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

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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.

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

ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Dr. Dominick DePhilippis, Education Coordinator at Philadelphia CESATE, in conjunction with Dr. Karen Drexler, National Mental Health Program Director, Substance Use Disorders for the Office of Mental Health Services for the purpose of examining the effectiveness and best practices for pharmacotherapy for cannabis use disorder. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

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

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

Operational Partners

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

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Technical Expert Panel (TEP)

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

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Peer Reviewers

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

EXECUTIVE SUMMARY

Aim: 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).

Methods: 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.

Results: 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.

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 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