QUERI

Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review

August 2017

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

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

Investigators:

Principal Investigator:
Devan Kansagara, MD, MCR

Co-investigators:
Maya O'Neil
Shannon Nugent
Michele Freeman
Allison Low
Karli Kondo
Camille Elven
Bernadette Zakher
Makalapua Motu'apuaka
Robin Paynter
Benjamin J. Morasco

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

PREFACE

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

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

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

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

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

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

Recommended citation: Kansagara D, O’Neil M, Nugent S, Freeman M, Low A, Kondo K, Elven C, Zakher B, Motu’apuaka M, Paynter R, Morasco BJ. Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review. VA ESP Project #05-225; 2017.

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

TABLE OF CONTENTS

EXECUTIVE SUMMARY

EVIDENCE REPORT

TABLES

FIGURES

EXECUTIVE SUMMARY

INTRODUCTION

Eight states and the District of Columbia have legalized cannabis use for recreational purposes, and 28 states plus the District of Columbia have legalized cannabis for medical purposes. Recent studies suggest that 45-80% of individuals who seek cannabis for medical purposes do so for pain management, and an estimated 6%-39% of patients prescribed opioid medication for pain are also utilizing cannabis. Over one-third of patients seeking cannabis for medical purposes list post-traumatic stress disorder (PTSD) as the primary reason for the request. Approximately 15% of Veterans who are treated in Department of Veterans Affairs (VA) outpatient PTSD clinics report recent (past 6 months) cannabis use.

Given the social, political, and legal changes surrounding cannabis use, physicians in both VA and non-VA settings will increasingly need to engage in evidence-informed discussions about the potential benefits and harms of cannabis use with their patients. Despite the rapidly moving legislative landscape, there is little comprehensive and critically appraised information available about what is known and not known about cannabis use for the treatment of chronic pain or PTSD.

The objectives of this systematic review are to: 1) assess the physical and mental health outcome effects of cannabis in patients with chronic pain; 2) assess the physical and mental health outcome effects of cannabis in patients with PTSD; 3) assess the impact of short- and long-term cannabis use on the risk of adverse effects such as pulmonary diseases, cardiovascular diseases, cancer, cannabis use disorder (CUD), and psychosis in the general adult population; and 4) provide a broad overview of more recently recognized “emerging harms” of cannabis use.

METHODS

DATA SOURCES AND SEARCHES

We developed search strategies in consultation with a research librarian. We searched multiple data sources including Ovid MEDLINE, Embase, PubMed, PsycINFO, PILOTS Database, EMB Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*), and grey literature sources from database inception through February 2016.

STUDY SELECTION

We included English-language studies of plant-based cannabis preparations including whole-plant preparations (*eg*, cannabis cigarettes, hashish, oils), whole plant extracts such as nabiximols (an oromucosal spray delivering 2.7 mg tetrahydrocannabinol [THC]/2.5 mg cannabidiol [CBD], currently available by prescription only in Europe), and capsular THC/CBD preparations. We did not include synthesized, pharmaceutically-prepared cannabinoids such as dronabinol or nabilone because the efficacy of synthetic cannabinoid preparations for chronic pain was examined in 2 recent review articles. We were broadly inclusive of different types of cannabis preparations because there are many different cannabis preparations in dispensaries, and clinicians may therefore encounter patients using many different forms.

To address the efficacy of cannabis in treating chronic pain or PTSD, we examined controlled clinical trials or rigorously designed observational studies with control groups that adjusted for important confounders and used validated outcome measures. We determined our study selection criteria for pre-specified harms based on whether the likelihood of the adverse outcome might be substantially different in populations with chronic pain or PTSD. For example, we anticipated that rates of depression and anxiety in patients with chronic pain or PTSD were likely to be substantially different than the general population, so we only included studies reporting these harms in the specific populations of interest. In contrast, we thought it unlikely that rates of pulmonary effects or cancer would be particularly influenced by the presence of chronic pain or PTSD, so we included studies in general adult populations for these outcomes.

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

DATA ABSTRACTION AND QUALITY ASSESSMENT

From each study, we abstracted the following where available: study design, objectives, setting, population characteristics, subject inclusion and exclusion criteria, number of subjects, duration of follow-up, the study and comparator interventions (formulation, strength, *etc*), important co-interventions, health outcomes, healthcare utilization, and harms. We assessed study quality and graded the strength of evidence using published criteria.

DATA SYNTHESIS AND ANALYSIS

We qualitatively synthesized the evidence on the benefits and harms of cannabis. For the subgroup of neuropathic pain studies, we conducted a study-level meta-analysis of the proportion of patients experiencing clinically significant (≥ 30%) pain relief.

RESULTS

RESULTS OF LITERATURE SEARCH

We included 12 systematic reviews and 48 primary studies after reviewing 10,875 titles and abstracts.

SUMMARY OF RESULTS FOR KEY QUESTIONS

Key Question 1. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have chronic pain?

We found low-strength evidence that cannabis preparations with precisely defined THC:CBD content (most in a 1:1 to 2:1 ratio) have the potential to improve neuropathic pain but insufficient evidence in other patient populations. Most studies are small, many have methodologic flaws, and the long-term effects are unclear given the brief follow-up duration of most studies. The applicability of these findings to current practice may be low in part because the formulations studied may not be reflective of what most patients are using, and because the consistency and accuracy of labeled content in dispensaries are uncertain.

Key Question 2. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have PTSD?

We found insufficient evidence examining the effects of cannabis in patients with PTSD. We found 2 observational studies comparing outcomes in cannabis users to a control group that had not used cannabis; cannabis use was not associated with improved outcomes in either study. We found no evidence addressing whether effects differed according to other comorbidities in patients with PTSD.

Key Question 3. What are the harms associated with cannabis use in adults?

General Adverse Events

Data from 2 systematic reviews examining cannabis for chronic pain suggest that cannabis may be associated with a higher risk of short-term adverse effects, although rates of adverse events did not significantly differ between groups in the additional trials we reviewed. While most adverse events were mild, there were possible treatment-related serious adverse events such as suicide attempts, paranoia, and agitation.

Medical Harms

Pulmonary effects

Moderate-strength evidence from 2 well-designed cohort studies suggest that low levels of cannabis smoking do not adversely impact lung function over about 20 years in young adults, but there is some evidence suggesting that heavy (*ie*, daily) use may have the potential to cause adverse pulmonary effects over an extended period of time. There were no studies in older users, or in those with medical comorbidities such as chronic obstructive pulmonary disease (COPD) or heart disease.

Cardiovascular events

There is insufficient evidence from 2 studies about the effect of cannabis use on the risk of cardiovascular events, due to methodological limitations including lack of longitudinal exposure measurement and potential recall bias.

Cancer

A meta-analysis of 9 case-control studies provided low-strength evidence that cannabis use does not appear to be associated with an increased risk of head and neck or lung cancer. There was insufficient evidence about the effects of cannabis on testicular or transitional cell cancer. We found no studies examining the effects on other types of cancer.

Motor vehicle accidents

Moderate-strength evidence from a recent meta-analysis of 21 multi-national observational studies found that acute cannabis intoxication was associated with a moderate increase in collision risk (odds ratio [OR] 1.35; 95% confidence interval [CI], 1.15 to 1.61).

Mental Health-related Harms

Suicidal behaviors

We found no studies examining the effects of cannabis use on suicide risk in patients with chronic pain or PTSD. A review and meta-analysis of 4 epidemiological studies in general populations found significantly increased odds of suicide death (pooled OR 2.56; 95% CI, 1.25 to 5.27) with any cannabis use.

Mania

We found no studies examining the effects of cannabis on the risk of mania among persons with PTSD or chronic pain. A systematic review of 6 longitudinal studies in other populations detected an association between cannabis use and exacerbation of manic symptoms in patients with known bipolar disorder, and an increased incidence of new-onset mania symptoms among populations without a diagnosis of bipolar disorder (OR 2.97; 95% CI, 1.80 to 4.90).

Psychosis

A systematic review and 7 studies consistently found an association between cannabis use (specifically related to THC content) and the development of psychotic symptoms (low-strength evidence). There is evidence of a dose-response relationship, and there is experimental evidence documenting the risk of acute, transient psychotic symptoms within hours of use; however, no studies were specifically in PTSD or chronic pain populations.

Cognitive effects

One systematic review of studies in general populations provides moderate-strength evidence that active, long-term cannabis use is associated with small negative effects on all domains of cognitive function, but there was insufficient evidence of cognitive effects in past users.

Cannabis use disorder (CUD)

Cannabis use was associated with incident cannabis use disorder (adjusted odds ratio, 9.5 [CI, 6.4 to 14.1]) in a large (N = 34 653) prospective cohort study.

We found no studies comparing rates of CUD in chronic pain or PTSD populations to other populations.

Other studies of CUD provide potentially relevant cross-sectional data examining the prevalence of CUD among patients with chronic pain. For example, one large cross-sectional study of Veterans using administrative data found that about 2% of Veterans with non-cancer pain had a diagnosis of CUD, and that this proportion increased (up to about 4%) among subgroups with higher numbers of opioid prescriptions. In a non-VA study using structured diagnostic interviews the prevalence of cannabis abuse was 2.4% and cannabis dependence was 0.9%.

Emerging Harms

Chronic cannabis use has been associated with a severe form of cyclic vomiting called the cannabinoid hyperemesis syndrome. There have also been reports of serious infectious diseases including aspergillosis and tuberculosis associated with smoked cannabis, and a severe acute illness associated with intravenous cannabis use. The recent availability of edible forms of

cannabis with high THC content has been associated with episodes of severe acute psychosis. There is mixed evidence regarding the effects of cannabis on violent behavior.

Key Question 4. What are important areas of ongoing research and current evidence gaps in research on cannabis for chronic pain or PTSD, and how could they be addressed by future research?

We identified 10 ongoing randomized controlled trials (RCTs) examining the effectiveness of cannabis for a variety of chronic pain conditions, including several populations included in this report (3 studies for cancer pain and 2 studies for neuropathic pain), as well as conditions for which there is currently very little or no evidence (osteoarthritis, sickle cell disease, low back pain, and ulcerative colitis).

There are 2 recently initiated RCTs examining the benefits and harms of cannabis for PTSD that should add to the body of evidence.

SUMMARY AND DISCUSSION

KEY FINDINGS AND STRENGTH OF EVIDENCE

We reviewed the literature examining benefits of cannabis in chronic pain and PTSD populations, as well as literature examining potential harms relevant to these populations. We found low-strength evidence that cannabis preparations with precisely defined THC-cannabidiol content (most in a 1:1 to 2:1 ratio) may alleviate neuropathic pain but insufficient evidence in populations with other types of pain. Most studies are small, many have methodological flaws, and the long-term effects are unclear given the brief follow-up of most studies. Among neuropathic pain studies, we found a discrepancy between continuous and dichotomous pain outcomes. Possible interpretations are that cannabis is simply not consistently effective or that, although cannabis may not have clinically important effects on average, subgroups of patients may experience large effects. We did not find data to clarify which subgroups of patients are more or less likely to benefit.

We found no trials that met our inclusion criteria examining the effects of cannabis in PTSD populations, and there was insufficient evidence from observational studies to draw conclusions about its effectiveness in patients with PTSD.

In younger populations, light to moderate cannabis use does not appear to be associated with adverse pulmonary effects over the long-term, but pulmonary effects have not been studied in older populations or individuals with comorbid medical conditions. There is insufficient to low-strength evidence examining the effects of cannabis use on the risk of various types of cancer. There is consistent evidence that suggests an association between cannabis use and psychotic symptoms, as well as cognitive impairment in active users in general populations, though there is limited evidence specific to patients with chronic pain or PTSD. There are a number of adverse effects that appear to be related to cannabis use and may be important for clinicians to be familiar with, but whose incidence has not been well-characterized. These include infectious disease complications, cannabis hyperemesis syndrome, and violent behavior.

The summary of findings and strength of evidence supporting these findings are detailed in the table that follows.

Summary of Evidence for the Benefits and Harms of Cannabis in Chronic Pain or PTSD Populations

	N studies (N combined participants)	Findings	Strength of Evidence[a]	Comments
Chronic Pain				
· Multiple sclerosis (MS)	4 Low ROB studies (combined N=1017; 24 to 424 per study): - 2 of THC/CBD capsules - 1 of nabiximols - 1 of sublingual spray delivering THC, CBD, or THC/CBD combined 3 Unclear ROB studies of nabiximols (combined N=562; 36 to 337 per study) 7 High ROB studies (combined N=430; 13 to 160 per study): - 3 of nabiximols - 2 of THC/CBD capsules - 1 of smoked THC - 1 of oral THC	**Favorable effect on pain and spasticity:** Significant relief from patient-reported muscle stiffness, pain, and spasticity occurred with 12 to 15 weeks of treatment with THC (2.5 mg)/CBD (1.25 mg) capsules in 2 studies. A 12-week study of nabiximols (2.7 mg THC/2.5 mg CBD oromucosal spray) reported significant improvement in spasticity. A sublingual spray delivering 2.5 mg of CBD, THC, or both for sequential 2-week periods reported mixed effects. THC alone significantly improved pain and spasticity, but CBD alone and THC/CBD combined had inconsistent effects.	Low	Few methodologically rigorous studies, but fair number of patients; inconsistent results; little long-term data; restrictive entry criteria in largest study which only included patients with initial response in run-in phase; applicability to formulations available in dispensaries may be low
	4 Low ROB studies (combined N=1017; 24 to 424 per study): - 2 of THC/CBD capsules - 1 of nabiximols - 1 of sublingual spray delivering THC, CBD, or THC/CBD combined	**Other outcomes:** **Small improvements in sleep in 4 studies:** Self-reported sleep quality improved in 2 studies of THC/CBD capsules. Nabiximols were significantly superior to placebo for reducing sleep disruption in a 12-week study (N=241). Sleep improved significantly in a small study (N=24) of a sublingual spray containing 2.5 mg each of CBD:THC. **Other:** Nabiximols were significantly superior to placebo for Barthel Activities of Daily Living (*P*=.0067), Physician Global Impression of Change (*P*=.005), Subject Global Impression of Change (*P*=.023), and Carer Global Impression of Change (*P*=.005) in Function in a 12-week study (N=241).	Low (sleep) Insufficient (other outcomes)	Few methodologically rigorous studies, but fair number of patients; inconsistent results; little long-term data; restrictive entry criteria in largest study which only included patients with initial response in run-in phase; applicability to current practice may be low Only one study of nabiximols – not tested otherwise

	N studies (N combined participants)	Findings	Strength of Evidence[a]	Comments
· Neuropathic pain	11 low ROB studies (combined N = 593) 4 of smoked THC (combined N = 150) 3 of vaporized THC (combined N = 97) 3 of nabiximols (combined N = 312) 1 of oromucosal spray delivering THC or THC+CBD (N = 34) 1 unclear ROB study of nabiximols (N = 30) 1 high ROB trial (N = 125)	Studies did not find a clinically significant between-group difference on continuous pain scales, but a higher proportion of intervention patients had clinically significant pain relief up to several months later. In a meta-analysis of 9 studies, intervention patients were more likely to report ≥30% improvement in pain (combined RR, 1.43 [95% CI, 1.16–1.88]; I^2 = 38.6%; P = 0.111).	Low	Few patients enrolled in most low ROB studies; inconsistent results; marked differences among studies in dosing and delivery mechanism; brevity of study duration; low applicability to formulations available in dispensaries.
	1 Low ROB study of smoked THC (N=23)	**Other outcomes reported in low ROB studies:** A study of vaporized cannabis reported that 25 mg with 9.4% THC administered as a single smoked inhalation 3 times daily resulted in significant improvements in sleep quality.	Insufficient	Only one small study
· General/other/mixed populations	2 Low ROB studies: - 1 trial of sublingual spray delivering THC, CBD, or THC/CBD combined (N=34) - 1 observational study of cannabis containing 12.5% THC (smoked, oral, or vaporized) (N=431) 3 Unclear ROB studies of nabiximols (combined N=428; 10 to 360 per study) 3 High ROB studies (combined N=265; 18 to 177 per study): - 2 of nabiximols - 1 of THC capsules	Small improvements in pain, but no effect on sleep, mood, quality of life.	Insufficient	Only one small low ROB study in which the bulk of the patients had MS; larger observational study had high drop-out rate
PTSD	2 observational studies in Veterans with PTSD: - 1 Medium ROB (N=2276) - 1 High ROB (N=700)	Cannabis was not associated with an improvement in mental health symptoms.	Insufficient	No trials; only 2 observational studies with methodologic flaws

	N studies (N combined participants)	Findings	Strength of Evidence[a]	Comments
Harms				
· General AEs	2 systematic reviews of chronic pain	Cannabis-based treatments were associated with an overall higher risk of short-term, non-serious AEs.	---	Consistent findings except for serious AE
· Medical harms				
Ø Pulmonary function	2 Low ROB prospective cohort studies with 20-32 years follow-up (combined N=6053) 1 systematic review of 5 observational studies (3 cohort, 2 cross-sectional) (combined N=851)	In young adults, low levels of cannabis smoking did not adversely affect lung function over about 20 years. A previous meta-analysis of 5 studies found no increased risk for pulmonary adverse effects, OR (95% CI): 0.80 (0.46-1.39).	*Young adults:* Moderate *Older adults:* No evidence	Two well-done prospective cohort studies, but limited information about effects of heavy use and no information in older or multimorbid populations
Ø Cardiovascular	2 High ROB observational studies: - 1 case-crossover (N=3882) - 1 cohort study (N=2097)	Cannabis use at the time of myocardial infarction was not associated with mortality after mean 12.7 years follow-up, but longitudinal use was not assessed. Risk of myocardial infarction within an hour of cannabis use was significantly elevated compared with periods of non-use but this finding may be inflated by recall bias, OR (95% CI): 4.8 (2.9-9.5).	Insufficient	Recall bias; inadequate controlling for confounders; lack of longitudinal exposure data
Ø Cancer				
§ Lung	1 patient-level meta-analysis of 6 case-control studies (2150 cases) 1 High ROB cohort study (N=49,231)	The meta-analysis found no association between light cannabis use and lung cancer.	Low	Recall bias; mostly light users, few heavy users; the large cohort study had no information about exposure over time
§ Head/neck/oral	Meta-analysis of 9 case-control studies (5732 cases)	No association between cannabis use and cancer, OR (95% CI): 1.02 (0.91-1.14); generally consistent across studies and no evidence of dose-response.	Low	Imprecise exposure measurement with potential recall bias; ever use among studies ranged from 1 to 83%
§ Testicular	Meta-analysis of 3 High ROB case-control studies (719 cases)	An increase in cancer risk for weekly users compared to never-users appeared with non-seminoma cancers but not seminoma cancers, OR (95% CI): 1.92 (1.35-2.72).	Insufficient	Potential confounding from recall bias and tobacco use
§ Transitional cell	1 High ROB VA case-control study (52 cases)	Risk of cancer with > 40 joint-years cannabis use compared to none, OR 3.4 (unadjusted, *P*=.012).	Insufficient	One very small case-control study with several methodologic flaws

	N studies (N combined participants)	Findings	Strength of Evidence[a]	Comments
Ø Motor vehicle accidents	Meta-analysis of 21 observational studies (combined N=239,739)	Increase in collision risk, OR (95% CI): 1.35 (1.15-1.61).	Moderate	The small but significant increase in risk was seen consistently across numerous sensitivity analyses and after adjustment in meta-regression analyses
· Mental health				
Ø Suicidal behaviors	No studies in chronic pain or PTSD populations.	---	No evidence (chronic pain or PTSD)	Meta-analysis of 4 studies in the general population reported significantly increased odds of suicide with any cannabis use, OR (95% CI): 2.56 (1.25-5.27).
Ø Mania	No studies in chronic pain or PTSD populations	---	No evidence (chronic pain or PTSD)	A systematic review found an increased incidence of new-onset mania symptoms among populations without a diagnosis of bipolar disorder, OR (95% CI): 2.97 (1.80 to 4.90).
Ø Psychosis	1 systematic review 7 studies including patients without psychotic symptoms at baseline: - 3 Low ROB studies - 3 Medium ROB studies - 1 High ROB study	History of cannabis use was associated with an increase in risk of developing psychotic symptoms.	Low	Consistent evidence from large observational studies and some evidence of increased risk with higher levels of use; consistent with data from small experimental studies suggesting risk of acute psychosis in some patients; magnitude of risk unclear and not specifically studied in chronic pain or PTSD populations
Ø Cognitive effects	1 systematic review of 33 studies	Active long-term cannabis use associated with small negative effects on all aspects of cognition. Mixed, inconsistent findings on long-term effects in past users.	Moderate Insufficient (past use)	Consistent data from large number of studies on effects on active long-term use, but inconsistent findings from smaller number of studies regarding effects in those that were abstinent and no data available specifically in chronic pain or PTSD populations

	N studies (N combined participants)	Findings	Strength of Evidence[a]	Comments
ØCUD	One large cohort study (N=34,653; N = 1279 past year cannabis use in last year)	OR incident CUD 9.5 (95% CI 6.4-14.1) Prevalence CUD (among those using in last year) 36% Prevalence past year cannabis dependence 7.7% Prevalence past year cannabis abuse 28%	Low	In cross-sectional studies, the prevalence of CUD in chronic pain populations was about 2%

Abbreviations: AE = adverse event; CBD = cannabidiol; CI = confidence interval; CUD = cannabis use disorder; MS = multiple sclerosis; N = number; OR = odds ratio; PTSD = post-traumatic stress disorder; ROB = risk of bias; THC = tetrahydrocannabinol; VA = Department of Veterans Affairs.

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

- 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.

APPLICABILITY

Efficacy trials often examined the use of precisely prepared THC:CBD preparations in capsular or spray form. Cannabis forms available in medical or recreational dispensaries vary widely: the content of preparations may not be known, may vary significantly from what is studied, and the actual contents may differ from what is labeled on the product. There is virtually no information to guide discussions of benefits and harms in older populations or populations with multiple comorbidities. The best observational studies we found typically included younger, healthier populations. We found relatively little information about mental health harms specifically in chronic pain or PTSD populations, but information about harms such as cognitive impairment obtained from other populations may still provide useful information for counseling patients for the time being.

RESEARCH GAPS/FUTURE RESEARCH

There is no conclusive information about the benefits of cannabis in chronic pain or PTSD populations and limited information about its harms, so methodologically strong research in almost any area of inquiry is likely to add to the strength of evidence. It appears that the United States (US) government is poised to lift restrictions on access to cannabis for research, which may speed the development of this evidence base that has lagged far behind policy changes regarding the use of cannabis for medical purposes in many states.

CONCLUSIONS

Although cannabis is increasingly available for medical and recreational use, there is very little methodologically rigorous evidence examining its effects in patients with chronic pain or PTSD. There is limited evidence suggesting that cannabis may improve pain and spasticity in patients with MS, but no consistent, high-quality data showing benefit from cannabis for the treatment of pain in other populations. Cannabis use is associated with an increased risk of short-term adverse effects, but data on its effects on long-term physical health vary. Cannabis use is associated with cognitive impairment in active users and potentially serious mental health adverse effects such as psychotic symptoms, though the absolute risk and application specifically to chronic pain and PTSD populations are uncertain.

Abbreviations Table

Abbreviation	Term
AHRQ	Agency for Healthcare Research and Quality
CBD	Cannabidiol
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CUD	Cannabis use disorder
DoD	Department of Defense
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDSP	Early Developmental Stages of Psychopathology
FEV1	Forced expiratory volume
FVC	Forced vital capacity
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IOM	Institute of Medicine
MS	Multiple sclerosis
N	Number
NRS	Numeric rating score
OR	Odds ratio
PICOTS	Patient population, intervention, comparator, outcome, timing parameters, and study designs
PTSD	Post-traumatic Stress Disorder
QOL	Quality of life
RCT	Randomized controlled trial
ROB	Risk of bias
T	Time point
THC	Tetrahydrocannabinol
UK	United Kingdom
US	United States
VA	Department of Veterans Affairs
VAS	Visual Analogue Scale