining NAC, we found moderate strength evidence of no difference from placebo for the reduction of cannabis use, study retention, and medication adherence. Although

both RCTs (N=418) reported no difference in dropouts from treatment due to adverse events, high attrition in both trials call into question reasons for dropout; therefore, we determined the evidence to be low-strength. There was also low strength evidence of no difference in the frequency of serious adverse events by group (see Table 5 and the Conclusions Table).

Figure 9. Number of negative-UAs in trials comparing N-acetylcysteine versus placebo for cannabis use disorder

Study or Subgroup	N-acetylcysteine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
N-acetylcysteine, 12 wk (Gray, 2012)	190	464	126	464	48.0%	1.51 [1.25, 1.81]
N-acetylcysteine, 12 wk (Gray, 2017)	819	3672	801	3576	52.0%	1.00 [0.91, 1.08]
Total (95% CI)		4136		4040	100.0%	1.22 [0.81, 1.83]
Total events	1009		927			
Heterogeneity: Tau² = 0.08; Chi² = 15.97, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 0.94 (P = 0.35)						
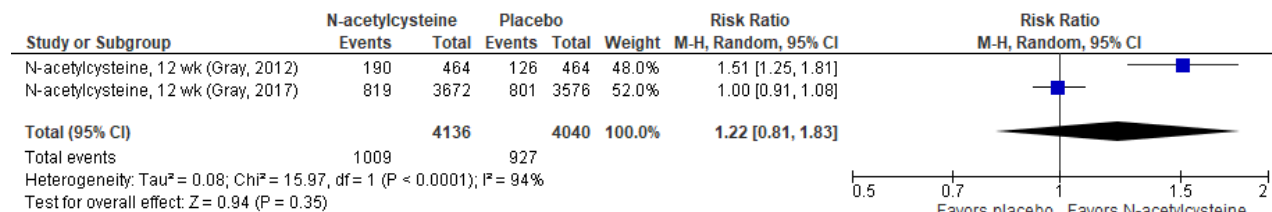
Events = Number of negative-UAs based on proportion of ITT total; Total = Maximum number of intended UA specimens (ITT) based on total randomized patients, number of weeks, and frequency of collection.

Figure 10. Number of patients who completed treatment in trials comparing N-acetylcysteine versus placebo for cannabis use disorder

Study or Subgroup	N-acetylcysteine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
N-acetylcysteine, 12 wk (Gray, 2012)	37	58	33	58	18.9%	1.12 [0.83, 1.51]
N-acetylcysteine, 12 wk (Gray, 2017)	113	153	103	149	81.1%	1.07 [0.93, 1.23]
Total (95% CI)		211		207	100.0%	1.08 [0.95, 1.23]
Total events	150		136			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
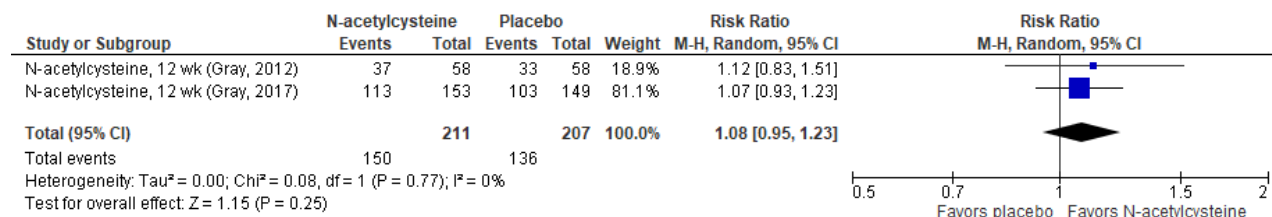
Antiemetic/Antinauseant: *Aprepitant*

One small (N=20), unpublished RCT[39] of aprepitant versus placebo provides insufficient evidence from which to form conclusions for the use of aprepitant for the treatment of concurrent cannabis and alcohol use disorders. There was a greater change in cannabis use from Week 0 to Week 8 with aprepitant; however, statistical significance was not determined. Only 60% of participants were retained in the aprepitant group as compared to 100% in the placebo group (see Tables 2, 3, and 5, and the Conclusions Table for more detail).

Hormone: *Oxytocin*

One small (N=16) high-ROB RCT[40] of adults with cannabis use disorder provides insufficient evidence from which to draw conclusions on the use of the hormone oxytocin for the treatment of cannabis use disorder. The trial examined whether the use of oxytocin prior to motivational enhancement therapy (MET) sessions resulted in better outcomes. Although findings are insufficient, the trial found no difference between groups on cannabis use for oxytocin versus placebo (see Tables 2, 3, and 5, and the Conclusion Table for more detail).

Table 2. Trials of pharmacotherapies for treating primary outcomes of cannabis use disorder

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
PSYCHOPHARMACOTHERAPIES

**Selective Serotonin Reuptake Inhibitors (SSRIs):** *Escitalopram, Fluoxetine*
Weinstein, 2014[22] N=52 Single site (Israel) 23-week follow-up DSM IV Cannabis Dependence Comorbid Major Depressive Disorder	26 vs 26 Escitalopram 10 mg 9 wks 60 min group CBT 1x/wk + MET. Instructed to stop cannabis use after 4 weeks. UA: every 2 wks after wk 4	75% male Age: 32.71 (6.8) Race: NR Education: 12.42 (2)	3/26 vs 7/26 No difference in "persistent" UA(-) (P=0.77).	NR	26 (50%) completed study: 10/26 (38.5%) vs 16/26 (61.5%) (P=0.43; analysis NR in study)	High
Cornelius, 2010[20] N=70 Single site (US) 12-week follow-up DSM IV CUD** or HAM-D ³ 15 Comorbid Major Depressive Disorder	34 vs 36 Fluoxetine 10mg first 2 weeks/ 20mg wks 3-12 12 wks CBT (9 therapy sessions over 12 wks) + MET CM: $20 for each assessment visit UA: frequency unspecified	61.4% male Age: 21 (2.4) Race: 55.7% White, 37.1 AA/Black, 7.1% Mixed SES: NR	NR	No difference in days used (based on self-report).	64 (91.4%) completed study: 31/34 (91.2%) vs 33/36 (91.7%) No difference	Low

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Other Antidepressants: *Bupropion, Nefazodone, Venlafaxine, Vilazodone*						
Carpenter, 2009[21] N=106 2 Sites (US) 13-week follow-up DSM IV Cannabis Dependence	40 vs 36 vs 30 Bupropion 300 mg/day vs Nefazodone 600 mg/day (or MTD) vs PBO CM for attendance ($5/visit; 26 visits) Individual coping skills-based CBT UA: 2x/week	76.4% male Age: 32(10) years Race: 34% White, 27% AA/Black, 28% Hispanic Education: 42.5% high school or less Employment: 9.4% Unemployed	4/40 vs 8/36 vs 7/30 No difference in 3+ week abstinence (P=0.58)	No difference in end-of-study UA(-) (P=0.17)	46 (43.4%) completed study: 18/40 (45%) vs 14/36 (38.9%) vs 14/30 (46.6%) No difference (P=0.55)	Low
Penetar, 2012[23] N=22 Single site (US) 4-week follow-up DSM-IV Cannabis Abuse or Dependence.	10 vs 12 7-day baseline period. Bupropion 300mg/day Instructed to stop cannabis use on day 8 Weekly MET UAs: every weekday	Of 9 Completers: 55.6% men Age: 31.2(9.6)	NR	NR	9 (40.9%) completed study: 5/10 (50%) vs 4/12 (33.3%)	High

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Levin, 2013[19] N=103 2 Sites (US) 12-week follow-up DSM IV-TR Cannabis Dependence or ³ 12 on the HAM-D. Comorbid Major Depressive Disorder or Dysthymia	51 vs 52 1-week placebo lead- in followed by Venlafaxine 225 mg/day (or MTD) 11 weeks CM for attendance (transportation; $5- 20/visit; 24 visits) and medication adherence ($10/week for returning pill bottles) Weekly CBT/RPT UA: 2x/week	73.8% male Age: approx. 35 years Race: 45.6% White, 21.3% AA/Black, 26.2% Hispanic, 2.9% Asian, 3.9% Other Education: 29.2% < high school, Employment: 59.2% unemployed/less than FT	6/51 vs 19/52 rates of 2+ weeks abstinence favored PBO (P=0.01)	Higher urine-THC levels in venlafaxine group in 2nd half of treatment (wks 6, 8, & 10); P=0.01	64 (62.1%) completed study: 31/51 (60.8%) vs 33/52 (63.5%) No difference between groups (P=0.36)	Low
McRae-Clark, 2016[18] N=76 Single site (US) 8 weeks DSM IV Cannabis Dependence	41 vs 35 Vilazodone max dose of 40 mg CM for attendance ($5/week increasing by $5 each consecutive week + bonuses in weeks 1 [$20] and 12 [$40]) and medication adherence ($10/week for returning pill bottles) 3 sessions MET	79.0% male Age: 22.2 (21.3 – 23.1) Race: 54.8% Caucasian Education: 94.7% high school graduate	NR	No difference in unadjusted odds (OR=1.22; 95% CI=0.24 to 6.37) or adjusted odds (OR=2.65; 95% CI=0.50 to 14.0) of weekly abstinence	31 (40.1%) completed study: 14/41 (34.2%) vs 17/35 (48.6%)	Low

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Antipsychotics (Atypical): *Clozapine, Ziprasidone*						
Schnell, 2014[24] N=30 Single site (Germany) Inpatient 12-month follow-up DSM-IV Cannabis Abuse or Dependence Comorbid psychotic spectrum disorder	16 vs 14 Ziprasidone (M = 200 mg [range 80-400]) Clozapine (M = 225 mg (range 50–425]) 12 months Outpatient: Clinical management with psychoED, group CBT, and social and occupational rehab. UA: Inpatient – daily, Outpatient – at 3, 6, 9, 12 mos	86.7% male Age: 29 years (8.1) Race: NR 3% homeless Education: 90% high school or less Employment: 83.3% Unemployed	NR	Both groups reduced frequency of cannabis use during follow-up (F=7.15; P=0.023). No differences between groups (F=2.75; P=0.128).	12 (40%) completed study: Ziprasidone: 7/16 (43.8%) Clozapine: 5/14 (35.7%)	High
Anxiolytic: *Buspirone*						
McRae-Clark, 2009[26] Single site (US) N=93 12 weeks DSM IV Cannabis Dependence	49 vs 44 Buspirone max dose of 60 mg (mean=46 ± 14) CM for attendance ($10 per visit) 3 sessions of MET UA:2x/week at beginning of study, but reduced to 1x/week to improve adherence	88% male Age: 31.4 (9.8) Race: 86% Caucasian	NR	No difference in rate of % negative UA (20.3% vs 6.5%, P=0.13). No difference on self-reported days of use,	24 (25.8%) completed study: 11/49 (22.5%) vs 13/44 (29.6%)	Unclear

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
McRae-Clark, 2015[25] Single site (US) N=175 12 weeks DSM IV Cannabis Dependence	88 vs 87 Buspirone max dose of 60 mg (mean=42 ± 18) CM for attendance ($5/wk increasing by $5 each consecutive wk + bonuses at in wks 1 [$20] and 12 [$40]) and medication adherence ($10/wk for returning pill bottles) 3 sessions MET	76.6% male Age: 24.0 (23.1 – 25.0) Race: 64.0% Caucasian Education: 90.3% high school graduate	NR	No difference in unadjusted odds (OR=1.09; 95% CI = 0.45 to 2.61) or adjusted odds (OR=0.75; 95% CI = 0.29 to 1.92) of weekly abstinence	92 (52.6%) completed study: 45/88 (51.1%) vs 47/87 (54.0%)	Low
Mood Stabilizer: *Divalproex Sodium, Lithium Carbonate*						
Levin, 2004[28] N=23 Single site (US) 12-week follow-up DSM IV Cannabis Dependence	13 vs 12 Divalproex Sodium 1500mg/day (250mg- 2000mg depending on response). 6 weeks Weekly individual relapse prevention therapy UA: 2x/week	99% male Age: 32 Race: 56% White, 24% AA/Black, 20% Hispanic Education: 2 yrs college	5/13 vs 4/12 No difference in 2+ week abstinence by group or in the length of abstinence.	No difference in % UA(-)s or quantitative THC level.	10/13 (76.9%) vs 9/12 (75%) for first 6 weeks 4/9 (44.4%) vs 5/10 (50%) for second 6 weeks (crossover) Study total: 5/13 (38.5%) vs 4/12 (33.3%); No difference in treatment retention.	High

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Johnson, 2014[27] N=31 Single site (Australia) Inpatient (7-day withdrawal) Dec 2010 – Aug 2012 90 days follow-up DSM IV-TR Cannabis Abuse or Dependence	19 vs 22 Lithium 100mg/day 7 days Also available: Paracetamol, Nitrazepam, nicotine treatment. RPT, relaxation, withdrawal counseling, individual and group psychoED Inpatient: daily Outpatient: UA at 14, 30, 90 days.	65.8 % male Age: 40.51(12.49) Race: % White NR, 5.3% Indigenous Education: 86.8%≥10th grade	3/19 vs 5/22 (90 day) Post-withdrawal 30-day continuous abstinence (no longer on lithium; after 7 day inpatient, assessed at 14, 30, 90 days): No difference	Both groups reduced mean # days of use in the past week (F=7.63, P<0.0001) and mean quantity of daily use (F=7.62, P<0.0001). No difference between groups.	Study completion: 13/19 vs 13/22 7-day inpatient stay: No difference in retention (P=0.75)	Low
Cognitive-Enhancing: _Atomoxetine_						
McRae-Clark, 2010[29] N=78 Single site (US) Nov 2005 – Jun 2008 12-week follow-up DSM IV Cannabis Dependence Comorbid ADHD	39 vs 39 Atomoxetine 100mg/day (or MTD) 4 wks CM for attendance (nominal) 3 MET sessions in weeks 1-4 UA: 1x week	80% male Age: 29.9(10.9) Race: 91% White	NR	No difference in week 12 mean self- reported use, UA results, or % of days used by group.	16 (20.5%) completed study: 9/39 (23.1%) vs 7/39 (17.9%)	Unclear

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
CANNABINOIDS: *Dronabinol, Nabilone, Nabiximols*						
Levin, 2011[30] N=156 Single-site (US) Outpatient 12-week DSM IV-TR Cannabis Dependence	79 vs 77 1-week placebo lead-in, DRO, 40mg/day 8-weeks + 2-wk taper CM for attendance and transportation ($5-20 depending on distance + $1.50/visit increasing by $1.50 each consecutive visit and medication adherence ($10/consecutive pair of visits for returning pill bottles); 24 visits up to $570 + transportation MET + RPT weekly UA: 2x/week	Sex: 82% male Age: 37.6 years Race: 48% White Education: 27.6% high school or less	No difference in proportion achieving 2 wks abstinence at end of maintenance phase (17.7% vs 15.6%)	Both groups showed reduction in use over time. No differences between groups.	99 (63.5%) completed study: 55/79 (69.6%) vs 44/77 (57.1%) DRO group had significantly higher retention at end of maintenance phase 77% vs 61% (P=.02)	Low

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	Risk of bias
Levin, 2016[31] N=122 Single-site (US) Outpatient 11 weeks DSM IV Cannabis Dependence	61 vs 61 Lofex–DRO "fixed- flexible" dose schedule, dose titrated to 1.8 and 60 mg/day or MTD 11 weeks CM attendance and transportation ($5-20 depending on distance) MET + RPT weekly UA: 1x/wk	Sex: 68.9% male Age: 35.1 (11.0) Race: 38.5% White Education: 30.3% high school or less	Proportion achieving abstinence in last 2 wks of trial: 12/61 (19.67%) vs 12/61 (19.67%). No difference in 2 consecutive wks abstinence (X_{12}=.02, P=.89) Proportion achieving abstinence during any 21 days: 17/61 (27.87%) vs 18/61 (29.51%). No difference in achieving 21 days consecutive abstinence (X_{12}=.17, P=.68).	NR	79 (64.8%) completed study: 37/61 (60.66%) vs 42/61 (68.85%). No difference between groups (X_{12}=1.36, P=.24)	Unclear

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Hill, 2017[32] N=18 Single site (US) 14 weeks DSM IV Cannabis Dependence	10 vs 8 Nabilone 2mg/day for 10 wks. CM for attendance ($40 bonus for all 4 visits) and completed diaries ($100 each) up to $955. MM weekly UA: Outpatient 2x/wk for 10-week study; Follow-up UA at 14 wks	Sex: 67% male Age: 26.4 (6.5) years Race: 67% White Education: 14.4 (3.4) years	NR	No difference in cannabis use sessions (P=0.53). No difference in the % days of use at the end of treatment (P=0.22) or follow- up (P=0.81). No difference in the urine cannabinoid levels at the end of treatment (P=0.17) or follow-up (P=0.34).	12 (66.7%) completed study: 6/10 (60%) vs 6/8 (75%)	Unclear

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Trigo, 2018[33] N=40 Single site (Canada) Outpatient 12 weeks DSM IV Cannabis Dependence	20 vs 20 Nabiximols (113.4 mg THC/105 mg CBD): self-titrated up to 42 sprays/day 12 weeks CM for attendance and transportation (C$6 visit + random non-monetary prize or C$5-50 gift card, up to C$855; 24 visits) CBT/MET UA: 2x week	72.5% male Age: 33.0 (11.75) Race: 60% White Education: 62.5% completed college Employment: 12.5% FT	NR	7-day point prevalence abstinence after medication phase 30.8% (N=4) vs 42.9% (N=6) Use declined for both groups, but no difference between groups (P=.179)	13/20 (65%) vs 14/20 (70%)	Unclear
Allsop, 2014[34] N=51 2 sites (Australia) Inpatient (9 days) 28-day follow-up DSM IV-TR Cannabis Dependence	27 vs 24 Nabiximols, maximum dose 86.4 mg THC, 80 mg CBD; 3 days washout; 6 days medication Self-completed CBT workbook CM for attending follow up visit AU$40 UA: Inpatient – 3x during 9-day phase. Outpatient – 1x at 28-day follow-up	76% male Age: 35.39 Race: % White NR; 6% Aboriginal/Native Education: 55% completed school Employment: 53% Unemployed	NR	No difference in use between groups from baseline to follow-up (P=0.29)	19 (37.3%) completed study: 11/27 (40.7%) vs 8/24 (33.3%) T group remained in treatment longer during medication phase (unadjusted HR=3.66 [95%CI= 1.18 to11.37]; P=.02)	Low

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator		Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
ANTICONVULSANTS: *Gabapentin, Topiramate*						
Mason, 2012[36] N=50 Single-site (US) 13 wks DSM IV Cannaibis Dependence	25 vs 25 Gabapentin 1200 mg/day 12 wks Weekly manual- guided (MET & CBT) individual counseling	80% Male Age: 33.9 (9.7) Race: 76% White Education years: 14 (1.9)	NR	More UA(-) with GAB (P=0.001), greater decrease of self-reported use days/week (P=0.004)	32 (64%) completed study: 18/25 (72%) vs 14/25 (56%)	Unclear
Miranda, 2017[35] N=66 Single-site (US) 7 wks DSM IV Cannabis Dependence	40 vs 26 Topiramate 200mg/day 6 wks 3-session manual- driven MET	Youth 15-24 48% Male Age: 19.5 Race: 52% White	NR	No difference in UA(-) (P=0.335) or change in UA results between weeks 1-6 (P=0.746)	39 (59.1%) completed study: 19/40 (52.5%) vs 20/26 (23.1%) Significant T effect (P=0.018)	Unclear

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
	OTHER PHARAMACOTHERAPIES					
Mucolytic: *N-acetylcysteine*						
Gray, 2012[38] N=116 Single-site (US) 12 wks No diagnosis necessary – self- reported regular cannabis users.	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	NS trend favoring NAC for end-of-treatment (2- week) abstinence: OR=2.32 (95% CI: 0.99 to 5.43); P=0.054 No difference in 4 wk end-of-treatment abstinence: OR=2.14 (95% CI: 0.85 to 5.42); P=0.108	More weekly UA(-) with NAC: 40.9% vs 27.2%, OR=2.35 (95% CI: 1.05 to 5.24); P=0.029 Posttreatment follow-up UA(-): 19% vs 10.3%; OR=2.4 (95% CI: 0.8 to 7.5); P=0.131	70 (60.3%) completed study: 37/58 (64%) vs 33/58 (57%) 54 (46.6%) completed 4-wk follow-up: 29 (50%) vs 25 (43%)	Low

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Gray, 2017[37] N=302 6 sites (US) 16 wks DSM IV-TR Cannabis Dependence	153 vs 149 NAC 2400mg/day 12 wks CM for attendance ($10 for first visit increasing by $2 each consecutive visit, maximum of $30/visit 24 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA-, maximum of $25/visit; 36 visits) MM 1x/wk UA 3x week	72% male Age: 30.3 (9.03) Race: 58.3% White, 27.8% AA/Black Education: 31.2%≤ high school Employment: 30.1% unemployed	NR	No difference between weekly UA(-): 22.3% vs 22.4%; OR=1.00 (95% CI: 0.63– 1.59), P=0.984	216 (71.5%) completed study: 113/153 (71.9%) vs 103/149 (68.5%)	Low
Antiemetic/Antinauseant: _Aprepitant_						
The Scripps Research Institute[39] Unpublished N=20 single-site (US) 2014-2016 12 wks DSM IV Cannabis Dependence	10 vs 10 Aprepitant 125mg/d 8 wks Manual-guided behavioral counseling	85% male Age: 35.0 (SD=11.3) Other demographics: NR	NR	Change in use from Week 0 to 8 using Urinary CN- THCCOOH Levels [Units: ng/mg]: 198.3 (SD=389.4) vs 55.9 (SD=239.3) No statistical analysis provided	16 (80%) completed study: 6/10 (60%) vs 10/10 (100%)	Unclear

Setting N Randomized # of Sites Mean follow-up Population Comorbidity	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Comparator			Risk of bias
			Abstinence, Lapse or Relapse: ≥2 weeks, N (%) and/or longest consecutive period, mean (SD)	Overall cannabis use	Retention in treatment	
Hormone: *Oxytocin*						
Sherman, 2017 [40] N = 16 Site(s) not reported 4-month follow-up DSM IV Cannabis Dependence	8 vs 8 Oxytocin (40 IU) administered intranasally prior to MET sessions 4 wks MET	62.5% male Age: 25.5 (7.6) Race: 56.3% White Education: 62.5% some college or more	NR	NS group by time interaction for mean daily cannabis use (P=0.785).	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.
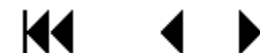** As reported.

Abbreviations: AA = African American; ADHD = Attention Deficit Hyperactivity Disorder; AE = adverse event; AU = Australian; BAI = Beck Anxiety Inventory; C = control group; Can = Canadian; CBD = cannabidiol; CBT = cognitive behavioral therapy; CI = Confidence interval; CM = contingency management; CN-THCCOOH = creatinine normalized 11-nor-9-carboxy-Δ9-tetrahydrocannnabinol; DRO = Dronabinol; DSM = Diagnostic and Statistical Manual of Mental Disorders; FT = full-time; GAB = gabapentin; HAM-D = Hamilton Depression Rating Scale; IU = international unit; MD = mean difference; MET= Motivational Enhancement Therapy; mg = milligrams; MM = medication management; MTD = maximum tolerated dose; MWC= Marijuana Withdrawal Checklist; NAC = N-acetylcysteine; ng = nanogram; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; PBO = placebo; PRN = as needed;- ROB = risk of bias; RPT= Relapse Prevention Therapy; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SERT = sertraline; SES = socioeconomic status; sig = statistically significant; SMD = standard mean difference; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; T = treatment group; THC = Tetrahydrocannabinol; UA = urinalysis; US = United States; wk(s) = week(s); yrs = years.

Table 3. Trials of psychopharmacotherapies for treating secondary outcomes of cannabis use disorder

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control		Other Outcomes	Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms		
PSYCHOPHARMACOTHERAPIES						
Selective Serotonin Reuptake Inhibitors (SSRIs): *Escitalopram, Fluoxetine*						
Weinstein, 2014[22] N=52 Single site (Israel) 23-week follow-up DSM IV Cannabis Dependence Comorbid Major Depressive Disorder	26 vs 26 Escitalopram 10 mg 9 wks 60 min group CBT 1x/wk + MET. Instructed to stop cannabis use after 4 weeks. UA: every 2 wks after wk 4	75% male Age: 32.71 (6.8) Race: NR Education: 12.42 (2)	No difference in dropouts due to AEs.	Withdrawal symptoms reduced in both groups, but no difference between groups.	No difference in medication adherence. Higher treatment compliance with placebo (P=0.016). No difference in depression or anxiety reduction.	High
Cornelius, 2010[20] N=70 Single site (US) 12-week follow-up DSM IV CUD** or HAM-D ³ 15 Comorbid Major Depressive Disorder	34 vs 36 Fluoxetine 10mg first 2 weeks/ 20mg wks 3-12 12 wks CBT (9 therapy sessions over 12 wks) + MET CM: $20 for each assessment visit UA: frequency unspecified	61.4% male Age: 21 (2.4) Race: 55.7% White, 37.1 AA/Black, 7.1% Mixed SES: NR	No dropouts due to AEs or SAEs	NR	Clinically (but not significant) improvement in depressive symptoms in both groups. No difference between groups.	Low

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control		Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	

continued below

Other Antidepressants: _Bupropion, Nefazodone, Venlafaxine, Vilazodone_						
Carpenter, 2009[21] N=106 2 Sites (US) 13-week follow-up DSM IV Cannabis Dependence	40 vs 36 vs 30 Bupropion 300 mg/day vs Nefazodone 600 mg/day (or MTD) vs PBO CM for attendance ($5/visit; 26 visits) Individual coping skills- based CBT UA: 2x/week	76.4% male Age: 32(10) years Race: 34% White, 27% AA/Black, 28% Hispanic Education: 42.5% high school or less Employment: 9.4% Unemployed	Dropouts: 1 vs 0 vs 0; no difference 5 vs 9 vs 1 moderate or serious AEs – no difference	No difference on difficulty falling asleep, sleep disturbances, irritability, or anxiety.	No difference in effect on cannabis dependency severity (P=0.14). Clinical improvement over course of study for all groups, but no difference between groups. More missed doses with nefazodone vs placebo (P=0.019). No difference from bupropion.	Low
Penetar, 2012[23] N=22 Single site (US) 4-week follow-up DSM-IV Cannabis Abuse or Dependence.	10 vs 12 7-day baseline period. Bupropion 300mg/day Instructed to stop cannabis use on day 8 Weekly MET UAs: every weekday	Of 9 Completers: 55.6% men Age: 31.2(9.6)	NR	No difference in withdrawal symptoms. Cannabis withdrawal scores increased for PBO but not BUP. Significantly lower craving for T vs C. No difference in depression, anxiety, or readiness to change. No difference in hours slept, latency to sleep, or ratings of sleep.	No difference on cognitive tests.	High

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Levin, 2013[19] N=103 2 Sites (US) 12-week follow-up DSM IV-TR Cannabis Dependence or ³ 12 on the HAM-D. Comorbid Major Depressive Disorder or Dysthymia	51 vs 52 1-week placebo lead-in followed by Venlafaxine 225 mg/day (or MTD) 11 weeks CM for attendance (transportation; $5-20/visit; 24 visits) and medication adherence ($10/week for returning pill bottles) Weekly CBT/RPT UA: 2x/week	73.8% male Age: approx. 35 years Race: 45.6% White, 21.3% AA/Black, 26.2% Hispanic, 2.9% Asian, 3.9% Other Education: 29.2% < high school, Employment: 59.2% unemployed/less than FT	NR	NR	Depressive symptoms improved for both groups, with no difference between groups. No differences in medication or behavioral therapy compliance.	Low
McRae-Clark, 2016[18] N=76 Single site (US) 8 weeks DSM IV Cannabis Dependence	41 vs 35 Vilazodone max dose of 40 mg CM for attendance ($5/week increasing by $5 each consecutive week + bonuses in weeks 1 [$20] and 12 [$40]) and medication adherence ($10/week for returning pill bottles) 3 sessions MET	79.0% male Age: 22.2 (21.3 – 23.1) Race: 54.8% Caucasian Education: 94.7% high school graduate	Dropouts: 2/41 vs 1/35 SAEs: 0/41 vs 1/35 (not considered study related)		One subscale of cannabis craving (purposefulness) decreased more for the vilazodone group (F=6.7,P=0.012). No differences on other subscales of cannabis craving.	Low

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control		Other Outcomes	Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms		
Antipsychotics (Atypical): *Clozapine, Ziprasidone*						
Schnell, 2014[24] N=30 Single site (Germany) Inpatient 12-month follow-up DSM-IV Cannabis Abuse or Dependence Comorbid psychotic spectrum disorder	16 vs 14 Ziprasidone (M = 200 mg [range 80-400]) Clozapine (M = 225 mg (range 50–425]) 12 months Outpatient: Clinical management with psychoED, group CBT, and social and occupational rehab. UA: Inpatient - daily, Outpatient – at 3, 6, 9, 12 mos	86.7% male Age: 29 years (8.1) Race: NR 3% homeless Education: 90% high school or less Employment: 83.3% Unemployed	Clozapine was associated with more side effects (F=8.2; P=0.017)	NR	Positive symptoms decreased in both groups, with a stronger decline with clozapine (P=0.05). Ziprasidone was associated with more emergency sessions (P=0.022), higher group therapy attendance (P=0.024), and higher drug attitude inventory score (P=0.005).	High
Anxiolytic: *Buspirone*						
McRae-Clark, 2009[26] Single site (US) N=93 12 weeks DSM IV Cannabis Dependence	49 vs 44 Buspirone max dose of 60 mg (mean=46 ± 14) CM for attendance ($10 per visit) 3 sessions of MET UA:2x/week at beginning of study, but reduced to 1x/week to improve adherence	88% male Age: 31.4 (9.8) Race: 86% Caucasian	Dropous: 1/49 vs 1/44 Serious AEs: none	NR	Trend toward faster time to first UA(-) in T group (P=0.098). No difference on anxiety, or measures of craving.	Unclear

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
McRae-Clark, 2015[25] Single site (US) N=175 12 weeks DSM IV Cannabis Dependence	88 vs 87 Buspirone max dose of 60 mg (mean=42 $\pm$ 18) CM for attendance ($5/wk increasing by $5 each consecutive wk + bonuses at in wks 1 [$20] and 12 [$40]) and medication adherence ($10/wk for returning pill bottles) 3 sessions MET	76.6% male Age: 24.0 (23.1 – 25.0) Race: 64.0% Caucasian Education: 90.3% high school graduate	Dropouts: 2/88 vs 4/87 Serious AEs: 2/88 vs 1/87 (none were considered study- related)	NR	Cannabis craving decreased during treatment, but no difference between groups (F=1.64, P=0.20).	Low
Mood Stabilizer: *Divalproex Sodium, Lithium Carbonate*						
Levin, 2004[28] N=23 Single site (US) 12-week follow-up DSM IV Cannabis Dependence	13 vs 12 Divalproex Sodium 1500mg/day (250mg- 2000mg depending on response). 6 weeks Weekly individual relapse prevention therapy UA: 2x/week	99% male Age: 32 Race: 56% White, 24% AA/Black, 20% Hispanic Education: 2 yrs college	Dropouts: 3/13 vs 1/12 SAEs: NR	No differences in craving or irritability.	Suggestion of poor medication compliance associated in divalproex (no statistical analysis reported).	High

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Johnson, 2014[27] N=31 Single site (Australia) Inpatient (7-day withdrawal) Dec 2010 – Aug 2012 90 days follow-up DSM IV-TR Cannabis Abuse or Dependence	19 vs 22 Lithium 100mg/day 7 days Also available: Paracetamol, Nitrazepam, nicotine treatment. RPT, relaxation, withdrawal counseling, individual and group psychoED Inpatient: daily Outpatient: UA at 14, 30, 90 days.	65.8 % male Age: 40.51(12.49) Race: % White NR, 5.3% Indigenous Education: 86.8%≥10th grade	None	Withdrawal severity: no difference between groups. T was more effective than C for attenuating nightmares/strange dreams for withdrawal period (P=0.005), as well as for loss of appetite (P=0.001), and stomach aches (P=0.05). Trend towards reducing withdrawal-related physical tension (P=0.06).	QOI: Physical, but not psychological, health or social relations improved in T group (P<0.05). No differences in severity of dependence or cannabis problems	Low

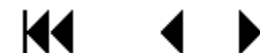| Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Cognitive-Enhancing: *Atomoxetine*						
McRae-Clark, 2010[29] N=78 Single site (US) Nov 2005 – Jun 2008 12-week follow-up DSM IV Cannabis Dependence Comorbid ADHD	39 vs 39 Atomoxetine 100mg/day (or MTD) 4 wks CM for attendance (nominal) 3 MET sessions in weeks 1-4 UA: 1x week	80% male Age: 29.9(10.9) Race: 91% White	Dropouts: No difference (1 vs 1)	NR	Greater improvement on CGI with T (P=0.02) No difference in change in ADHD severity ratings. T had a greater rate of ADHD symptom decline than C in weeks 1-4 (P=0.023), but there was no subsequent difference between groups. No difference in heavy use days by group.	Unclear

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control		Other Outcomes	Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms		
CANNABINOIDS: *Dronabinol, Nabilone, Nabiximol*s						
Levin, 2011[30] N=156 Single-site (US) Outpatient 12-week DSM IV-TR Cannabis Dependence	79 vs 77 1-week placebo lead-in, DRO, 40mg/day 8-weeks + 2-wk taper CM for attendance and transportation ($5-20 depending on distance + $1.50/visit increasing by $1.50 each consecutive visit and medication adherence ($10/consecutive pair of visits for returning pill bottles); 24 visits up to $570 + transportation MET + RPT weekly UA: 2x/week	Sex: 82% male Age: 37.6 years Race: 48% White Education: 27.6% high school or less	SAEs: 3 vs 1	Significantly greater drop in withdrawal symptoms over time in T vs C (P=.02)	NR	Low
Levin, 2016[31] N=122 Single-site (US) Outpatient 11 weeks DSM IV Cannabis Dependence	61 vs 61 Lofex–DRO "fixed-flexible" dose schedule, dose titrated to 1.8 and 60 mg/day or MTD 11-weeks CM attendance and transportation ($5-20 depending on distance) MET + RPT weekly UA: 1x/wk	Sex: 68.9% male Age: 35.1 (11.0) Race: 38.5% White Education: 30.3% high school or less	SAEs: 1 vs 1	Main effects model: No effect of T on withdrawal scores across time ($F_{1,633}$=.05, P=.83)	NR	Unclear

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Hill, 2017[32] N=18 Single site (US) 14 weeks DSM IV Cannabis Dependence	10 vs. 8 Treatment: 2mg/day of Nabilone; Placebo for the 10-week duration CM for attendance ($40 bonus for all 4 visits) and completed diaries ($100 each) up to $955. MM weekly UA: Outpatient 2x weekly for the duration of the 10-week study; Follow-up UA at 14 wk.	Sex: 67% male Age: 26.4 (6.5) years Race: 67% White Education: 14.4 (3.4) years	NR	No differences at end of treatment (Z=0.34, P= 0.74) or end of follow-up (Z=0.40, P=0.69)	Craving: no difference at end of treatment (P=0.74), or end of follow-up (P=0.69) Anxiety: No difference at end of treatment (P=0.50), or end of follow-up (P=0.92)	Unclear
Trigo, 2018[33] N=40 Single site (Canada) Outpatient 12 weeks DSM IV Cannabis Dependence	20 vs 20 Nabiximols (113.4 mg THC/105 mg CBD): self-titrated up to 42 sprays/day 12 weeks CM for attendance and transportation (C$6 visit + random non-monetary prize or $5-50 gift card, up to C$855; 24 visits) CBT/MET UA: 2x week	72.5% male Age: 33.0 (11.75) Race: 60% White Education: 62.5% completed college Employment: 12.5% FT	NR	Withdrawal symptoms decreased for both, but no difference between groups over time (P=.601)	Lower craving with T vs C (P<.05)	Unclear

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control		Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Allsop, 2014[34] N=51 2 sites (Australia) Inpatient (9 days) 28-day follow-up DSM IV-TR Cannabis Dependence	27 vs 24 Nabiximols, maximum dose 86.4 mg THC, 80 mg CBD; 3 days washout; 6 days medication Self-completed CBT workbook CM for attending follow up visit AU$40 UA: Inpatient– 3x during 9-day phase. Outpatient 1x at 28- day follow-up	76% male Age: 35.39 Race: % White NR; 6% Aboriginal/Native Education: 55% completed school Employment: 53% Unemployed	Dropout: 0 vs 0 SAEs; 0 vs 1, No difference (P=.10)	Over the duration of the study: T reduced overall severity of cannabis withdrawal vs C (P=.01) Reduction of cravings: Favored T (P=.03) Lower irritability, anger, and aggression: Favored T (P=.004) Reduction in depressive symptoms: Favored T (P=.05) Shorter course of withdrawal: Favored T (P=.04) NS positive benefit on sleep disturbance, anxiety, appetite loss, physical symptoms, and restlessness.	NR	Low

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control		Other Outcomes	Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms		
ANTICONVULSANTS: *Gabapentin, Topiramate*						
Mason, 2012[36] N=50 Single-site (US) 13 wks DSM IV Cannaibis Dependence	25 vs 25 Gabapentin 1200 mg/day 12 wks Weekly manual-guided (MET & CBT) individual counseling	80% Male Age: 33.9 (9.7) Race: 76% White Education years: 14 (1.9)	Dropouts: 1 vs 1 Serious AE: None	Greater improvement in withdrawal symptoms with GAB (P<0.001) Sleep: Better sleep quality, duration, and efficiency, and lower sleep medication use, sleep disturbance, and daytime dysfunction with GAB (all P<0.001)	Depressive symptoms: Greater improvement with T (P=0.009) Craving: Greater reduction with T (P<0.001) Cannabis-related consequences: Greater reductions with T (P=0.02) Cannabis related problems: Greater improvement with T on psychological (P=0.028) and physical (P=0.046). Neurocognitive performance: Greater improvement with T (P=0.029). Medication compliance: No difference	Unclear

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Miranda, 2017[35] N=66 Single-site (US) 7 wks DSM IV Cannabis Dependence	40 vs 26 Topiramate 200mg/day 6 wks 3-session manual-driven MET	Youth 15-24 48% Male Age: 19.5 Race: 52% White	Dropouts: 14 vs 1 Serious AE: NR	NR	Depressive symptoms: No difference in overall scores, greater reduction in symptoms with PBO (P=0.022). Neurocognitive performance: Decreased retrieval performance and memory with T Medication compliance: No difference	Unclear
OTHER PHARAMACOTHERAPIES						
Mucolytic: *N-acetylcysteine*						
Gray, 2012[38] N=116 Single-site (US) 12 wks No diagnosis necessary – self-reported regular cannabis users.	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	Dropouts: 1 vs 0 Serious AEs: None	NR	Adherence (% of dispensed doses taken): 95% vs 93%	Low

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Gray, 2017[37] N=302 6 sites (US) 16 wks DSM IV-TR Cannabis Dependence	153 vs 149 NAC 2400mg/day 12 wks CM for attendance ($10 for first visit increasing by $2 each consecutive visit, maximum of $30/visit 24 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA- , maximum of $25/visit; 36 visits) MM 1x/wk UA 3x week	72% male Age: 30.3 (9.03) Race: 58.3% White, 27.8% AA/Black Education: 31.2%≤ high school Employment: 30.1% unemployed	Dropouts: 0 Serious AEs: 1 vs 6	NR	Adherence (UA confirmed N taking ≥80% of medication /week): 31 vs 26 Adherence (self- report + pill count) N taking ≥80% of medication/ wk: 87 vs 78	Low
Antiemetic/Antinauseant: *Aprepitant*						
The Scripps Research Institute[39] Unpublished N=20 single-site (US) 2014-2016 12 wks DSM IV Cannabis Dependence	10 vs 10 Aprepitant 125mg/d 8 wks manual-guided behavioral counseling 8 wks	85% male Age: 35.0 (SD=11.3) Other demographics: NR	NR	NR	NR	Unclear

Setting N Randomized, # of Sites Mean follow-up	N, T vs C; Treatment dose & duration; Concomitant treatment; UA frequency	Population* Male % Age, mean (SD) Race % SES	Treatment vs Control			Risk of bias
			Treatment dropouts due to AE; Serious AEs	Cannabis withdrawal symptoms	Other Outcomes	
Hormone: *Oxytocin*						
Sherman, 2017 [40] N = 16 Site(s) not reported 4-month follow-up DSM IV Cannabis Dependence	8 vs 8 Oxytocin (40 IU) administered intranasally 4 wks MET for 4 wks	62.5% male Age: 25.5 (7.6) Race: 56.3% White Education: 62.5% some college or more	None	NR	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.
** As reported.

Abbreviations: AA = African American; ADHD = Attention Deficit Hyperactivity Disorder; AE = adverse event; AU = Australian; BAI = Beck Anxiety Inventory; C = control group; Can = Canadian; CBD = cannabidiol; CBT = cognitive behavioral therapy; CI = Confidence interval; CM = contingency management; CN-THCCOOH = creatinine normalized 11-nor-9-carboxy-Δ9-tetrahydrocannnabinol; DRO = Dronabinol; DSM = Diagnostic and Statistical Manual of Mental Disorders; FT = full-time; GAB = gabapentin; HAM-D = Hamilton Depression Rating Scale; IU = international unit; MD = mean difference; MET= Motivational Enhancement Therapy; mg = milligrams; MM = medication management; MTD = maximum tolerated dose; MWC= Marijuana Withdrawal Checklist; NAC = N-acetylcysteine; ng = nanogram; NR = Not reported; NS = not significant; OR = Odds ratio; P = p-value; PBO = placebo; PRN = as needed;- ROB = risk of bias; RPT= Relapse Prevention Therapy; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SERT = sertraline; SES = socioeconomic status; sig = statistically significant; SMD = standard mean difference; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; T = treatment group; THC = Tetrahydrocannabinol; UA = urinalysis; US = United States; wk(s) = week(s); yrs = years.

KEY QUESTION 2: Are there known subpopulations for whom currently used pharmacotherapy is most/least effective for cannabis use disorder?

We identified 7 RCTs exploring the differential effects of pharmacotherapy for subjects with cannabis use disorder by subpopulation. Overall, findings are insufficient due to the limited number of studies examining each subpopulation/outcome.

Demographic Subpopulations: *Gender, Race, Age*

Four RCTs examined subgroup differences by gender.[18,20,37,38] Findings suggest no gender differences in abstinence or time to dropout associated with N-acetylcysteine,[37,38] that vilazodone may be less effective than placebo for the reduction of cannabis use in females but not males,[18] and that females may experience greater benefit from fluoxetine than males (*ie*, cannabis dependence criteria and depressive symptoms).[20] Two trials of N-acetylcysteine explored racial and ethnic differences and differences by age. Findings from 1 trial suggest that regardless of group assignment, non-White and Hispanic subjects may have lower proportions of negative UAs.[37] The second trial reported no differences in time to dropout by race.[38] For comparisons by age, in a trial of N-acetylcysteine in adults, when limiting abstinence results to subjects aged 18-21 (N=58), rates of achieving abstinence were 2 times higher with N-acetylcysteine versus placebo; however, the difference was not statistically significant.[37] The other trial, of adolescents and young adults, found no difference in time to dropout by age (see Table 4 for more detail).[38]

Other Subpopulations: *Baseline Cannabis Use, Baseline Tobacco Use, Comorbid ADHD and other Mental Health Conditions*

Three RCTs examined differences in effect by baseline cannabis use.[21,29,38] Findings indicate that baseline use was a stronger predictor of end-of-study use than randomization to atomoxetine or placebo.[29] Among subjects with severe cannabis dependence at baseline, there was no difference between nefazodone or bupropion over placebo for end-of-study severity reduction.[21] No difference by baseline cannabis use or severity was observed when comparing N-acetylcysteine to placebo.[38] Two RCTs of N-acetylcysteine compared effects by baseline tobacco use and found higher rates of abstinence among non-tobacco users, and no effect on time to dropout.[37,38] Three RCTs examined subgroup differences related to mental health conditions. Among subjects with both ADHD and cannabis use disorder randomized to atomoxetine or placebo, results indicate no significant difference in cannabis use reduction or ADHD symptoms by baseline ADHD severity.[29] In addition, a trial comparing N-acetylcysteine to placebo found no difference in time to dropout by ADHD or any other comorbid mental health condition.[38] Finally, 1 RCT of venlafaxine in subjects with major depressive disorder examined the relationship between improvement in depressive symptoms and urine THC levels. Results indicated that for subjects randomized to placebo, THC levels went down as depressive symptoms decreased. For those randomized to venlafaxine, THC levels remained high despite mood improvements (see Table 4 for more detail).[19]

Table 4. Subgroup analyses in studies of pharmacotherapy for cannabis use disorder, stratified by population characteristic

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
		DEMOGRAPHICS		
Gender				
Cornelius, 2010[20] N=70 Single site (US) 12-week follow-up Comorbid Major Depressive Disorder	34 vs 36 Fluoxetine 10mg first 2 weeks/ 20mg wks 3-12 12 wks CBT (9 therapy sessions over 12 wks) + MET UA: frequency unspecified	61.4% male Age: 21 (2.4) Race: 55.7% White, 37.1 AA/Black, 7.1% Mixed SES: NR	No differences in the reduction of cannabis use or end-of-study depressive symptom scores by gender. However, females showed greater improvement in depression symptoms and a greater reduction in cannabis abuse criteria over time.	No differences in the reduction of cannabis use or end-of-study depressive symptom scores by gender. However, females showed greater improvement in depression symptoms and a greater reduction in cannabis abuse criteria over time.
McRae-Clark, 2016[18] N=76 Single site (US) 8 weeks	41 vs 35 Vilazodone max dose of 40 mg CM for attendance ($5/week increasing by $5 each consecutive week + bonuses in weeks 1 [$20] and 12 [$40]) and medication adherence ($10/week for returning pill bottles) 3 sessions MET	79.0% male Age: 22.2 (21.3 – 23.1) Race: 54.8% Caucasian Education: 94.7% high school graduate	Study cannabinoid levels: Males vs females (Ln[Cannab]=0.99±0.15 vs 1.72±0.28, P=0.25). Males randomized to vilazodone had lower urinary cannabinoid levels vs placebo (Ln[Cannab]=0.86±0.24 vs 1.16±0.19). Females randomized to vilazodone had higher urinary cannabinoid levels vs placebo (Ln[Cannab]=1.84±0.31 vs 1.17±0.36). Prevalence of UA-: Male vs female (5.6% [27–480] vs. 0.8% [1/128], P=0.079). Primary effect of T vs C on use in males = NS. Craving: A reduction in the Purposefulness subscale of the MCQ in males randomized to vilazodone (7.0±0.7 vs. 10.0±0.6, P < .001) but not in females (12.8± 1.6 vs. 12.0± 1.8, P=0.761). Total MCQ Score: No difference by gender.	Males randomized to vilazodone had lower cannabinoid levels vs placebo; however, the opposite was true for females.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
Gray, 2017[37] N=302 6 sites (US) 16 wks	153 vs 149 NAC 2400mg/day 12 wks CM for attendance ($10 for first visit increasing by $2 each consecutive visit, maximum of $30/visit 24 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA- , maximum of $25/visit; 36 visits) MM 1x/wk UA 3x week	72% male Age: 30.3 (9.03) Race: 58.3% White, 27.8% AA/Black Education: 31.2%≤ high school Employment: 30.1% unemployed	Gender was not a significant predictor of cannabis abstinence, and there was no sex-by-treatment interaction.	No difference in abstinence by gender.
Gray, 2012[38] N=116 Single-site (US) 12 wks	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	No difference in time to dropout by gender.	No difference in time to dropout by gender.
Race				
Gray, 2017[37] N=302 6 sites (US) 16 wks	153 vs 149 NAC 2400mg/day 12 wks CM for attendance ($10 for first visit increasing by $2 each consecutive visit, maximum of $30/visit 24 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA- ,	72% male Age: 30.3 (9.03) Race: 58.3% White, 27.8% AA/Black Education: 31.2%≤ high school Employment: 30.1% unemployed	Proportion UA-: Lower proportions of UA-s amongst non-White subjects. However, there was a trend towards non-Whites higher rates of UA-s with NAC (vs placebo) than Whites: White (OR=0.81, 95% CI: 0.46–1.44); non-White (OR=1.97, 95% CI: 0.84–4.63), P=0.083. Hispanics were half as likely as non-Hispanics to test negative for	Lower proportions of UA-s amongst non-White subjects Lower rates of UA- among Hispanic subjects vs non-Hispanics regardless of treatment group.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
	maximum of $25/visit; 36 visits) MM 1x/wk UA 3x week		cannabinoids during treatment (OR=0.52, 95% CI: 0.27–1.00, P=0.030), but there was no ethnicity-by-treatment interaction (P=0.881).	
Gray, 2012[38] N=116 Single-site (US) 12 wks	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	No difference between White and non-White subjects in time to dropout.	No difference between White and non-White subjects in time to dropout.
Age				
Gray, 2017[37] N=302 6 sites (US) 16 wks	153 vs 149 NAC 2400mg/day 12 wks CM for attendance ($10 for first visit increasing by $2 each consecutive visit, maximum of $30/visit 24 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA- , maximum of $25/visit; 36 visits) MM 1x/wk UA 3x week	72% male Age: 30.3 (9.03) Race: 58.3% White, 27.8% AA/Black Education: 31.2%≤ high school Employment: 30.1% unemployed	Age 18-21 (N=58): When the sample was limited to ages 18-21, subjects receiving NAC had twice the rate of achieving abstinence. The difference was not significant (OR=2.03, 95% CI: 0.70–5.86, P=0.187).	Among subjects 18-21 rates of abstinence were 2 times higher with NAC (difference was not significant).
Gray, 2012[38] N=116 Single-site (US) 12 wks	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	No difference in time to dropout by age (among adolescents and young adults).	No difference in time to dropout by age (among adolescents and young adults).

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
	visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling			

SUBSTANCE USE

Baseline Cannabis Use or Severity

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
Carpenter, 2009[21] N=106 2 Sites (US) 13-week follow-up	40 vs 36 vs 30 Bupropion 300 mg/day vs Nefazodone 600 mg/day (or MTD) vs PBO CM for attendance ($5/visit; 26 visits) Individual coping skills-based CBT UA: 2x/week	76.4% male Age: 32(10) years Race: 34% White, 27% AA/Black, 28% Hispanic Education: 42.5% high school or less Employment: 9.4% Unemployed	No difference in cannabis dependence symptoms at baseline on a reduction in symptom severity in the bupropion and nefazodone groups vs placebo (P=0.07). There was no significant difference in the effect of treatment on severity reduction (P=0.14).	No difference in dependence severity with nefazodone and bupropion vs placebo in subjects with more severe symptoms at baseline.
McRae-Clark, 2010[29] N=78 Single site (US) Nov 2005 – Jun 2008 12-week follow-up Comorbid ADHD	39 vs 39 Atomoxetine 100mg/day (or MTD) 4 wks CM for attendance (nominal) 3 MET sessions in weeks 1-4 UA: 1x week	80% male Age: 29.9(10.9) Race: 91% White	Higher baseline use was associated with higher week 12 mean self-reported use ($\hat{\beta}$=0.51, SE=0.12; P<0.001), explaining 36% of the residual variation. In contrast, the randomized treatment assigned only explained 1.7% of the residual variance after adjustment for baseline use.	Baseline use was a stronger predictor of end-of-study use than atomoxetine.
Gray, 2012[38] N=116 Single-site (US) 12 wks	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits)	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	No difference in time to dropout by baseline cannabis use or severity.	No difference in time to dropout by baseline cannabis use or severity.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
	Brief weekly cessation counseling			
Baseline Tobacco Use				
Gray, 2017[37] N=302 6 sites (US) 16 wks	153 vs 149 NAC 2400mg/day 12 wks CM for attendance ($10 for first visit increasing by $2 each consecutive visit, maximum of $30/visit 24 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA- , maximum of $25/visit; 36 visits) MM 1x/wk UA 3x week	72% male Age: 30.3 (9.03) Race: 58.3% White, 27.8% AA/Black Education: 31.2%≤ high school Employment: 30.1% unemployed	Baseline tobacco smokers were half as likely as non-tobacco smokers to achieve cannabis abstinence during treatment (OR=0.52, 95% CI: 0.31–0.88, P=0.008), but there was no tobacco-by-treatment interaction (P=0.883)	Higher rates of abstinence among baseline non-tobacco smokers regardless of treatment group.
Gray, 2012[38] N=116 Single-site (US) 12 wks	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	No difference in time to dropout by baseline cigarette use.	No difference in time to dropout by baseline cigarette use.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
		MENTAL HEALTH CONDITIONS		
ADHD				
McRae-Clark, 2010[29] N=78 Single site (US) Nov 2005 – Jun 2008 12-week follow-up Comorbid ADHD	39 vs 39 Atomoxetine 100mg/day (or MTD) 4 wks CM for attendance (nominal) 3 MET sessions in weeks 1-4 UA: 1x week	80% male Age: 29.9(10.9) Race: 91% White	No significant difference in reduction of ADHD symptoms or cannabis use reduction (P=0.11) by ADHD severity.	No significant difference in reduction of ADHD symptoms or cannabis use reduction (P=0.11) ADHD severity.
Gray, 2012[38] N=116 Single-site (US) 12 wks	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	No difference in time to dropout by ADHD diagnosis	No difference in time to dropout by ADHD diagnosis
Other Mental Health Conditions				
Levin, 2013[19] N=103 2 Sites (US) 12-week follow-up Comorbid Major Depressive Disorder or Dysthymia	51 vs 52 1-week placebo lead-in followed by Venlafaxine 225 mg/day (or MTD) 11 weeks CM for attendance (transportation; $5-20/visit; 24 visits) and medication adherence ($10/week for returning pill bottles) Weekly CBT/RPT UA: 2x/week	73.8% male Age: approx. 35 years Race: 45.6% White, 21.3% AA/Black, 26.2% Hispanic, 2.9% Asian, 3.9% Other Education: 29.2% < high school, Employment: 59.2% unemployed/less than FT	For placebo, decreased in depressive symptoms were related to lower THC levels. With venlafaxine, there was no association.	For placebo, decreased in depressive symptoms were related to lower THC levels. With venlafaxine, there was no association.

Study	N, T vs C Dose and duration Concomitant Tx UA frequency	Population* Male % Age, mean (SD) Race % SES	Outcome: Findings	Summary of findings
Gray, 2012[38] N=116 Single-site (US) 12 wks	58 vs 58 NAC 2400mg/day 8 wks CM for attendance ($5 for first visit increasing by $2 each consecutive visit, 16 visits) and UA- ($5 for UA- increasing by $2 each consecutive UA 16 visits) Brief weekly cessation counseling	Youth 13 to 21 73% male Age: 18.9 (1.5) Race: 83.5% White	No difference in time to dropout by diagnoses of Conduct/Oppositional Defiant Disorder, Major Depressive Disorder, Anxiety Disorders, or any other mental health disorder.	No difference in time to dropout by any mental health disorder.

Abbreviations: AA = African American; ADHD = Attention Deficit Hyperactivity Disorder; CBT = cognitive behavioral therapy; CI = Confidence interval; CM = contingency management; FT = full time; Ln = natural logarithm; MCQ = Marijuana Craving Questionnaire ; MET= Motivational Enhancement Therapy; MD = mean difference; mg = milligrams; MM = medication management; MTD = maximum tolerated dose; NAC = N-acetylcysteine; OR = Odds ratio; P = p-value; PBO = placebo; RPT = relapse prevention therapy; SD = standard deviation; SE = standard error; THC = Tetrahydrocannabinol; UA = urinalysis; US = United States

DISCUSSION

We identified 23 randomized control trials examining pharmacotherapies for the treatment of CUD. Overall, the evidence base is quite limited because of the relatively small number of studies examining most drug classes, small sample sizes, nearly universal high attrition rates, and other methodological flaws in nearly half the trials. Table 5 provides a high-level summary of the evidence, and Table 6 provides a more detailed summary of evidence findings.

As a drug class, antidepressants were by far the best studied, and they were ineffective. We found moderate strength evidence that antidepressants were less effective than placebo for (2 or more-week) abstinence, and moderate strength evidence that they are not beneficial (studies favored placebo or found no difference) for reducing cannabis use. Interestingly, among this population of subjects with comorbid CUD and major depressive disorder, there was consistently no difference between antidepressants and placebo on the reduction of depressive symptomology. These findings however, may be due to high rates of attrition and doses that were insufficient to experience a clinically significant effect.

Among individuals with CUD we found low to moderate strength evidence that buspirone, cannabinoids, and N-acetylcysteine were not effective for achieving abstinence or reducing cannabis use. There was insufficient evidence to draw conclusions about the effects of antipsychotics, mood stabilizers, and the drugs atomoxetine, aprepitant, and oxytocin.

The only potentially promising medications were the anticonvulsants topiramate and gabapentin, which each improved treatment retention. However, there were only 2 small, unclear-ROB trials, and the strength of evidence was low.

Another area which may deserve further exploration is the use of pharmacotherapy to relieve withdrawal symptoms in those with CUD. We expanded our search to include short term (less than 4-week) studies specifically for this outcome; despite this, we were unable to find adequate literature to draw conclusions. However, we did find low strength evidence that cannabinoids might relieve withdrawal symptoms, though there were important inconsistencies in results across studies.

The high rates of attrition in most studies made it difficult to assess harms, particularly study dropouts due to adverse events. Most trials reported very low rates of dropouts due to adverse events, but given the high rates of drop out, and the often incomplete accounting of reasons for drop out, we could not say with confidence to what extent adverse events may have contributed to attrition.

Table 5. Summary of findings

	Abstinence	Use	Retention	Withdrawal Symptoms	Other	Harms
Antidepressants: Escitalopram, Fluoxetine, Bupropion, Nefazodone, Venlafaxine, Vilazodone	««	««	««	NA	«	«

	Abstinence	Use	Retention	Withdrawal Symptoms	Other	Harms
Antipsychotics: Clozapine, Ziprasidone	NA	Ø	Ø	NA	Ø	Ø
Anxiolytic: Buspirone	NA	««	««	NA	Ø	««
Mood Stabilizers: Divalproex Sodium, Lithium Carbonate	Ø	Ø	Ø	Ø	Ø	Ø
Cognitive Enhancing Drug: Atomoxetine	NA	Ø	Ø	NA	Ø	Ø
Cannabinoids: Nabilone, Nabiximols, Dronabinol	««	««	«««	««	Ø	««
Anticonvulsants: Gabapentin, Topiramate	NA	Ø	««	Ø	Ø	Ø
Glutamatergic modulator: N-acetylcysteine	Ø	«««	«««	NA	«««	««
Antiemetic/Antinauseant: Aprepitant	NA	Ø	Ø	NA	NA	NA
Hormone: Oxytocin	NA	Ø	NA	NA	NA	NA

Shading represents the direction of effect: (No color)=Unclear, Green=Evidence of benefit, Gray=No benefit, Red=Favors placebo

Symbols represent the strength of the evidence: NA=No evidence or not applicable, Ø Insufficient, ««Low, ««« Moderate, ««««« High

Attrition rates were high in nearly all trials, and the reasons for the high dropout rates are unclear. The one exception was a 12-week trial (N=70) comparing the antidepressant fluoxetine to placebo in adolescents and young adults with moderately severe depression who were also receiving contingency management, cognitive behavioral therapy, and motivation enhancement therapy.[20] Study retention was over 90% in this trial (though the rate did not differ between the intervention and control groups), but it is unclear why study retention was so much higher in this trial as compared to others. Contingency management for treatment retention was a common co-treatment strategy in many studies; 14 of the 23 trials included contingency management with or without travel reimbursements. Indeed, many trials offered considerably larger monetary incentives for treatment attendance than the high-retention trial and still had substantially lower rates of retention.

Studies examining subpopulations were extremely limited, and all pharmacotherapy/population combinations identified were insufficient to form conclusions.

LIMITATIONS

There are several important limitations to this evidence base beyond the overall paucity of trials and small sample sizes. The assessment of the primary outcomes – cannabis use and abstinence – were complicated by several factors. The majority of the trials included urinalysis testing for THC; however, the frequency of collection varied widely. Although we limited inclusion for trials examining these outcomes to 4 weeks or longer, the fact that THC is detectable in urine for up to a month after last cannabis use in frequent users hampers the ability to quantify relative

reductions in use beyond reliance on self-report data. Similarly, the possibility of false positive or negative results, diluted samples, as well as factors like donor hydration, metabolic, and activity status, etcetera, may result in uncertainties in outcomes when using THC/creatinine ratios to determine increases or reductions in use, or abstinence. Finally, currently available urine tests are unable to distinguish among different cannabinoids, which complicates studies of cannabinoids for the treatment of CUD.

There was substantial variation in the types of co-interventions used in these studies. Many, but not all, studies included some form of concomitant behavioral or contingency management treatment. We are unable to comment on differential effects of various drugs according to co-interventions used, given the variety of drugs studied and the differences in co-intervention strategies.

For studies examining subpopulation differences, we were unable to form conclusions due to the lack of studies examining similar pharmacotherapies and outcomes. In addition, among included studies of subpopulations, it is possible that the lack of positive findings may reflect small samples and the lack of power to detect differences.

Our review adds to, and differs slightly from, a previous systematic review which concluded with moderate strength evidence that cannabinoids were more effective than placebo for study retention.[1] More recent trials have reported poorer retention, and we found moderate strength evidence that there is no difference between cannabinoids and placebo.

RESEARCH GAPS/FUTURE RESEARCH

There are many areas ripe for further research in this field. As described above, further research on the effectiveness of certain potentially promising drug classes such as the anticonvulsants and cannabinoids is needed before these could be recommended for clinical practice. Given the change in the legal status of cannabis in many states, studies should assess outcomes beyond abstinence, use, withdrawal symptoms, and study retention, and include those related to function and changes in high-risk behaviors. The treatment of withdrawal symptoms in those with cannabis use disorder should be further studied as well. In addition, the lack of reduction in depressive symptoms among those with comorbid CUD and MDD treated with antidepressants should be explored. Finally, identification of subpopulations in which treatment retention might be higher, or in whom certain medications might be more effective, is needed. We did not find adequate evidence to comment on this issue.

IMPLICATIONS FOR THE VHA

Our findings have a number of implications for the VHA. They will be used to help guide future Health Services Research and Development (HSR&D) priorities. However, the current lack of effective pharmacotherapies leave Veterans seeking treatment for CUD reliant on psychotherapeutic options that can be time-consuming, and less accessible for some (*eg*, Veterans living in rural areas). These factors may hinder treatment utilization and adherence – thus reinforcing the need to emphasize efforts that increase the accessibility of mental health services for Veterans. With the increased acceptance of cannabis use in the community,[2] changes in its potency,[3] and low rates for treatment seeking for CUD,[7] it is especially important that clinicians be prepared to discuss potential risks of use and assess for potential CUD.

CONCLUSION

There is limited research examining the effectiveness of pharmacotherapies for CUD, and many of the existing studies are hampered by poor methodological quality or reporting. There is moderate strength evidence that antidepressants do not reduce cannabis use or improve treatment retention, and may be associated with lower rates of abstinence. There is low to moderate strength evidence that buspirone, and N-acetylcysteine do not improve outcomes. Although we found that cannabinoids do not improve retention, increase rate of abstinence, or reduce cannabis use, we did find low strength evidence that they may reduce withdrawal symptoms. We found insufficient evidence to comment on effects of all other drug classes. Given the increasing access to and use of cannabis in the general population (including Veterans), along with the high prevalence of cannabis use disorder among current cannabis users, there is an urgent need for more research to identify effective pharmacologic treatments.

Conclusions Table. Summary of the evidence on pharmacotherapies for cannabis use disorder, stratified by drug class

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Findings on abstinence, drug use, study retention, cannabis withdrawal symptoms, dropout due to AE, serious AEs, and other	Strength of Evidence*	Comments and rationale for strength of evidence rating
		PSYCHOPHARMACOTHERAPIES		
Antidepressants: Escitalopram, Fluoxetine, Bupropion, Nefazodone, Venlafaxine, Vilazodone				
Abstinence	2 low-ROB RCT[19,21] (N=209); and 1 high-ROB RCT[22] (N=52) Total N=261	**Favors placebo:** RR=0.49 (95% CI: 0.30 to 0.83); P=0.007	Moderate	Consistent results across 3 trials of 4 medications.
Use	3 low-ROB[18-20] Total N=249	**No benefit:** Two trials found no difference between groups, and 1 trial found higher THC levels with venlafaxine.	Moderate	Consistent results of no benefit across trials. Limitations of studies include incomplete outcome data and high rates of attrition.
Retention	4 low-ROB RCTs[18-21] (N=355); and 2 high-ROB RCTs[22,23] (N=74) Total N = 429	**No benefit:** RR=0.95 (95% CI: 0.85 to 1.07); P=0.40	Moderate	Consistent results across trials. Precise estimate.
Dropouts due to AEs/Serious AEs	3 low-ROB RCTs[18,20,21] (N=252); and 1 high-ROB RCT[22] (N=52) Total N=304	**No benefit:** Three low-ROB and 1 high-ROB RCT found no difference in the number and severity of AEs or study dropouts due to serious AEs or AEs. Most studies have high rates of attrition, but findings are consistent in 1 study with very low rates of attrition	Low	Consistent finding across trials. Downgraded SOE due to high attrition and lack of clarity related to reasons for dropout.
Other Outcomes	4 low-ROB RCTs[18-21] (N=355); and 2 high-ROB RCTs[22,23] (N=74) Total N=429	**No benefit:** Overall there were no effects of antidepressant medications on secondary outcomes.	Low	Outcomes measured varied across studies and high rates of attrition across studies
Antipsychotics: Clozapine, Ziprazadone				
§ Use	1 high-ROB RCT[24] (N=30)	One high-ROB head to head trial found that both ziprasidone and clozapine reduced the frequency of cannabis consumption in subjects with a comorbid psychotic spectrum disorder. There was no difference in reduction between groups.	Insufficient	Small single study. High attrition.
§ Retention		One high-ROB head to head trial found high rates of attrition in both groups, with no significant difference between groups.	Insufficient	
§ Dropouts due to		One high-ROB head to head trial found that clozapine was	Insufficient	

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Findings on abstinence, drug use, study retention, cannabis withdrawal symptoms, dropout due to AE, serious AEs, and other	Strength of Evidence*	Comments and rationale for strength of evidence rating
AEs/Serious AEs		associated with more AEs – specifically hypersalivation (F=8.2; P=0.017).		
§ Other Outcomes		Treatment compliance: One high-ROB head-to-head trial found more regular group therapy attendance among the ziprasidone group (P=0.024). Drug attitude: One high-ROB head-to-head trial found that ziprasidone was associated with and a higher drug attitude inventory score (P=0.005). Other mental health: One high-ROB head-to-head trial found that positive symptoms decreased in both groups, with a stronger decline with clozapine (P=0.05), and that subjects receiving ziprasidone requested a higher number of emergency sessions (P=0.022).	Insufficient	
Anxiolytic: *Buspirone*				
Use	1 low-ROB RCT[25] (N=175); and 1 unclear-ROB RCT[26] (N=93) Total N=268	**No benefit:** In 1 low-ROB and 1 unclear-ROB RCT, there were no differences in odds of weekly abstinence between buspirone and placebo.	Low	Consistent results across 2 trials with high rates of attrition
Retention		**No benefit:** RR=0.92 (95% CI: 0.71 to 1.19); P=0.52	Low	
Dropouts due to AEs/Serious AEs		**No benefit:** One low-ROB and 1 unclear-ROB RCT found no differences in the number and severity of AEs or serious AEs.	Low	Low rate of adverse events
Other Outcomes		One low-ROB RCT found that cannabis craving decreased for both groups during treatment, but did not differ by condition. A unclear-ROB RCT found that cannabis craving did not significantly change during treatment and there was no difference between groups.	Insufficient	Inconsistent results across 2 trials with high rates of attrition
Mood Stabilizers: *Lithium Carbonate, Divalproex Sodium*				
§ Abstinence	1 high-ROB RCT[28] (N=25); and 1 low-ROB RCT[27] (N=31) Total N=56	1 high-ROB RCT reported no difference in end of treatment abstinence (divalproex vs placebo), and a low-ROB RCT found no difference in post-withdrawal abstinence (lithium vs placebo).	Insufficient	Consistent findings across 2 small studies. High attrition.
§ Use		1 high-ROB RCT and1 low-ROB RCT reported no difference in between lithium and divalproex respectively vs placebo in frequency or quantity of end of treatment/post	Insufficient	

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Findings on abstinence, drug use, study retention, cannabis withdrawal symptoms, dropout due to AE, serious AEs, and other	Strength of Evidence*	Comments and rationale for strength of evidence rating
		withdrawal use.		
§ Retention		RR=1.07 (95% CI: 0.79 to 1.44), P=0.68	Insufficient	Consistent findings across 2 small studies. High attrition. Imprecise estimate.
§ Dropouts due to AEs/Serious AEs		One low-ROB RCT found no difference in the number and severity of AEs, with no dropouts due to AEs or reported serious AEs.	Insufficient	Single small study. High attrition.
§ Cannabis Withdrawal Symptoms		1 high-ROB RCT found no difference in craving or irritability (divalproex vs placebo). A low-ROB RCT found no difference in withdrawal severity, but that lithium was more effective for attenuating nightmares, loss of appetite, and stomach aches.	Insufficient	Consistent findings across 2 small studies. High attrition.
§ Other Outcomes	1 low-ROB RCT[27] (N=31)	Quality of Life: One low-ROB RCT found greater physical health but not psychological health or social relations improvement with lithium vs placebo. Severity of Dependence: One low-ROB RCT found no difference between lithium and placebo. Cannabis Problems: One low-ROB RCT found no difference between lithium and placebo.	Insufficient	Single small study. High attrition.
	1 high-ROB RCT[28] (N=25)	Medication Compliance: One high-ROB RCT suggests lower rates of medication compliance associated with divalproex, but there was no statistical analysis.	Insufficient	Single small study. High attrition.
Cognitive-Enhancing: *Atomoxetine*				
Use	1 unclear-ROB RCT[29] (N=78)	No difference in week 12 mean self-reported use, UA results, or % of days used by group.	Insufficient	Single small study. High attrition.
Retention		No difference	Insufficient	
Dropouts due to AEs/Serious AEs		No difference	Insufficient	
Other		CGI improved. No difference in change in ADHD severity. Greater rate of ADHD symptom decline in weeks 1-4, but there was no subsequent difference between groups. No difference in heavy use days.	Insufficient	

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Findings on abstinence, drug use, study retention, cannabis withdrawal symptoms, dropout due to AE, serious AEs, and other	Strength of Evidence*	Comments and rationale for strength of evidence rating
CANNABINOIDS: *Dronabinol, Nabilone, Nabiximols*				
§ Abstinence	1 low-ROB RCT[30] (N=156); and 1 unclear-ROB RCT[31] (N=122) Total N =278	**No benefit (Dronabinol)**: RR=1.07 (95% CI: 0.65 to 1.76); P=0.80	Low	Consistent findings across studies. Outcomes based on self-report, high rates of attrition.
§ Use	2 low-ROB RCTs[30,34] (N=207); and 2 unclear-ROB RCT[32,33] (N=58) Total N=265	**No benefit:** Two low-ROB RCTs and 2 unclear-ROB RCTs found no difference in reduction in use between groups.	Low	Consistent findings across studies. Outcomes based on self-report, high rates of attrition.
§ Retention	2 low-ROB RCTs[30,34] (N=207); and 3 unclear-ROB RCTs[31-33] (N=180) Total N=387	**No benefit:** RR=1.06 (95% CI: 0.89 to 1.25); P=0.53	Moderate	Consistent findings across 4/5 studies. Outcomes based on self-report, high rates of attrition.
§ Dropouts due to AEs/Serious AEs	2 low-ROB RCTs[30,34] (N=207); and 1 unclear-ROB RCT[31] (N=122) Total N=329	**No benefit**: High rates of attrition make it difficult to evaluate rates of dropout to adverse events. Of studies that reports dropouts due to AE no significant differences were reported between groups. One low-ROB placebo-controlled trial reported no dropouts to AEs; Two low-ROB RCTs reported similar SAEs.	Low	Consistent findings across studies. Downgraded SOE due to high attrition and lack of clarity related to reasons for dropout.
§ Cannabis Withdrawal Symptoms	2 low-ROB RCT[30,34] (N=207); and 3 unclear-ROB RCTs[31-33] (N=180) Total N=387	**Favors cannabinoids**: Two low-ROB RCTs found that cannabinoids significantly reduce withdrawal symptoms. Three unclear-ROB RCTs found no treatment effect.	Low	Downgraded due to inconsistent findings across studies, although overall findings, including of high quality studies, favor treatment.
§ Other Outcomes	2 unclear-ROB RCTs[32,33] (N=58)	Craving: One unclear-ROB trials found no difference between treatment groups. One unclear-ROB trial found decreased craving for treatment group. Anxiety: No difference. One unclear-ROB study reported no treatment effect on anxiety.	Insufficient	Inconsistent findings and different outcomes evaluated.

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Findings on abstinence, drug use, study retention, cannabis withdrawal symptoms, dropout due to AE, serious AEs, and other	Strength of Evidence*	Comments and rationale for strength of evidence rating
OTHER PHARMACOTHERAPIES				
Anticonvulsants: *Gabapentin, Topiramate*				
§ Use	2 unclear-ROB RCTs[35,36] (N=116); and 1 unclear-ROB RCT[36] (N=50)	One RCT found more UA(-) with gabapentin vs placebo. The second found no difference between topiramate and placebo in UA(-) or change in UA results in weeks 1-6.	Insufficient	Inconsistent findings across trials. Applicability limited due to younger sample in topiramate study.
§ Retention	Total N=166	**Favors topiramate and gabapentin**: 2 unclear-ROB RCTs found significantly higher retention for both topiramate and gabapentin vs placebo.	Low	Consistent findings across 2 trials.
§ Dropouts due to AEs/Serious AEs		High rates of attrition make it difficult to evaluate rates of dropout to adverse events. 1 RCT found a higher rate of dropouts due to AEs with topiramate. The second found no difference between gabapentin and placebo. No differences were reported in SAEs.	Insufficient	Inconsistent findings across 2 trial and high rates of attrition.
§ Cannabis withdrawal	1 unclear-ROB RCT[36] (N=50)	1 RCT found greater improvement in cannabis withdrawal symptoms (including sleep symptoms) with GAB	Insufficient	Inconsistent findings across 2 trials. Applicability limited due to younger sample in topiramate study.
§ Other	2 unclear-ROB RCTs[35,36] (N =116)	Depressive symptoms: 1 RCT found greater improvement with gabapentin. The other found no difference in overall symptom scores, but a greater reduction in symptoms with placebo than topiramate. Neurocognitive performance: One RCT found greater improvement with GAB. The second found decreased retrieval performance and memory with topiramate. Medication compliance: Two RCTs found no difference for GAB or topiramate vs placebo	Insufficient	Inconsistent findings across 2 trials. Applicability limited due to younger sample in topiramate study.
	1 unclear-ROB RCT[36] (N=50)	Craving: One RCT found greater reduction with GAB (P<0.001)	Insufficient	Single small study.

Treatment; Outcomes	N studies per outcome; ROB (N=combined participants)	Findings on abstinence, drug use, study retention, cannabis withdrawal symptoms, dropout due to AE, serious AEs, and other	Strength of Evidence*	Comments and rationale for strength of evidence rating
		Cannabis-related consequences: One RCT found greater reductions with GAB (P=0.02) Cannabis related problems: One RCT found greater improvement with GAB on psychological and physical cannabis-related problems.		
Glutamatergic Modulator: *N-acetylcysteine*				
§ Abstinence	1 low-ROB RCT[38] (N=116)	1 low-ROB RCT[38] found a non-significant trend towards 2-week end-of-trial abstinence favoring NAC.	Insufficient	Applicability due to adolescent sample, single study.
§ Use	2 low-ROB RCTs[37,38] (N=418)	**No benefit:** 2 low-ROB RCTs found no difference in use (RR=1.22, 95% CI [0.81 – 1.83], P=0.35)	Moderate	Consistent findings across trials. Applicability due to age differences in study populations. High rates of attrition
§ Retention		**No benefit:** 2 low-ROB RCTs found no difference in treatment retention. Combined RR=1.08, 95% CI [0.95 – 1.23], P=0.25.	Moderate	
§ Dropouts due to AEs § Serious AEs		**No benefit:** High rates of attrition make it difficult to evaluate rates of dropout to adverse events. 2 low-ROB RCTs found no difference on harms in dropouts due to AE or SAEs.	Low: dropouts due to AEs Low: SAEs	
Other		Medication adherence**: No benefit:** 2 low-ROB RCTs found no difference in medication adherence	Moderate	
Antiemetic/Antinauseant: *Aprepitant*				
§ Use	1 unclear-ROB RCT[39] (N=20)	Greater change in urinary CN-THCCOOH Levels from week 0 to 8 with aprepitant [Units: ng/mg]: 198.3 (SD=389.4) vs 55.9 (SD=239.3) No statistical analysis provided	Insufficient	Single study, low power, not yet published
§ Retention		Poorer retention in aprepitant group than placebo group. No statistical analysis provided	Insufficient	
Hormone: *Oxytocin*				
§ Use	1 high-ROB RCT[40] (N=16)	One high-ROB trial found no significant differences in Oxytocin compared to placebo.	Insufficient	Lack of blinding, many-ROB factors not reported, low power.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; AE = Adverse event; CI = Confidence interval; CN-THCCOOH = creatinine normalized 11-nor-9-carboxy-Δ9-tetrahydrocannnabinol; DRO = Dronabinol; DSM = Diagnostic and Statistical Manual of Mental Disorders; GAB= gabapentin; MD = mean difference; mg = milligram; NAC = N-acetylcysteine; ng = nanogram; NR = no response; P = p-value; PBO = placebo; RCT = randomized control trial; RD = risk difference; RR = Risk ratio;-ROB = Risk of bias; SAE = serious adverse event; SMD = standard mean difference; SSRI = Selective Serotonin Reuptake Inhibitors; SR = Systematic review; THC = Tetrahydrocannabinol; UA = urinalysis

◀◀   ◀ ▶

[*] 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:[17]

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.   Marshall K, Gowing L, Ali R, Le Foll B. Pharmacotherapies for cannabis dependence. *The Cochrane database of systematic reviews.* 2014(12):CD008940.

2.   Pacek LR, Mauro PM, Martins SS. Perceived risk of regular cannabis use in the United States from 2002 to 2012: differences by sex, age, and race/ethnicity. *Drug and alcohol dependence.* 2015;149:232-244.

3.   Legalizing marijuana and the new science of weed (video) [press release]. https://www.acs.org/content/acs/en/pressroom/newsreleases/2015/march/legalizing-marijuana-and-the-new-science-of-weed-video.html2015.

4.   Keyhani S, Steigerwald S, Ishida J, et al. Risks and Benefits of Marijuana Use: A National Survey of U.S. Adults. *Ann Intern Med.* 2018;169(5):282-290.

5.   Laprevote V, Schwan R, Schwitzer T, Rolland B, Thome J. Is There a Place for Off-Label Pharmacotherapy in Cannabis Use Disorder? A Review on Efficacy and Safety. *Current pharmaceutical design.* 2015;21(23):3298-3305.

6.   Danovitch I, Gorelick DA. State of the art treatments for cannabis dependence. *The Psychiatric clinics of North America.* 2012;35(2):309-326.

7.   Hasin DS, Kerridge BT, Saha TD, et al. Prevalence and Correlates of DSM-5 Cannabis Use Disorder, 2012-2013: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions–III. *American Journal of Psychiatry.* 2016;173(6):588-599.

8.   American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing. 2013.

9.   Blanco C, Hasin DS, Wall MM, et al. Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study. *JAMA Psychiatry.* 2016;73(4):388-395.

10.   Bonn-Miller MO, Harris AH, Trafton JA. Prevalence of cannabis use disorder diagnoses among veterans in 2002, 2008, and 2009. *Psychological services.* 2012;9(4):404-416.

11.   Kondo K, Ayers C, Morasco B, O'Neil M, Nugent S, Kansagara D. Pharmacotherapy for the treatment of cannabis use disorder: a systematic review. PROSPERO 2018 CRD42018108064 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018108064.

12.   McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of clinical epidemiology.* 2016;75:40-46.

13.   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.

14.   Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed).* 2011;343:d5928.

15.   Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* 2011; http://handbook.cochrane.org/. Accessed March 24, 2017.

16.   Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

17.   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.* 2013;

http://www.effectivehealthcare.ahrq.gov/ehc/products/457/1752/methods-guidance-grading-evidence-131118.pdf. Accessed December 28, 2016.

18. McRae-Clark AL, Baker NL, Gray KM, Killeen T, Hartwell KJ, Simonian SJ. Vilazodone for cannabis dependence: A randomized, controlled pilot trial. *The American journal on addictions.* 2016;25(1):69-75.

19. Levin FR, Mariani J, Brooks DJ, et al. A randomized double-blind, placebo-controlled trial of venlafaxine-extended release for co-occurring cannabis dependence and depressive disorders. *Addiction.* 2013;108(6):1084-1094.

20. Cornelius JR, Bukstein OG, Douaihy AB, et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. *Drug Alcohol Depend.* 2010;112(1-2):39-45.

21. Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR. A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *Am J Addict.* 2009;18(1):53-64.

22. Weinstein AM, Miller H, Bluvstein I, et al. Treatment of cannabis dependence using escitalopram in combination with cognitive-behavior therapy: a double-blind placebo-controlled study. *The American journal of drug and alcohol abuse.* 2014;40(1):16-22.

23. Penetar DM, Looby AR, Ryan ET, Maywalt MA, Lukas SE. Bupropion reduces some of the symptoms of marihuana withdrawal in chronic marihuana users: a pilot study. *Substance abuse : research and treatment.* 2012;6:63-71.

24. Schnell T, Koethe D, Krasnianski A, et al. Ziprasidone versus clozapine in the treatment of dually diagnosed (DD) patients with schizophrenia and cannabis use disorders: a randomized study. *The American journal on addictions.* 2014;23(3):308-312.

25. McRae-Clark AL, Baker NL, Gray KM, et al. Buspirone treatment of cannabis dependence: A randomized, placebo-controlled trial. *Drug and alcohol dependence.* 2015;156:29-37.

26. McRae-Clark AL, Carter RE, Killeen TK, et al. A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug Alcohol Depend.* 2009;105(1-2):132-138.

27. Johnston J, Lintzeris N, Allsop DJ, et al. Lithium carbonate in the management of cannabis withdrawal: a randomized placebo-controlled trial in an inpatient setting. *Psychopharmacology.* 2014;231(24):4623-4636.

28. Levin FR, McDowell D, Evans SM, et al. Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium. *Am J Addict.* 2004;13(1):21-32.

29. McRae-Clark AL, Carter RE, Killeen TK, Carpenter MJ, White KG, Brady KT. A placebo-controlled trial of atomoxetine in marijuana-dependent individuals with attention deficit hyperactivity disorder. *Am J Addict.* 2010;19(6):481-489.

30. Levin FR, Mariani JJ, Brooks DJ, Pavlicova M, Cheng W, Nunes EV. Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend.* 2011;116(1-3):142-150.

31. Levin FR, Mariani JJ, Pavlicova M, et al. Dronabinol and lofexidine for cannabis use disorder: A randomized, double-blind, placebo-controlled trial. *Drug and alcohol dependence.* 2016;159:53-60.

32. Hill KP, Palastro MD, Gruber SA, et al. Nabilone pharmacotherapy for cannabis dependence: A randomized, controlled pilot study. *The American journal on addictions.* 2017;26(8):795-801.

33.   Trigo JM, Soliman A, Quilty LC, et al. Nabiximols combined with motivational enhancement/cognitive behavioral therapy for the treatment of cannabis dependence: A pilot randomized clinical trial. *PloS one.* 2018;13(1):e0190768.

34.   Allsop DJ, Copeland J, Lintzeris N, et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA psychiatry.* 2014;71(3):281-291.

35.   Miranda R, Jr., Treloar H, Blanchard A, et al. Topiramate and motivational enhancement therapy for cannabis use among youth: a randomized placebo-controlled pilot study. *Addiction biology.* 2017;22(3):779-790.

36.   Mason BJ, Crean R, Goodell V, et al. A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. *Neuropsychopharmacology.* 2012;37(7):1689-1698.

37.   Gray KM, Sonne SC, McClure EA, et al. A randomized placebo-controlled trial of N-acetylcysteine for cannabis use disorder in adults. *Drug and alcohol dependence.* 2017;177:249-257.

38.   Gray KM, Carpenter MJ, Baker NL, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry.* 2012;169(8):805-812.

39.   Institute TSR, Abuse NIoD. Pharmacological Treatment of Comorbid Alcohol and Marijuana Withdrawal and Dependence. In: https://ClinicalTrials.gov/show/NCT02210195; 2014.

40.   Sherman BJ, Baker NL, McRae-Clark AL. Effect of oxytocin pretreatment on cannabis outcomes in a brief motivational intervention. *Psychiatry research.* 2017;249:318-320.

APPENDIX A. SEARCH STRATEGIES

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily 1946 to July 17, 2018
Date Searched: July 18, 2018
Searched by: Robin Paynter, MLIS

#	Searches	Results
1	Marijuana Abuse/dt, th or ((Cannabis/ or Marijuana Smoking/) and (Drug Dependency/dt, th or Substance Related Disorders/dt, th))	630
2	((cannabis or canabis or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas) adj3 (abuse* or abusing or addict* or chronic* or daily or disorder* or depend* or habitual* or heavy or misuse* or overuse or quit*)).tw,kf.	4367
3	or/1-2	4699
4	Substance Withdrawal Syndrome/dt, th or exp Inactivation, Metabolic/ or Drug Therapy/ or ae,ai,co,ct,dt,po,th,to.fs.	40116
5	(abstain* or abstinen* or craving or detox* or desintox* or medication* or pharmacotherap* or pharmaco-therap* or reduce* or reducing or reduction or relaps* or retain* or retention or sobriety or therap* or treat* or withdraw*).tw,kf.	8279582
6	or/4-5	8289740
7	and/3,6	2502
8	randomized controlled trial.pt.	464336
9	controlled clinical trial.pt.	92503
10	randomized.ti,ab.	448654
11	placebo.ti,ab.	195474
12	"drug therapy".ti,ab.	33021
13	randomly.ti,ab.	294694
14	trial.ti,ab.	508714
15	groups.ti,ab.	1838965
16	or/8-15	2713265
17	and/7,16	720
18	(animals not (humans and animals)).sh.	4441716
19	17 not 18	701
20	limit 19 to yr="2014-Current"	286

Ovid PsycINFO 1806 to July Week 2 2018
Date Searched: July 18, 2018

#	Searches	Results
1	(Cannabis/ or Hashish/ or Marijuana/ or Marijuana Usage/) and (Addiction/ or Drug Abuse/ or Drug Addiction/ or Drug Dependency/ or "Substance Use Disorder"/)	3014
2	((cannabis or canabis or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas) adj3 (abuse* or abusing or addict* or chronic* or daily or disorder* or depend* or habitual* or heavy or misuse* or overuse or quit*)).tw.	3996
3	or/1-2	5413
4	exp Drug Therapy/ or drug withdrawal/ or detoxification/ or drug rehabilitation/ or craving/ or drug abstinence/	161862

#	Searches	Results
5	(abstain* or abstinen* or craving or detox* or desintox* or "drug therap*" or medication* or pharmacotherap* or pharmaco-therap* or reduce* or reducing or reduction or relaps* or retain* or retention or sobriety or "substance withdrawal syndrome" or therap* or treat* or withdraw*).tw.	1228340
6	or/4-5	1241264
7	and/3,6	2835
8	Treatment Effectiveness Evaluation/ or exp Treatment Outcomes/ or Placebo/ or Followup Studies/	71506
9	(((placebo* or random* or comparative or clinical) adj3 trial*) or (research adj3 design) or ((evaluat* or prospect*) adj3 stud*) or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.	182379
10	or/8-9	237297
11	and/7,10	534
12	limit 11 to yr="2014 -Current"	199

Ovid EBM Reviews Cochrane Central Register of Controlled Trials June 2018,
Cochrane Database of Systematic Reviews 2005 to July 11, 2018
Database of Abstracts of Reviews of Effects 1st Quarter 2016
Health Technology Assessment 4th Quarter 2016

Date Searched: July 18, 2018

#	Searches	Results
1	((cannabis or canabis or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas) adj3 (abuse* or abusing or addict* or chronic* or daily or disorder* or depend* or habitual* or heavy or misuse* or overuse or quit*)).tw.	774
2	(abstain* or abstinen* or craving or detox* or desintox* or "drug therap*" or medication* or pharmacotherap* or pharmaco-therap* or reduce* or reducing or reduction or relaps* or retain* or retention or sobriety or therap* or treat* or withdraw*).tw.	824767
3	1 and 2	639
4	limit 3 to yr="2014 -Current" [Limit not valid in DARE; records were retained]	297

ClinicalTrials.gov
Date Searched: July 18, 2018

(cannabis OR canabis or marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas) AND (abuse* OR abusing OR addict* OR chronic* OR daily OR disorder* OR depend* OR habitual* OR heavy OR misuse* OR overuse OR quit*) | (cannabis OR canabis or marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas) | First posted from 01/01/2014 to 07/18/2018
= 92 studies

WHO ICTRP
Date Searched: July 18, 2018

CONDITION: (cannabis OR canabis or marijuana OR marihuana OR hashish OR hash) AND (abuse* OR abusing OR addict* OR chronic* OR daily OR disorder* OR depend* OR habitual* OR heavy OR misuse* OR overuse OR quit*)
INTERVENTION: ("drug therap*" OR medication* OR pharmacotherap* OR pharmaco-therap* OR therap* OR treat*)
RECRUITMENT STATUS: ALL
DATE OF REGISTRATION: 01/01/2018 and 18/07/2018
= 53 results

Open Trials
Date Searched: July 18, 2018

CONDITION: (cannabis OR canabis OR marijuana OR marihuana OR hashish OR hash)
REGISTRATION PERIOD START DATE: 01/01/2014

APPENDIX B. STUDY SELECTION

Inclusion codes, code definitions, and criteria

1. Is the population made up of non-pregnant/non-postpartum adolescents and/or adults with known or suspected cannabis use disorder?

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

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

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

3. Is the study design a randomized controlled trial with follow-up of 4 weeks or longer (unless the outcome being examined is withdrawal, in which case shorter studies are acceptable)?

   Yes ˮ   Proceed to 4.
   No ˮ   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
   Also exclude RCTs that compare dosage levels of the same drug, without a placebo group or other active comparator. Duration of less than 4 weeks for studies of abstinence/reduction in use.

   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 – conference proceeding potentially useful

4. Does the study measure cannabis abstinence and/or use by urinalysis and/or validated self-report scale (*ie*, TimeLine Follow Back, ASI, ASSIST, DAST, SCID, DIS, MINI, results of diagnostic interviews)? AND/OR Does it measure withdrawal with validated measures (*eg*, Cannabis Withdrawal Scale, Drug Effects Questionnaire (DEQ), Marijuana Withdrawal Checklist (MWC); Marijuana Craving Questionnaire± Short Form (MCQ-SF)).

   Yes ˮ   Proceed to 5.

No ˝ STOP. **Code X4** *(No outcomes of interest)*

Note: We will not analyze the following outcomes:
- Outcomes with lack of clinical implication (*eg,* brainwave Stroop)

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 cannabis use disorder?
   Yes ˝ **Code H2H.** Proceed to 7.
   No ˝ **Code RCT.** Proceed to 7.

7. Enter the medication(s) being tested.

APPENDIX C. QUALITY ASSESSMENT CRITERIA

Domain	Criteria[15]
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

Risk of Bias	Interpretation	Within a Trial
Low	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains
Unclear	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains
High	Bias may alter the results seriously	High risk of bias for one or more key domains

APPENDIX D. 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
Allsop, 2014[34]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Carpenter, 2009[21]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Cornelius, 2010[20]	Yes	Unclear	Yes	Yes	Yes	Yes	Low
Gray, 2012[38]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Gray, 2017[37]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hill, 2017[32]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Johnston, 2014[27]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Levin, 2004[28]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	High
Levin, 2011[30]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Levin, 2013[19]	Yes	Yes	Yes	Unclear	Yes	Yes	Low
Levin, 2016[31]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Mason, 2012[36]	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
McRae-Clark, 2009[26]	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear
McRae-Clark, 2010[29]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear
McRae-Clark, 2015[25]	Yes	Yes	Yes	Yes	Yes	Yes	Low
McRae-Clark, 2016[18]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Miranda, 2017[35]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
The Scripps Research Institute[39]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Penetar, 2012[23]	Unclear	Unclear	Yes	Unclear	Unclear	No	High
Schnell, 2014[24]	Yes	Yes	No	No	Yes	No	High
Sherman, 2017[40]	Unclear	Unclear	Unclear	No	Unclear	Unclear	High
Trigo, 2018[33]	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear
Weinstein, 2014[22]	Unclear	Unclear	Yes	Unclear	Yes	No	High

Yes = adequately addressed; Unclear = unclear or not reported; No = not adequately addressed

APPENDIX E. PEER REVIEW

Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?		
1	Yes	Thank you.
2	Yes	Thank you.
3	Yes	Thank you.
4	Yes	Thank you.
5	Yes	Thank you.
6	Yes	Thank you.
7	Yes	Thank you.
8	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?		
1	No	Thank you.
2	No	Thank you.
3	No. There does not appear to be bias based on the study design, and information.	Thank you.
4	No	Thank you.
5	No	Thank you.
6	No	Thank you.
7	No	Thank you.
8	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?		
1	No	Thank you.
2	No	Thank you.
3	No. I am not aware of any study that has been overlooked, and the authors describe inclusion/exclusion criteria well.	Thank you.
4	No	Thank you.
5	No	Thank you.
6	No	Thank you.
7	No	Thank you.
8	No	Thank you.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.		
1	Overall comment: Would use terminology "treatment dropout" rather than "treatment withdrawal" so as not to risk confusion with measurement of withdrawal symptoms.	Thank you. We have made this change.
1	Page 7, line 14: Change "control" to "controlled."	Thank you, corrected.
1	Page 10, line 26: Physiologic dependence is NOT required to make a diagnosis of cannabis use disorder. See DSM-5 page 509.	Changed to "consequences in daily living."

Reviewer Number	Comment	Response
1	Page 11, line 11: Check Drexler's title. What is there does not seem to be correct.	Thank you, corrected.
1	Table 1 under "Outcomes," should "severe" be changed to "serious?"	Yes – I think this may be discipline specific; however, we have changed all instances of "severe adverse events" to "serious adverse events."
1	Page 16, line 35: Presumably, the THC levels referred to here are urinary THC. This point should be explicitly stated.	Thank you, we added "urinary" for clarity.
1	Page 20, line 27: Add "evidence" after "strength."	Thank you, added.
1	Page 20, line 30: Change "a" to "across."	Thank you, this has been changed.
1	Page 21, line 38: Should "severe" be changed to "serious?" Same question for Table 3 and Table 5, possibly elsewhere.	Yes – I think this may be discipline specific; however, we have changed all instances of "severe adverse events" to "serious adverse events."
1	Page 46, line 25: Awkward wording. Rewrite.	changed
1	Page 47, line 42: Specify urinary cannabinoid levels	Added "urinary"
1	Page 52, line 43: Specify urinary cannabinoid levels.	Added "urinary"
1	Page 54, lines 26-28: This summary seems far too critical of the methods and outcomes reporting of the gabapentin study. It may be that lumping gabapentin with topiramate as anticonvulsants obscures the findings with gabapentin.	Thank you. We've revised the summary to read," However, there were only 2 small unclear ROB trials…" the gabapentin study was an unclear ROB study with N=50, so alone would result in insufficient SOE.
1	Page 54, lines 30-36: Gabapentin was found to reduce withdrawal symptoms. Why is that finding not mentioned here? It may be that lumping gabapentin with topiramate as anticonvulsants obscures the findings with gabapentin.	Thank you. This is because the study examining gabapentin had a sample size of 50 and was determined by dual review to be unclear ROB. Alone, this small study provides insufficient evidence on the use of gabapentin to mitigate withdrawal symptoms.
1	Page 55, Limitations: It may be worth mentioning the limitations in interpreting quantitative urine THC metabolite levels. If not mentioned, readers may assume that urinary levels are somehow superior to self-report or perhaps a reliable, objective outcome measure.	Thank you. We have revised this statement to include additional concerns related to the interpretation of THC metabolite levels.
1	Page 58, line 28: Is this p-value correct? It does not indicate significance.	Thank you – great catch! It should be 0.024. We have corrected it.
1	Page 58, line 38: Is this p-value correct? It does not indicate significance.	Another great catch. We have corrected it to 0.022. Thank you!
2	The present systematic review provides a needed comprehensive summary of a generally limited literature. Below are some minor comments for authors to consider: 1. Consider asking the expert panelists to review their affiliations (e.g., see at least two individuals	Thank you. We have confirmed affiliations with those authors.

Reviewer Number	Comment	Response
	affiliated with CESATE who are not listed as such).	
2	2. Buspirone and N-acetylcysteine are mentioned by name in the conclusions but not in the results section of the Executive Summary. Consider consistency across sections for the uneducated reader and/or listing the drug classes examined somewhere in the Executive Summary (if the goal is to have the executive summary be a stand-alone document). It was surprising to see Busprione and N-acetylcystine listed in the conclusion when there had been no prior mention of these drugs earlier in the summary.	Thank you. We have added both Buspirone and N-acetylcysteine to the results.
2	3. On page 15, the text above the figure notes "The 7 RCTs included in KQ2 were also included in KQ1", however, the footnote states "*All 6 KQ 2 studies were also included in KQ 1."	Thank you. Corrected so all read "7."
2	4. On page 15, authors note "Trials examined antidepressants (ie, escitalopram, fluoxetine, bupropion, nefazodone, venlafaxine, vilazodone), antipsychotics (ie, clozapine, ziprasidone), buspirone, mood stabilizers (ie, divalproex, lithium), and atomoxetine" but later in this section additional categories/types of drugs are given their own section/group (e.g., glutamatergic modulator, antinauseant, etc). Is there a reason these latter categories/groups weren't included in the above-referenced list?	Thank you. The listed trials are those that fall under the subheading of psychopharmacological interventions; whereas, the others you mentioned do not fit this category. We have added an introductory paragraph for the KQ1 section to make this clearer.
2	5. There are two periods at the end of the first sentence at the top of page 46.	Thank you, corrected.
3	Overall, this systematic review is of very high quality.

The most important issue that I have is the unclear definition of cannabis use disorder. If possible, early on it would be helpful if the authors gave a definition of what cannabis use disorder is, and whether they use the DSM or another convention. Relatedly, it would be helpful for each study in the table (Table 2) to have a description of what classification system was used (DSM-IV abuse and/or dependence; DSM-5 cannabis use disorder, etc), and potentially examine differences by studies that included, e.g., those with DSM-IV abuse versus those that did not. | Thank you, we have added an abbreviated description of DSM V criteria and cited it.

We have added the inclusion criteria to tables. We did not perform additional analyses because no studies used DSM V criteria (all were DSM IV or DSM IV-TR, or self reported use). The one study that used self-reported use was in a drug/outcome that was SOE insufficient. Furthermore, there were two studies that included Two studies included participants meeting DSM IV/IV-TR criteria for Cannabis abuse and dependence. Once drug/outcome was insufficient, and the other was a high ROB study that was the only trial that found a positive impact of bupropion on retention – the exclusion of this study would not have made a difference in the conclusion of no difference from placebo. |

Reviewer Number	Comment	Response
3	Also, I may have missed where the authors define "risk of bias" levels. If this is not included, it may be helpful to include for readers (e.g., what does "low" risk of bias entail?).	Thank you. We have added an in-text citation, as well as an additional table to Appendix C that better describes the interpretation of risk of bias.
3	Minor- There is a typo on pg. 56 line 39 "addition"	Thank you, corrected.
4	1) Page 7, Line 33: spell out 'risk of bias' before the acronym is presented in parentheses.	Thank you, corrected.
4	2) Page 10, last paragraph: Include contingency management as an available psychosocial treatment for cannabis use disorder.	Thank you, that was an oversight – added.
4	3) Page 12, line 50: Present the rationale for including studies that were at least 4 weeks in duration, i.e. because of the detection window for THC via toxicology testing. This rationale is referenced later in the report on page 55. Also note that the 4 or more week inclusion criterion was not used for the selection of studies on withdrawal symptoms.	Thank you. We have revised this for clarity.
4	4) Page 16, lines 52-54: The data appear to suggest that cannabis use might blunt the antidepressant effects of antidepressant medication among patients with severe depression. This would be an important, possible adverse effect to explore further in the report.	Thank you. We have added a statement in the conclusion addressing the lack of reduction in depressive symptoms in the comorbid CUD/MDD population, and have also added a statement in the section on future research.
4	5) Page 20, line 30: Change "a" to "across"	Thank you, corrected.
5	Page 7, Line 41: It's odd that these two medications are mentioned in the conclusion, but not in the Results?	Thank you. We have added both Buspirone and N-acetylcysteine to the results.
5	Page 10, Line 12: Clarify whether this is a national estimate of the prevalence.	Thank you, revised
5	Page 10, Line 27: Use of prevalence here is confusing (implies overall prevalence), as the next sentence reports prevalence of CUD among patients with prior year cannabis use.	Thank you. We have added a statement and reference for population based prevalence, followed by the statement related to those with prior year use.
5	Page 16, Line10: Should this [12] be 23?	Thank you. We apologize for the confusion, and for clarity, we have added a paragraph at the beginning of the results section clarifying different drug classes. This particular reference/section is specific to Psychopharmacology.
5	Page 16, Line 20-21: I believe this sentence suggests that there was insufficient evidence for all other findings. Regardless, consider clarifying to make it clear.	Thank you. We have revised this sentence for clarity.
5	Page 16, Line 44: It's not clear what "these authors" is referring to here.	Thank you, this refers to the authors of the Fluoxetine trial. We have edited the sentence for clarity.
5	Page 20, Lines 29-31: Sentence is unclear.	Thank you, corrected.

Reviewer Number	Comment	Response
5	Page 46, Line 19: Less effective in terms of which outcomes?	Thank you, we have revised this sentence for clarity.
5	Page 46, Line 20: Clarify on what outcome might women receive greater benefit.	Thank you, we have revised this sentence for clarity.
5	Page 54, Line 26-28: Consider highlighting gabapentin in this paragraph as only treatment retention was the only promising finding among topiramate users.	Thank you. The study examining gabapentin was a small (N=50) unclear ROB study; thus, alone provides insufficient evidence to form conclusions. We have added the sample size to the text to better clarify.
6	This evidence-based synthesis was comprehensive and well-written. The key questions are clear and directly addressed by the review. I have no substantive concerns about the EBS. Minor comments: The conclusions section begins "The effectiveness of pharmacotherapies for cannabis use disorder remains, for the most part, poorly studied." I'm not sure that I would describe this topic as "poorly studied". The findings are not particularly encouraging but… several of the studies were reasonably well-designed. I would suggest leading this section with a statement that involves less conjecture (e.g., there are few studies, the findings do not provide strong support for pharmacotherapy for CUD, *etc*).	Thank you. We have revised this sentence to read, "There is limited research examining the effectiveness of pharmacotherapies for cannabis use disorder, and many of the existing studies are hampered by poor methodological quality or reporting."
6	I was intrigued by the finding that antidepressants may be associated with lower rates of abstinence. This seems to have important implications for a large system like VHA that treats many patients with antidepressants. It would be helpful to comment on the implications of this finding within the sections on research gaps and/or implications for VHA.	Thank you. We have added a statement in the conclusion addressing the lack of reduction in depressive symptoms in the comorbid CUD/MDD population, and have also added a statement in the section on future research.
6	It is worth noting that the subgroup analyses likely lacked power to detect meaningful differences between groups. Thus, there is the potential that important differences exist between subgroups but these have yet to be identified in the literature.	We have added a statement to the limitations section addressing the lack of power in subgroup analyses.
7	This is a well-written report and thorough examination of outcomes of pharmacotherapy for CUD. Comments below are meant to improve the clarity and consistency of writing. 1. In the Executive Summary (p. 7, line 14), the search strategy is stated to have included articles up to November 2018. In Appendix A, the search appears to have ended in July 2018.	Thank you for noting the discrepancy. The search ended in July 2018, and the ES has been revised.
7	2. In figure 2 on p. 15, it is unclear how many articles were extracted from the 2014 review and, thus, how many of the 23 studies analyzed for this	Thank you. We have edited the figure and text for clarity.

Reviewer Number	Comment	Response
	review were new literature not previously synthesized. Also, line 60 on this page indicates 6 studies were included for KQ2. This should be 7.	
7	3. In the narrative description of results, the authors make statements about studies' risk of bias (e.g., p. 16, line 26), yet all studies appear to provide equal weighting in determining strength of evidence and are low ROB studies are not differentiated from high/unclear ROB studies in the narrative description. I suggest greater explanation of how risk of bias factors in to determining strength of evidence in order to make this determination more transparent to readers.	Thank you. The determination of strength of evidence (SOE) is based on a number of factors, of which the ROB of studies is an important and often driving factor. The conclusions table provides rationale for SOE determinations. In addition, for clarity, we have added more detail about the factors considered in SOE determinations to the methods section.
7	4. It would be helpful to see combined sample size (N), RR, and 95% CIs for all outcomes. For example, this is not presented for the outcome reduction in cannabis use for antidepressants on p. 17, lines 7-9.	There was heterogeneity in the definition of and reporting of reduction of use outcomes, and we only combined outcomes that provided data that could be combined. This was true for these antidepressant studies. Given the consistent findings we were able to conclude moderate strength evidence of no benefit, but were not able to combine them in a meta-analysis
7	5. It is unclear why in Figure 4, some of the percentage weightings do not add to 100% (e.g., venlafaxine, p. 18, line 12; other antidepressants, p. 18, lines 20-21).	The weights were incorrect because the figure combined results from multiple subgroup analyses. The weights have been removed from the figure to avoid confusion
7	6. In Table 2, retention in treatment data sometimes include percentages and other times do not. Please be consistent with reporting format.	Thank you, the formatting has been corrected to include percentages for all retention data.
7	7. A strength of evidence determination is not made for studies synthesized in KQ2 on p. 46, lines 16 and 34.	Thank you. We state in the first paragraph that all findings were insufficient to form conclusions – this is due heterogeneity in pharmacotherapy/sub-population studies. We have added an additional statement in the conclusion to better clarify.
7	8. The report would benefit from additional detail of how risk of bias (as summarized in Appendix D) is quantified. Appendix C provides categories over with ROB is assessed but provides no detail of how ratings across categories are used to determine and overall ROB.	Thank you. We have added an additional table to Appendix C that better describes the interpretation risk of bias.
8	Excellent, thorough review of a very small research literature. Conclusions are appropriate given the results. No additional comments.	Thank you.