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U.S. Department of Veterans Affairs

**Veterans Health Administration**
Washington DC 20420

June 9, 2017

FOIA Request No.: 17-08991-F

John Greenewald, Jr.
The Black Vault
27305 W. Live Oak Road
Suite 1203
Castaic, CA 91384

Dear Mr. Greenewald:

This letter is the initial agency decision on your June 1, 2017, request under the Freedom of Information Act (FOIA), 5 U.S.C. § 552, requesting a copy of records, electronic or otherwise, of the following: Health Science Research & Development Evidence Brief: Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review dated November 2016.

Your FOIA request was received in the Department of Veterans Affairs (VA), Veterans Health Administration (VHA) Central Office FOIA office on June 1, 2017.

A search for VHA Central Office records, located in Washington, D.C., responsive to your request was conducted within the Office of Research and Development office. The Office of Research and Development provided a PDF document totaling 125 pages, as responsive to your request. This information is provided to you in its entirety therefore, no information has been redacted or otherwise withheld.

Thank you for your interest in VA. If you have any further questions, please feel free to contact me at (319) 530-7694.

Sincerely,

Amber Smith
VHA FOIA Officer

Enclosure

Department of Veterans Affairs
Health Services Research & Development Service

Evidence-based Synthesis Program

QUERI

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

November 2016

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

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**NOTE: This publication is for internal use of the Department of Veterans Affairs and should not be distributed outside the agency.**

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# PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for 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; 2016.

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.

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# 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. Clinical heterogeneity and the small number of trials precluded the possibility of combining the findings in a meta-analysis.

# 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?

Overall, there is limited evidence examining the effects of cannabis on chronic pain. There are relatively few methodologically sound trials, and most trials had small sample sizes. There is 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 pain, spasticity, and sleep in populations with multiple sclerosis (MS). However, the results are inconsistent across studies, the long-term benefits and harms are unclear given the brief follow-up duration of most studies, and there is insufficient evidence of the effects on quality of life or functional status. The applicability 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. There is insufficient evidence to determine the effects of cannabis in populations other than MS.

### 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)*

We found no studies assessing the risk of CUD among people using cannabis, and 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. There is low-strength evidence that cannabis (mostly in the form of cannabis preparations with precisely defined THC:CBD concentrations) may improve pain, spasticity, and sleep in populations with MS. Given the paucity of high-quality trials and the poor applicability of studies to current general medical practice, the evidence is insufficient to determine effects in other chronic pain populations. There is insufficient evidence to determine effects on quality of life or mental health outcomes in any chronic pain population. 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 | Findings | Strength of Evidence[a] | Comments |
|---|---|---|---|---|
| ***Chronic Pain*** | | | | |
| · Multiple sclerosis (MS) | 4 Low ROB studies (combined N=1017; 24 to 424 per study):<br>- 2 of THC/CBD capsules<br>- 1 of nabiximols<br>- 1 of sublingual spray delivering THC, CBD, or THC/CBD combined<br><br>3 Unclear ROB studies of nabiximols (combined N=562; 36 to 337 per study)<br><br>7 High ROB studies (combined N=430; 13 to 160 per study):<br>- 3 of nabiximols<br>- 2 of THC/CBD capsules<br>- 1 of smoked THC<br>- 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.<br>A 12-week study of nabiximols (2.7 mg THC/2.5 mg CBD oromucosal spray) reported significant improvement in spasticity.<br>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):<br>- 2 of THC/CBD capsules<br>- 1 of nabiximols<br>- 1 of sublingual spray delivering THC, CBD, or THC/CBD combined | **Other outcomes:**<br>**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.<br>**Other:**<br>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)<br><br>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<br><br>Only one study of nabiximols – not tested otherwise |

| | N studies | Findings | Strength of Evidence[a] | Comments |
|---|---|---|---|---|
| · Neuropathic pain | 2 Low ROB studies (combined N=62):<br>- 1 of vaporized cannabis (N=39)<br>- 1 of smoked THC (N=23)<br><br>4 Unclear ROB studies of nabiximols (combined N=681; 30 to 339 per study)<br><br>12 High ROB studies (combined N=1304; 16 to 380 per study):<br>- 9 of nabiximols<br>- 3 of smoked cannabis | **Small, inconsistent improvements in pain:** A study in which 25 mg of cannabis containing 9.4% THC was delivered by a single smoked inhalation 3 times daily reported significant improvements in average daily pain intensity. Another study reported short-term pain relief with inhaled cannabis at doses of 3.53% and 1.29% THC administered using a vaporizer. Peak pain relief appeared to occur after the second dosing at 180 minutes, then dropped off 1 to 2 hours later. | Insufficient | Few patients enrolled in the low ROB studies; statistically significant results but likely below clinical significance thresholds; marked differences among studies in dosing and delivery mechanism |
| | 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:<br>- 1 trial of sublingual spray delivering THC, CBD, or THC/CBD combined (N=34)<br>- 1 observational study of cannabis containing 12.5% THC (smoked, oral, or vaporized) (N=431)<br><br>3 Unclear ROB studies of nabiximols (combined N=428; 10 to 360 per study)<br><br>3 High ROB studies (combined N=265; 18 to 177 per study):<br>- 2 of nabiximols<br>- 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:<br>- 1 Medium ROB (N=2276)<br>- 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 |
| ***Harms***<br>· 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 |

| | N studies | Findings | Strength of Evidence[a] | Comments |
|---|---|---|---|---|
| · Medical harms | | | | |
| Ø Pulmonary function | 2 Low ROB prospective cohort studies with 20-32 years follow-up (combined N=6053)<br><br>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.<br>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<br>*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:<br>- 1 case-crossover (N=3882)<br>- 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.<br>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)<br><br>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 |
| 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 |

| | N studies | Findings | Strength of Evidence[a] | Comments |
|---|---|---|---|---|
| · Mental health<br>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<br><br>7 studies including patients without psychotic symptoms at baseline:<br>- 3 Low ROB studies<br>- 3 Medium ROB studies<br>- 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.<br>Mixed, inconsistent findings on long-term effects in past users. | Moderate<br><br>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 |
| Ø CUD | No studies examining risk of CUD over time, or rates in cannabis-using populations | --- | No evidence | In cross-sectional studies, the prevalence of CUD in chronic pain populations was about 2%, though the rate among a group of cannabis-using patients is unclear |

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 |

# EVIDENCE REPORT

## INTRODUCTION

Cannabis use has become more common among United States (US) adults, with the prevalence of adults reporting past-year cannabis use nearly doubling between 2001 and 2013 to one in 10 adults.[1] Young adults ages 18-29 are nearly 4 times more likely to have used cannabis in the past year than adults ages 45-64.

The use of cannabis for medicinal purposes has also become increasingly accepted. In California, which was the first state to legalize cannabis for medical purposes in 1996, about 5% of all adults reported having used cannabis for medical purposes in 2012.[2] In a recent poll, 76% of physicians supported the use of cannabis for medical purposes in certain circumstances.[3]

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. Both houses of Congress recently passed H.R. 2577, which would allow federally-employed physicians working for the Veterans Health Administration to recommend cannabis for medical purposes to Veterans if appropriate in states that have legalized its use.[4]

The conditions that would qualify a patient to use cannabis for medical purposes differ across states, but nearly all include chronic pain itself or diseases which are likely to cause chronic pain (such as multiple sclerosis [MS]-related spasticity). Several states also list post-traumatic stress disorder (PTSD) as a qualifying condition, which is of particular importance to Veterans and, indeed, was one of the rationales cited for the genesis of H.R. 2577.

Approximately 30% of Americans currently experience chronic pain,[5] a figure that is estimated to increase as the population ages and manages more chronic medical conditions.[6] Recent studies suggest that 45-80% of individuals who seek cannabis for medical purposes do so for pain management[7,8] and among patients who are prescribed long-term opioid therapy for pain, an estimated 6%-39% are also utilizing cannabis.[9,10]

Recent research suggests that over one-third of patients seeking cannabis for medical purposes in states where it is legal list PTSD as the primary reason for the request.[11] Approximately 15% of Veterans who are treated in Department of Veterans Affairs (VA) outpatient PTSD clinics report recent (past 6 months) cannabis use.[12]

In the past, use had been limited to inhalation or ingestion of parts of the whole plant of the genus Cannabis. More recently, many more formulations of cannabis have become available in recreational and medical cannabis dispensaries including an array of edibles, oils, tinctures, as well as plant extracts with varying ratios of the 2 active ingredients of cannabis: tetrahydrocannabinol (THC) and cannabidiol (CBD). There are also 2 purely synthetic cannabinoids available in the US by prescription only (dronabinol and nabilone).

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 with their patients about the potential benefits and harms of cannabis use. 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

## TOPIC DEVELOPMENT

The research questions for this systematic review 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 proposed Key Questions are as follows:

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

> **Key Question 1A:** Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?

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

> **Key Question 2A:** Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?

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

> **Key Question 3A:** Do the harms differ by patient subgroup, such as patient medical and mental health comorbidities?

**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?

A protocol describing the review plan was posted to a publicly accessible website before the study was initiated.[13]

## SEARCH STRATEGY

Search strategies were developed in consultation with a research librarian. To identify relevant articles, we searched MEDLINE, PubMed, EMBASE, PsycINFO, PILOTS Database, EMB Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*), and grey literature sources from database inception through February 2016 (Appendix A). We reviewed the bibliographies of relevant articles and contacted experts to identify additional studies.

To identify in-progress or unpublished studies for Key Question 4, we searched ClinicalTrials.gov, International Clinical Trials Registry Platform (WHO ICTRP), ISRCTN Registry, NIH Reporter, AHRQ Gold, and the American Cancer Society Database of Studies. We also queried the Technical Expert Panel and used snowball sampling techniques to identify relevant ongoing research.

## STUDY SELECTION

The criteria for patient population, intervention, comparator, outcome, timing parameters, and study designs (PICOTS) that apply to each key question are specified in Table 1. We included English-language studies of plant-based cannabis preparations or whole plant extracts such as nabiximols, which is a non-synthetic pharmaceutical product with a standard composition and dose (oromucosal spray delivering 2.7 mg THC/2.5 mg CBD) available only in select European countries. 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.[14-16] However, we broadly defined plant-based cannabis preparations to include any preparation of the cannabis plant itself (*eg*, cannabis cigarettes, hashish, oils), or cannabis plant extracts. We chose to be broadly inclusive of herbal preparations because US dispensaries offer a wide variety of concentrations and products, and clinicians may encounter patients who have used a variety of preparations.[17]

To address the efficacy of cannabis in treating chronic pain or PTSD (Key Questions 1 and 2), we examined controlled clinical trials or rigorously designed observational studies with control groups that adjusted for important confounders. Appendix B provides the study selection criteria in detail.

Our study selection criteria to examine harms (Key Question 3) depended on the outcome of interest. In initial discussions within our research group and in consultation with our technical expert panel, we categorized a prespecified list of harms of interest according to whether the likelihood of the 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. 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. We felt that the incidence of adverse cognitive effects and psychotic symptoms in the general population was likely to provide information that was relevant to chronic pain and PTSD populations, though we recognized that, theoretically, chronic pain and PTSD populations might have a different risk. We chose, therefore, to look more broadly at these outcomes but to report population-specific data where available. In an effort to provide clinicians with at least descriptive information about important harms likely to be related to cannabis use whose incidence and relative risk has not been well-characterized, we also included case series and descriptive studies of these “emerging harms,” such as cannabis hyperemesis syndrome and infectious diseases associated with various preparations.

We conducted a primary literature search, but given the broad scope of this review, we summarized data from existing 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. We only included reviews that fulfilled key quality criteria: 1) clearly reported their search strategy; 2) reported inclusion and exclusion criteria; and 3) conducted an appraisal of the internal validity of the included trials.[18] If there was more than one review within each category fulfilling these criteria, we prioritized the most recent review and, if there were several recent reviews meeting quality criteria, we prioritized those with the broadest scope. We discussed the ultimate choice of which reviews to include as a group and resolved any disagreements through consensus.

**Table 1. PICOTS and Key Questions**

<table>
<tr><td>Key Question (KQ)</td><td>KQ 1. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have chronic pain?<br>KQ 1A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</td><td>KQ 2. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have PTSD?<br>KQ 2A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</td><td>KQ 3. What are the harms associated with cannabis use in adults?<br>KQ 3A: Do the harms differ by patient subgroup, such as patient medical and mental health comorbidities?</td><td>KQ 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?</td></tr>
<tr><td>Population</td><td>Adults with chronic pain</td><td>Adults with PTSD</td><td>Adults (not otherwise specified)</td><td>Adults with chronic pain or PTSD</td></tr>
<tr><td>Intervention</td><td colspan="4">Cannabis preparations, including marijuana, hashish, tincture, hashish oil, infusion, and plant extract.<br>Exclude: Synthesized, pharmaceutically prepared cannabinoids (eg, dronabinol, nabilone).</td></tr>
<tr><td>Comparator</td><td colspan="4">Any comparator</td></tr>
<tr><td>Outcomes</td><td>§ Validated measures of pain intensity and pain-related function (including spasticity)<br>§ Validated measures of pain-related outcomes (mood, depression, anxiety)<br>§ Validated measures of sleep quality<br>§ Validated measures of quality of life<br>§ Utilization of health services<br>§ Reduction in opioid use or dosage<br>§ Social functioning/disability/ employment</td><td>§ Validated PTSD clinical interviews and symptom inventories, such as: Clinician Administered PTSD Scale (CAPS), PSTD Checklist (PCL), PTSD Symptom Scale (PSS), Posttraumatic Diagnostic Scale (PDS), etc<br>§ Validated measures of mental health symptoms commonly associated with PTSD (mood, depression, anxiety)<br>§ Validated measures of sleep quality<br>§ Validated measures of quality of life<br>§ Utilization of health services<br>§ Reduction in benzodiazepine use or dosage<br>§ Social functioning/disability/ employment</td><td><table><tr><td></td><td>Control group required</td><td>No control group required (case series accepted)</td></tr><tr><td>General Population</td><td>§ Psychotic symptoms (in previously non-psychotic population)<br>§ Cardiovascular events<br>§ Pulmonary outcomes (eg, forced expiratory volume [FEV1])<br>§ Infectious disease complications<br>§ Mortality<br>§ Cognitive effects (eg, intelligence quotient [IQ], SLUMS Saint Louis University Mental Status [SLUMS])</td><td>§ Fungal infections<br>§ Cannabinoid hyperemesis syndrome<br>§ Other emerging harms</td></tr><tr><td>Chronic</td><td>§ Other substance</td><td>§ CUD</td></tr></table></td><td>Not applicable</td></tr>
</table>

<table>
<tr><td>Key Question (KQ)</td><td>KQ 1. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have chronic pain?<br>KQ 1A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</td><td>KQ 2. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have PTSD?<br>KQ 2A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</td><td>KQ 3. What are the harms associated with cannabis use in adults?<br>KQ 3A: Do the harms differ by patient subgroup, such as patient medical and mental health comorbidities?</td><td>KQ 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?</td></tr>
<tr><td></td><td></td><td></td><td><table><tr><td>Pain or PTSD patients</td><td>use/substance use disorder<br>§ Mental health symptoms (not including psychotic symptoms) including depression, anxiety, etc<br>§ Employment<br>§ Weight gain<br>§ Diversion<br>§ Utilization of health services<br>§ Insomnia</td><td>§ Withdrawal symptoms</td></tr></table><br><u>Exclude:</u> Imaging findings, lab/blood test results.</td><td></td></tr>
<tr><td>Timing</td><td colspan="4">Short- and long-term outcomes</td></tr>
<tr><td>Study design</td><td colspan="2">Systematic reviews, meta-analyses, controlled clinical trials (randomized or non-randomized), and methodologically rigorous observational studies with a comparison group (case-control/cohort studies) that adjust for important confounders.<br><u>Exclude:</u> Non-systematic or narrative reviews, opinions, case studies, case series, and cross-sectional studies.</td><td>Study designs included for KQ1 and KQ2, plus case series for certain harms (see Outcomes box).<br><u>Exclude:</u> Non-systematic or narrative reviews, opinions, cross-sectional studies, and individual case reports.</td><td>Not applicable</td></tr>
</table>

One of 9 investigators examined titles and abstracts for potential relevance to the key questions using Abstrackr.[19] We dual-reviewed a random 5% sample of abstracts in order to ensure reliability between reviewers. Two investigators independently reviewed the full text of all potentially relevant articles for inclusion. Disagreements were resolved through consensus using a third reviewer.

## DATA ABSTRACTION

Data from published reports were abstracted into a customized database by one reviewer and confirmed by a second reviewer. 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.

## QUALITY ASSESSMENT

Two reviewers independently assessed the quality of each study (Appendix C). Disagreements were resolved through discussion. To assess the quality of trials we used a tool developed by the Cochrane Collaboration.[20] Each trial was given an overall summary assessment of low, high, or unclear risk of bias. To assess the risk of bias of observational studies we considered potential sources of bias most relevant to this evidence base and adapted existing assessment tools.[21,22] While there are no validated criteria for ranking observational studies, we chose to assign a summary risk of bias rating to represent confidence in each study's results as follows:

- High risk of bias: studies with one or more methodologic deficiencies which would be considered "fatal flaws"; in other words, an answer of "no" to the question: "Are study results believable, taking study limitations into consideration?" For example, studies with minimal information about the exposure of interest would be considered as having a high risk of bias.
- Medium risk of bias: studies that had important methodologic deficiencies that were not fatal flaws, but should be considered when weighing the strength of evidence. For example, recall bias is an inherent limitation to case-control studies that is important to consider in this evidence base.
- Low risk of bias: studies that had no or minor methodologic deficiencies and reflect the strongest observational study designs.

## DATA SYNTHESIS

We qualitatively synthesized the evidence on the benefits and harms of cannabis. Clinical heterogeneity and the small number of trials precluded the possibility of combining the findings in meta-analysis.

## RATING THE BODY OF EVIDENCE

We assessed the overall strength of evidence for outcomes using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPCs).[23] The AHRQ EPC method considers study limitations, directness, consistency, precision, and reporting bias to classify the strength of evidence for individual outcomes independently for randomized controlled trials (RCTs) and observational studies, with supplemental domains of dose-response association, plausible confounding that would decrease the observed effect, and strength of association, as well as separate guidance for applicability.[24] Ratings were based on the following criteria:

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

## PEER REVIEW

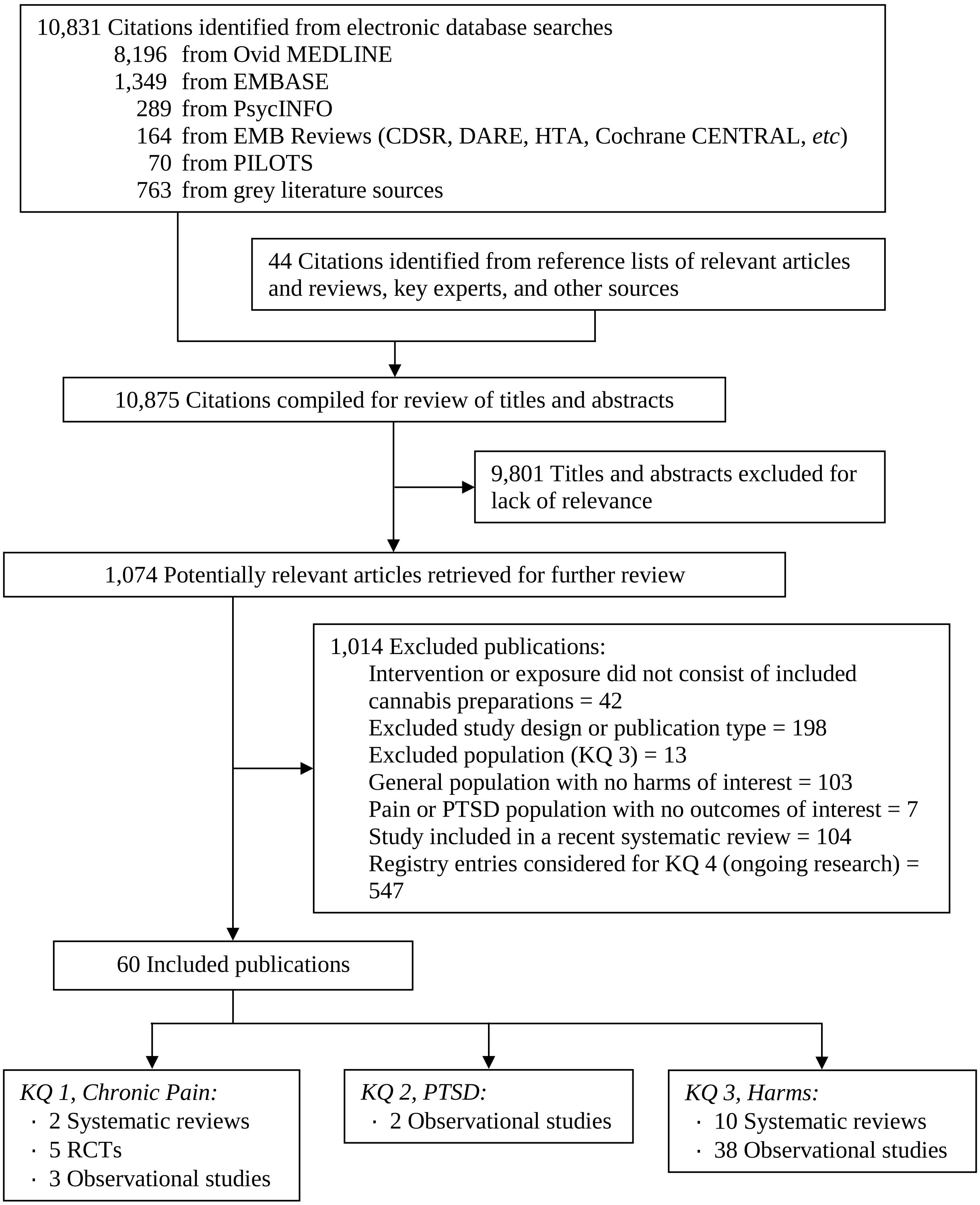
A draft version of this report was reviewed by 8 individuals with technical expertise and clinical leadership. Their comments and our responses are presented in Appendix D.

# RESULTS

## LITERATURE FLOW

We included 12 systematic reviews and 48 primary studies after reviewing 10,875 titles and abstracts (Figure 1).

**Figure 1. Literature Flow Diagram**



# KEY QUESTION 1: What are the effects of cannabis on health outcomes and healthcare utilization for adults who have chronic pain?

## KEY QUESTION 1A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?

### Summary of Findings

Overall, there is limited evidence examining the effects of cannabis on chronic pain. There are relatively few methodologically sound trials, and most trials had small sample sizes. There is low-strength evidence that cannabis-based treatments with precisely defined THC:CBD content (most in a 1:1 to 2:1 ratio) have the potential to improve pain, spasticity, and sleep in select populations with MS. However, the results are inconsistent across studies, the long-term benefits and harms are unclear given the brief follow-up duration of most studies, and there is insufficient evidence of the effects on quality of life or functional status. Moreover, the applicability 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. There is insufficient evidence to determine the effects of cannabis in populations other than MS.

Two recent systematic reviews examined the efficacy of cannabis and cannabinoids for the treatment of chronic pain,[14,15] and reported mixed findings for the management of various chronic pain symptoms related to conditions such as MS, fibromyalgia, peripheral and central neuropathy, human immunodeficiency virus (HIV), rheumatoid arthritis, and cancer. Specifically, across a subset of 8 trials (N=1370) that evaluated non-synthetic cannabinoids (THC or nabiximols), cannabis treatments were associated with a non-significant trend toward benefit (proportion showing greater than 30% reduction in pain: 37% versus 31%; odds ratio [OR] 1.41; 95% confidence interval [CI], 0.99 to 2.00]) compared to placebo and no difference in quality of life among groups.[14] While the authors concluded that there is low- to moderate-strength evidence supporting efficacy of cannabis in chronic pain (limited mainly to MS or neuropathic pain), a separate group reviewed and re-analyzed a similar set of published articles, and determined that there is insufficient to low-strength evidence examining the use of medical cannabis to treat chronic non-cancer pain.[15] Our own interpretation of the evidence is consistent with the latter review because the vast majority of the trials cited in support of a moderate-strength evidence rating were methodologically flawed. Both reviews found insufficient evidence examining the use of medical cannabis for pain related to other conditions such as cancer, rheumatoid arthritis, and musculoskeletal pain.

While the prior reviews included the pharmaceutical, synthetic prescription medications dronabinol and nabilone, studies of these drugs did not contribute substantially to the body of evidence for chronic pain. There was only one small study with high risk of bias examining the effects of nabilone in chronic pain.

We also searched the primary literature and found an additional 8 studies[25-32] that met our inclusion criteria and were not included in the prior reviews. Those additional studies included patients with pain related to MS (4 studies) and mixed pain-related conditions (4 studies), but we found no additional studies of neuropathy (Table 2).

No studies directly compared effects according to patient comorbidity. Rather, we describe detailed findings according to patient subgroup below.

**Table 2. Studies of the Effects of Cannabis in Patients with Chronic Pain**

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age (SD) % male | Intervention and comparator | Primary findings | Adverse effects |
|---|---|---|---|---|
| ***Multiple sclerosis (MS)*** | | | | |
| Notcutt 2012[27]<br>UK, 5 sites<br>RCT (N=36)<br>Unclear ROB | Age 57<br>100% Caucasian<br>41.7% male<br>MS: 16.4 years<br>Spasticity: 12.7 years<br>Nabiximols use: 3.6 years; Subjects experienced ongoing benefit with nabiximols.<br>Mean daily dose of nabiximols: 8.25 sprays<br>Mean baseline scores, Treatment vs placebo:<br>Spasticity score on NRS: 3.6 (SD=1.7) vs 4.13 (SD=2.2),<br>Disability scale (EDSS): 6.75 vs 6.92 | T: Nabiximols (oromucosal spray delivering 2.7 mg THC/2.5 mg CBD), mean daily dose 7.7 sprays.<br>C: Placebo, mean daily dose 9.0 sprays | 4-week treatment period<br>**Pain: NR**<br>**Spasticity:** no differences (*P*>.1) between groups on NRS score. Treatment failure, defined as cessation of nabiximols use, worsening of spasticity, or increase in anti-spasticity meds: 44% of nabiximols group vs 94% of placebo group (hazard ratio for failure in placebo group 0.335, 90% CI: 0.162-0.691, *P*=.013 in favor of nabiximols group).<br>**Other:** No differences in sleep disruption NRS score, Modified Ashworth Scale, Timed 10-meter walk test, or Motricity Index, CGIC ease of transfer; statistically significant improvement in nabiximols vs placebo group on SGIC (OR 4.55, 90% CI: 1.59-14.00, *P*=.017) and CGIC general function scores (OR 18.55, 90% CI: 3.94-118.77, *P*=.001). | During treatment period, 83% (15/18) on nabiximols and 78% (14/18) on placebo had treatment-related AEs, most commonly pain (2 vs 5), spasticity (2 vs 3), muscle spasm (4 vs 4), and depressed mood (0 vs 2); 4 participants had severe AEs (2 vs 2). |

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age (SD) % male | Intervention and comparator | Primary findings | Adverse effects |
|---|---|---|---|---|
| Novotna 2011[25]<br>Europe, 51 sites<br>RCT (N=241)<br>Low ROB | Age 48.6<br>40% male<br>100% white/Caucasian,<br>18% with previous cannabis use in last year,<br>MS years: 12.6<br>Spasticity years: 7.7<br>Mean baseline spasticity score on NRS 7.0 To qualify for the RCT, patients must have had at least a 20% reduction in spasticity NRS score with initial exposure to nabiximols. | T **=** Nabiximols (oromucosal spray delivering 2.7 mg THC/2.5 mg CBD).<br>C **=** Placebo oromucosal spray.<br>Maximum permitted dose was 12 sprays in any 24 hour period. | **Pain: NR**<br>**Spasticity:** Change in mean NRS score at 12 weeks: -0.84 (95% CI, -1.29 to -0.40), *P*=.0002<br>% with at least 30% improvement, T vs C: 74% vs 51%; OR 2.73 (95% CI, 1.59-4.69), *P*=.0003.<br>**Other:** Nabiximols were significantly superior (*P*<.05) to placebo for sleep disruption, Barthel Activities of Daily Living, Physician Global Impression of Change, Subject Global Impression of Change, and Carer Global Impression of Change in Function. | No difference between groups; no AEs occurred in > 10% in either group. Most common AEs were vertigo, fatigue, muscle spasms, and urinary tract infections. |
| Ungerleider 1987[26]<br>US, single site<br>Double-blind, placebo-controlled, crossover clinical trial<br>(N=13)<br>High ROB | Age 48.3<br>39% male<br>53% wheelchair bound<br>60% with prior cannabis use | T (THC) or C (placebo) for 5 days, followed by 2 day wash-out and 5 day trial with crossover drug.<br>Patients were initiated at varying oral doses of THC (range: 2.5 to 7.5 mg in first paired trial).<br>If patient had inadequate relief, they could be re-randomized and started at a higher dose (increased by 2.5 mg to maximum 15 mg). | **Pain: NR**<br>**Spasticity:** self-report on scale of 1 to 5, where 5=more) was lower with T: 2.2 (SD=0.9) vs C: 3.4 (SD=0.7), *P*=.03; improvement started at 7.5 mg dose.<br>No change from baseline on physician ratings on all measures (limb weakness, limb spasticity, limb coordination, gait impairment, reflexes; all *P*-values > 0.05). | No difference in AEs for 7.5 mg THC vs C.<br>AEs were more frequent and less tolerable with higher doses of THC.<br>Common AEs: weakness, dry mouth, dizziness, relaxation, mental clouding, short term memory impairment, and spatial-time distortions. |

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age (SD) % male | Intervention and comparator | Primary findings | Adverse effects |
|---|---|---|---|---|
| Wade 2003[28]<br>UK, single site outpatient clinic<br>Pilot study: double-blind, placebo-controlled single-patient cross-over RCT (N=24)<br>Low ROB | Age 48<br>50% male<br>Types of pain:<br>MS (n=14)<br>Spinal cord injury (n=4)<br>Brachial plexus damage (n=1)<br>Limb amputation due to neurofibromatosis (n=1)<br>Target symptoms:<br>pain (n=13), muscle spasm (n=17), spasticity (n=9), impaired bladder control (n=11), tremor (n=8) | Pump-action sublingual spray delivering 2.5 mg<br>T1: CBD<br>T2: THC<br>T3: Both THC and CBD, 1:1 ratio<br>C: Placebo<br>Maximum permitted dose was 120 mg every 24 hours. | Mean (SD) daily VAS (0-100) over last 7 days of each 2-week period, *P*-value vs C:<br>**Pain:** baseline 30.1 (17.8) to<br>T1: 54.8 (22.6), *P*<.05<br>T2: 54.6 (27.4), *P*<.05<br>T3: 51.3 (27.0), *P*=NS<br>C: 44.5 (22.7)<br>**Spasm**: baseline 40.9 (18.5) to<br>T1: 54.6 (19.1), *P*=NS<br>T2: 58.4 (22.3), *P*<.05<br>T3: 55.8 (24.4), *P*<.05<br>C: 47.3 (22.6)<br>**Spasticity:** baseline 29.0 (16.1) to<br>T1: 47.8 (18.5), *P*=NS<br>T2: 57.3 (22.2), *P*<.05<br>T3: 43.8 (15.6), *P*=NS<br>C: 42.3 (18.1) | AEs reported by 33% in CBD, 55% in THC, 30% in CBD:THC, and 48% in placebo;<br>Common AEs during periods of cannabinoid use included headache (n=5), nausea (n=3), diarrhea (n=4), sleepiness (n=3), fall (n=3); 3 patients withdrew during open-label phase due to one each of intoxication, vasovagal episodes, and sublingual burning sensation; one patient withdrew during the blinded phase due to excess sensitivity to THC; Some patients in all periods took rescue medications. |

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age (SD) % male | Intervention and comparator | Primary findings | Adverse effects |
|---|---|---|---|---|
| ***Other chronic pain*** | | | | |
| Fiz 2011[32]<br>Spain, single site<br>Retrospective cohort study (N=56)<br>High ROB | Adults with fibromyalgia, with moderate to severe symptoms, and who were resistant to pharmacological treatment.<br>Age 50 years<br>5% male (users 7%, non-users 4%)<br>Median disease duration: 5.0 years in users, 4.0 years in non-users | T: cannabis use, method of administration: smoking 11%; oral 46%; combined 43%.<br>C: non-users (for QOL comparison)<br>Duration of use:<br>40% < 1 year<br>32% 1 to 3 years<br>29% ≥ 3 years<br>THC/CBD content NR. | **Pain:**<br>2 hours post-cannabis use, VAS (100 mm) scores showed significant mean reduction in pain (37.1 mm reduction) and stiffness (40.7 mm reduction), *P*<.001.<br>**Other:**<br>Patients used cannabis for almost all symptoms associated with fibromyalgia with no reported worsening of symptoms (strong relief reported by 81% for sleep disorders to 14% for headaches).<br>68% of patients reported reduction in pharmacological treatment (not otherwise specified) when they started using cannabis.<br>Increased perception of well-being (40.0 mm increase); relaxation (27.6 mm increase), and somnolence scores (20.0 mm increase) were significantly<br>increased from baseline, *P*<.05;<br>QOL: (SF-36) mental health component summary score was significantly higher in users (mean=29.6, SD =8.2) compared to non-users (mean=24.9, SD=8.9), *P*<.05; No significant group differences found on SF-36 physical component (*P*=.53), PSQI (*P*=.73), FIQ (*P*=.36). | 96% of users reported at least one side effect, most commonly:<br>Somnolence (64%)<br>Dry mouth (61%)<br>Sedation (43%)<br>Dizziness (36%)<br>High (32%)<br>Tachycardia (29%)<br>Conjunctival irritation (25%)<br>Hypotension (21%)<br>No serious AEs reported. |

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age (SD) % male | Intervention and comparator | Primary findings | Adverse effects |
|---|---|---|---|---|
| Notcutt 2004[31]<br>Canada<br>Single site<br>"N of 1"double-blind, placebo-controlled, crossover RCT<br>(N=34)<br>Low ROB | Age 46.7<br>32% male<br>100% with chronic pain (mostly neuropathic)<br>47% with MS | Sublingual spray that delivered 2.5 mg each of:<br>T1: THC<br>T2: CBD<br>T3: both CBD and THC (1:1 ratio),<br>C: 0.1 mL matching placebo;<br>In order to qualify for the study, patients must report benefit during a run-in period; 8-week trial where each week for first 4 weeks they randomly received a different cannabinoid or placebo; at start of each week, patients underwent supervised titration and each preparation was then given in random order over next 4 weeks so that each patient received each cannabinoid or placebo for 2 separate one-week periods; patients administered sprays daily and titrated up to a dose of their choosing depending on onset of side effects and attenuation of pain (range 1 to 8 sprays daily) | **Pain:** VAS 10 cm<br>Symptom 1 score (median [IQR]) pain reduction:<br>T1: 4.63 (1.74-6.06)<br>T2: 5.45 (3.6-7.4)<br>T3: 4.4 (2.6-5.8)<br>C: 5.9 (2.8-7.3)<br>T1 and T3 both significantly better than C (*P*<.05, *P*<.01, respectively)<br>Symptom 2 score (median [IQR]) pain reduction:<br>C: 4.98 (2.61-7.50)<br>T1: 4.08 (1.33-5.43)<br>T2: 5.03 (3.16-6.88)<br>T3: 4.28 (2.33-5.51)<br>T1 and T3 significantly better than placebo (*P*=.054, *P*<.001, respectively)<br>38% (9/24) of patients had a decrease in VAS of 50% or more for either symptom 1 or symptom 2 when using active preparations vs placebo; all 9 patients experienced this with THC and/or THC:CBD and 3 of these<br>patients also had reduction with CBD.<br>**Other:**<br>Sleep Quality: Percentage of "good" nights during trial period, median (IQR):<br>T1: 42.9% (57.2-35.7)<br>T2: 36.9% (47.9-28.6)<br>T3: 55.4% (78-34.5)<br>C: 17.0% (35.7-3.6)<br>T1, T2, and T3 were each significantly better than placebo (*P*<.001, *P*<.001, *P*<.05, respectively). | Side effects: Most commonly drowsiness, euphoria/dysphoria, and dry mouth; hallucination in one patient; vasovagal in one patient; change in neural function in 2 patients (return of absent ankle reflex, return of touch sensation to dermatome) |

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age (SD) % male | Intervention and comparator | Primary findings | Adverse effects |
|---|---|---|---|---|
| Storr 2014[30]<br>Canada, outpatient GI clinic<br>Retrospective cohort study (N=313)<br>High ROB | Adults with IBD<br>Age 39.6 years (non-users 40.2, users 36.6 years)<br>31% male (27.4% non-users; 50.0% users)<br>Note: Significant between group differences in race, household income, and education level (*P*<.05)<br><br>Mean time since IBD diagnosis was 13.9 (range: 1 to 40) years in users, 13.2 (range: 1 to 43) years in nonusers; Among users vs non-users, 75.0% vs 71.9% had Crohn's Disease, 17.9% vs 20.2% had ulcerative colitis, 7.1% vs 8.0% had indeterminate colitis.<br><br>Note: Significant between-group difference in type of disease (*P*=.035) | Patients self-reported cannabis use; varied between smoking (95%), oral (9%) and drinking (5%); no info provided about dose or frequency<br>Comparator: non-users (*ie*, those who did not endorse cannabis use for treatment of IBD) | Risk of surgery for those with Crohn's Disease was significantly associated with cannabis use for at least 6 months vs never use (OR 5.03; 95% CI, 1.45-17.46) after controlling for multiple factors; Intermittent use was not associated with higher surgery rates vs never use (OR 1.28; 95% CI, 0.31-5.27).<br><br>Risk of hospitalization for IBD was not associated with cannabis use for at least 6 months (OR 2.86; 95% CI, 0.96-8.46) or intermittent (OR 1.99; 95% CI, 0.41-9.73) cannabis use vs never use | Most cannabis users experienced side effects like anxiety, increased appetite, dry mouth, drowsiness, and a "high" (75% of users); generally rated as mild in severity; 19.6% reported that they needed a "high" to get symptom improvement while remainder did not |

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age (SD) % male | Intervention and comparator | Primary findings | Adverse effects |
|---|---|---|---|---|
| Ware 2015[29]<br>Canada, 7 sites<br>Prospective cohort<br>(N=431)<br>Low ROB | Age: 49.0 (cannabis vs control: 45.5 vs 52.4)<br>43.1% male (cannabis vs control: 51.2% vs 35.2%)<br>Groups differed significantly for age and gender (*P*<.001)<br><br>Type of pain, cannabis vs control:<br>Nociceptive 16.3% vs 18.1%<br>Neuropathic 38.6% vs 32.4%<br>Both 45.1% vs 49.5%<br>Mean pain intensity 6.6 (range: 0 to 10) vs 6.1 | T: Cannabis contained 12.5 ± 1.5% THC; max of 5 g/day;<br>median daily dosing was 2.5 g/day<br>Patients used any delivery system that they were comfortable with (27% smoked, 61% combined smoking, oral, and vaporization, 8% consumed orally)<br>C: Non-cannabis users | **Pain:** greater reduction in pain intensity noted in cannabis users: VAS (0-10 pain intensity over last 24 hours, mean (SD):<br>T: 5.54 (2.11)<br>C: 6.10 (2.13)<br>Difference = 1.10 (95% CI, 0.72-1.56)<br>Significant reduction in average pain intensity over 1 year with T (change=0.92; 95% CI, 0.62-1.23) but not C (change=0.18; 95% CI, -0.13-0.49)<br><br>**Other:**<br>Mood: POMS (total mood disturbance): Cannabis = 23.92 (SD 19.04); Control = 27.09 (SD 21.29), fixed regression coefficient (-5.52, *P*=.0060; higher scores equal more mood disturbance)<br>QOL: SF-36. Improvement of physical function among cannabis users at 1 year (1.62 points higher; 95% CI, 0.10-3.14); No between or within group differences on mental component. | T vs C:<br>Serious AEs: no sig. difference, 13% vs 19%; 40 vs 56 events<br>Adjusted IRR (95% CI) for event = 1.08 (0.57-2.04)<br>Most common AEs:<br>surgical/medical procedures 25% vs 20%<br>GI disorders 25% vs 13%<br>Most common serious AEs in cannabis group:<br>-abdominal pain (n=3, 12%),<br>-intestinal obstruction (n=3, 12%)<br>-nephrolithiasis (n=3, 12%)<br>-2 withdrawals from treatment due to serious side effects (1 convulsion, 1 alcohol problem);<br>Cannabis users had significantly higher number/rate of non-serious AEs (T vs C: 818 vs 574 events), adjusted IRR for event = 1.73; 95% CI, 1.42-2.14);<br>Most common AEs, cannabis group:<br>-nervous system: n=165 (20%)<br>-gastrointestinal: n=109 (13.4%)<br>-respiratory: n=103 (12.6%);<br>Cannabis group had significantly higher rates, unadjusted IRR (95% CI): nervous system disorders 2.05 (1.46-2.86); respiratory disorders 1.77 (1.16-2.70); infections disorder 1.51 (1.04-2.20); and psychiatric disorders 2.74 (1.45-5.18) vs control group. No significant between group differences were found in pulmonary or neurocognitive function. |

Abbreviations: AE = adverse event; C = control/comparator group; CBD = cannabidiol; CGIC = Carer Global Impression of Change; CI = confidence interval; EDSS = Expanded

Disability Status Scale; FIQ = Fibromyalgia Impact Questionnaire; GI = gastrointestinal; IBD = inflammatory bowel disease; IQR = interquartile range; IRR = incidence rate ratios; MS = multiple sclerosis; N = number; NR = not reported; NRS = Numeric Rating Scale; NS = not significant; OR = odds ratio; POMS = Profile of Mood States; PSQI = Pittsburgh Sleep Quality Index; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation; SF-36 = 36-Item Short Form Health Survey; SGIC = Subject Global Impression of Change ; T = treatment group; THC = tetrahydrocannabinol; UK = United Kingdom; US = United States; VAS = Visual Analogue Scale.

Footnotes on concomitant therapy:

- Fiz 2011: Participants continued their current pharmacologic regimen; at baseline (users vs non-users), analgesic/anti-inflammatory drugs used by 75% vs 64%, antidepressants used by 50% vs 61%, anxiolytics used by 36% vs 36%, opioids used by 21 vs 39%, myorelaxants used by 4% vs 21%, hypnotics used by 18% vs 29%.
- Notcutt 2004: Patients maintained their regular medications and were allowed to use non-cannabinoid medication for breakthrough pain as long as they documented it (n=7 patients used rescue THC:CBD during trial).
- Notcutt 2012: Participants maintained other medications at stable doses: 16% taking baclofen; 16% taking benzodiazepines; 16% taking analgesics and antipyretics; 12% taking quinine or derivatives; 3% taking antiepileptics; 3% taking amantadine; 3% taking herbal supplements.
- Novotna 2011: Antispasticity agents and/or disease-modifying medications were maintained at a stable dose for 30 days prior to and throughout the study. 13% taking adamantane derivatives, 22% taking benzodiazepine derivatives, < 0.5% taking dantrolenes, < 0.5% taking naltrexone, 24% taking antiepileptics, 73% taking centrally-acting medications, 58% taking baclofen, 17% taking tizanidine, 17% taking tolperisone, 1% taking “other” medications.
- Storr 2014: Patients continued all other prescribed medications; 35.7% taking aminosalicylates, 42.6% taking steroids, 41.4% taking immunomodulators, 37.9% taking analgesics, 24.8% taking narcotics, 17.2% taking loperamide, 32.0% taking biologicals, 9.7% taking IV medications, 32.0% taking complimentary and alternative medicine.
- Wade 2003: Patients continued current medication regimen and were asked not to use any other cannabis.
- Ware 2015: Patients continued pharmacotherapy (opioids, antidepressants, and anticonvulsants).

## Detailed Findings According to Patient Subgroup

### *Multiple Sclerosis (MS)*

Two prior systematic reviews and 4 additional published trials examined the effects of cannabis-based preparations on pain and spasticity in patients with MS. Overall, there is low-strength evidence to support cannabis-based treatments for the potential to improve pain, spasticity, and sleep in select populations with MS, but results were inconsistent across studies. The body of evidence is limited by the paucity of methodologically rigorous studies, inconsistent findings across studies, the lack of long-term outcomes, and the small number of patients included in many trials. Moreover, the largest low risk of bias trial used restrictive entry criteria which may reduce the applicability of the evidence to broader populations.

A recent systematic review included 11 (2,653 participants) trials examining the use of cannabis preparations compared with placebo (it also included studies of synthetically produced cannabinoids which are not covered in our review).[14] The authors of this review found low- to moderate-strength evidence mostly from trials of nabiximols on spasticity in MS. However, the findings were mixed with evidence of no effect on some spasticity related outcomes and small effects on others. Moreover, 9 of 11 trials had high or unclear risk of bias; only 2 of the trials were found to be at low risk of bias.

One RCT analyzed data from 414 patients from 33 outpatient neurology and rehabilitation centers in the United Kingdom (UK).[33] Patients were randomized to cannabis extract (containing 2.5 mg THC) and matched placebo capsules. The study had a 5-week dose titration phase and a 10-week maintenance phase; the maximum allowable dose was 25 mg daily. The study results did not identify a significant effect on mean change in spasticity between groups (mean changes in groups were 1.24 and 0.92 for cannabis extract and placebo, respectively). On secondary outcome measures, there were no differences in timed 10-minute walk test, self-reported mobility, disability score, or general health. Participants randomized to cannabis extract had a greater likelihood of self-reported improvement on 3 of 9 symptom categories (including spasticity, pain, and spasms).

In a study of 277 patients with MS, patients were randomized to cannabis extract (contained 2.5 mg THC) and matched placebo capsules.[34] The study had a 2-week dose titration phase and a 10-week maintenance phase; the maximum allowable dose was 25 mg. The proportion of patients who achieved significant relief from muscle stiffness was 29.4% in the cannabis group versus 15.7% in the placebo group (OR 2.26; 95% CI, 1.24 to 4.13; $P = .004$, one-sided). Secondary analyses were also in favor of the cannabis group, as patients reported improvements in body pain, muscle spasms, and sleep quality.

Another systematic review focused on non-cancer pain treatment and covered literature over the same time frame. This review differed in that it intentionally re-analyzed data excluding unpublished studies (most of which were industry-funded). They identified 4 studies (510 participants) examining the efficacy of cannabis preparations for patients with pain related to MS (2 other studies examined synthetically produced cannabinoids, which are not part of our review).[15] The authors concluded that there was low-strength evidence showing no significant difference between cannabis preparations and placebo in improving pain in patients with MS.

We identified an additional 4 trials (314 participants) examining cannabinoids to treat spasticity and/or pain in patients with MS.[25-28] Two studies were rated as low risk of bias,[25,28] one was at high risk of bias,[26] and one was unclear.[27] In a large multicenter European trial with low risk of bias (N=241), patients with MS and moderately severe spasticity were randomized to open-label nabiximols or placebo if they initially experienced at least a 20% reduction in spasticity Numeric Rating Scale (NRS) during an open-label nabiximols run-in period. Over half (52.2%) of participants failed to meet this criteria and were not enrolled. Active treatment consisted of nabiximols, containing 2.7 mg THC and 2.5 mg CBD delivered via oromucosal spray. Participants self-titrated their dose; the maximum permitted dose was 12 sprays in any 24 hour period. The intervention lasted for 12 weeks, with the final follow-up visit 2 weeks after treatment completion. The intervention group experienced a significant reduction in mean spasticity score from baseline to end of treatment compared with the placebo group (change in mean NRS score -0.84 [95% CI, -1.29 to -0.40]). The number of responders (defined as at least a 30% improvement in spasticity from baseline) was significantly higher in treatment versus placebo (74% versus 51%; OR 2.73; 95% CI, 1.59 to 4.69). The study medication was also superior to placebo for 6 of 15 secondary outcomes.

The remaining 3 trials revealed mixed findings. In a 5-day treatment study, patients with MS treated with THC 7.5 mg had no significant differences in any outcome (limb weakness, limb spasticity, limb coordination, gait impairment, reflexes) based on physician rating, though patient self-reported spasticity was lower when on THC versus placebo when doses were 7.5 mg or higher.[26] In a double-blind cross-over trial with 20 patients with MS or other neurological diagnosis, participants received each of THC, CBD, THC and CBD, and placebo for 2 weeks in randomized order.[28] Study findings were mixed: pain relief assessed with a Visual Analog Scale (VAS) was improved for both the THC and CBD groups relative to placebo, but not the group receiving THC and CBD combined; spasm VAS score improved following use of THC and combined THC and CBD; spasticity improved for THC only; and no significant improvements were seen in coordination or bladder control. Study medications, relative to placebo, were not consistently associated with significant treatment benefit on other secondary outcome measures. In a 5-site study of 36 patients who demonstrated a positive response to nabiximols during an open-label phase, participants were randomized to 4 weeks of continued nabiximols use or placebo.[27] Those randomized to placebo were more likely than participants randomized to nabiximols to demonstrate a treatment failure (defined as increase in spasticity, addition of anti-spasticity medicine, or treatment drop-out): treatment failure was observed in 44% of the nabiximols group versus 94% of the placebo group (hazard ratio [HR] 0.335; 90% CI, 0.162 to 0.691). Findings on secondary outcomes were mixed. The risk of bias from this trial is unclear, as it was underpowered and participants who withdrew from the trial may have returned to taking other medications before returning for formal study withdrawal visit.

### *Neuropathic Pain*

While our search yielded no additional studies pertinent to neuropathic pain, prior systematic reviews included 14 RCTs that focused on neuropathic pain populations.[14,15] Of these, only 2 small trials (N=72) were determined to be at low risk of bias.[35,36] In a randomized, crossover trial, 23 individuals with post-surgical or post-traumatic neuropathic pain inhaled an herbal preparation of a 25 mg dose through a pipe of one of 4 potencies (0%, 2.5%, 6%, and 9.4%); THC was inhaled 3 times daily over a 14-day period. Participants in the 9.4% THC group reported a significantly lower average daily pain intensity compared to the 0% THC group ($P$ = .023; difference of 0.7 [95% CI, 0.02 to 1.4]). However, those in the 2.5% and 6% potency group did not have a significant reduction in pain. Regarding secondary outcomes, there was no statistically significant impact on overall mood or quality of life; there was a statistically significant improvement in sleep.[35]

In a double-blind, placebo-controlled, crossover trial, there was a statistically significant improvement in pain intensity among both low-dose (1.29% THC) and medium-dose (3.55% THC) treatment groups compared to placebo in 39 patients with central and peripheral neuropathic pain ($P < .01$).[36] Improvements in short-term pain intensity were stable over a 6 hour time-frame, during which participants inhaled 4 puffs of vaporized cannabis at one hour and 4 to 8 puffs at 3 hours and completed hourly pain assessments. No differences were found in mood or neurocognitive function outcomes between groups.

### *Other/Mixed Pain Conditions*

Overall, there are a limited number of studies of patients with chronic pain that are not related to MS or neuropathy. Generally, the evidence is inconsistent and of low quality. As noted above in the prior systematic reviews, there were 2 studies with unclear risk of bias which both included patients with cancer-related pain (described more below); 3 other studies had a high risk of bias (and are not summarized here).[14,15] We found only 2 additional studies, one low risk of bias RCT[31] and one observational study[29] (N=465) (Table 2).

Of the additional studies, the best evidence for the treatment of mixed pain conditions comes from a randomized, double-blind, placebo-controlled, crossover trial that was conducted in the UK among 34 patients with various pain conditions, 47% of whom were diagnosed with MS.[31] Participants were each administered 3 different medicinal cannabis extract preparations (1:1 THC/CBD, CBD only, THC only) and a placebo control group over an 8-week trial period. Participant-reported that pain symptoms decreased significantly among the THC:CBD and THC only groups compared to CBD only and placebo group ($P < .001$) and 38% (9/24) patients had a decrease in VAS of 50% or more when using active preparations versus placebo. No significant improvements were found on validated measures of sleep, general health, and mood among the THC:CBD and THC only groups. There were no follow-up assessments conducted to determine whether symptom improvements were maintained over time.

An observational prospective-cohort study of 431 patients provides some information about long-term treatment effects.[29] This study assessed the efficacy of a standardized herbal cannabis product (12.5% ± 1.5% THC titrated up to a recommended maximum of 5g daily) among patients with chronic non-cancer pain over the course of 1 year. Participants in the cannabis group were defined as “patients using cannabis as part of their treatment” and were compared to individuals from the same clinics who denied using cannabis. Compared with baseline, there was a significant reduction in average pain intensity in cannabis group (0.92 change [95% CI, 0.62 to 1.23]), but not in control group (0.18 change [95% CI, -0.13 to 0.49]) at 1 year after adjusting for demographic variables, other substance use, and pain-related variables. Also, a greater reduction in pain intensity was observed among cannabis users versus controls (1.10 difference [95% CI, 0.72 to 1.56]). The cannabis group reported a significant reduction in mood disturbance, as well as improved physical quality of life compared to controls. All changes were stable across the 3-, 6-, and 12-month follow-ups. The limitations of this study were that the majority (66%) of the cannabis users were experienced, making the generalizability to cannabis-naïve users difficult, and this study reported a high drop-out rate (over 30%), which may be a source of selection bias. Reasons for attrition among the cannabis group included perceived lack of efficacy, experience of adverse events, and/or a dislike of the study product. However, authors noted that those who dropped out were comparable to those who completed the study.

The 2 studies of patients with cancer-related pain had an unclear risk of bias and were both included in one of the aforementioned systematic reviews.[37,38] In a randomized, double-blind, placebo-controlled graded dose study, patients with opioid-refractory cancer pain received a placebo or one of 3 doses of nabiximols (low: 1 to 4 sprays per day; medium: 6 to 10 sprays per day; or high: 11 to 16 sprays per day) during a 5-week treatment period. A separate double-blind, placebo-controlled crossover study evaluated cancer patients who each received placebo, 10 and 20 mg of THC, and 60 and 120 mg of codeine over 5 successive days. These studies both found an improvement in cancer-related pain among medical cannabis users who ingested a 10 mg THC capsule over a 7 hour observation period[37] and among the low-dose (1 to 4 sprays per day) and medium-dose (6 to 10 sprays per day) nabiximols groups.[38] The nabiximols trial also identified a significant change in an opioid composite score that was defined as either a reduction in pain with a stable opioid consumption (morphine equivalent) or a reduction in opioid consumption with stable pain ($P = .038$) among those only in the low-nabiximols dose group.[38] Methodological limitations of the nabiximols trial were a high attrition rate (27%), the exclusion of patients who reported highly variable pain scores over the course of 3 days, and the use of a non-validated sleep measure. The study comparing THC to codeine did not utilize a validated measure of pain.[37]

# KEY QUESTION 2: What are the effects of cannabis on health outcomes and healthcare utilization for adults who have PTSD?

## KEY QUESTION 2A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?

### Summary of Findings

There are very few methodologically rigorous studies examining the effects of cannabis in patients with PTSD. We found only 2 observational studies which suggest that cannabis is potentially associated with neutral effects on PTSD or depression symptom severity, and employment status, and negative effects in terms of violent behavior, drug and alcohol abuse, and suicidal ideation. However, the strength of evidence is rated as insufficient due to the potential for bias in the 2 included studies in this review and the small number of controlled studies reporting data on benefits and harms of cannabis for treating PTSD symptoms. We found no evidence addressing whether effects differed according to other comorbidities in patients with PTSD.

### Detailed Findings

We found one systematic review[16] and only 2 primary studies[39,40] meeting our inclusion criteria (Table 3), primarily because most of the literature on cannabis use in populations with PTSD was cross-sectional and/or did not include a comparison group.

The systematic review by Wilkinson and colleagues (2016) searched the literature through March 2015,[16] and the 2 primary studies we included were not included in their review because they were both published after March 2015. The Wilkinson et al systematic review included 6 studies related to PTSD.[41-46] Of the 6 included studies, 3 were on nabilone, a synthetic form of cannabis.[41-43] One of these was an RCT, though it included only 10 participants, and the other 2 were retrospective chart review studies. The other 3 studies on non-synthetic forms of cannabis were 2 prospective open-label trials,[44,45] and the last was a prospective observational study;[46] none of these 3 studies included a control group. Due to the focus on synthetic cannabis or the lack of a control group, none of the 6 primary studies included in the Wilkinson et al (2016) systematic review met our inclusion criteria. In spite of having broader inclusion criteria, the synthesized findings from the Wilkinson et al systematic review suggest that the evidence of the effectiveness of cannabis for reducing PTSD symptoms is insufficient.[16]

The primary study by Wilkinson et al (2015) examined data from all Veterans in VA specialized intensive PTSD programs from 1992 to 2011, with a total sample size of over 47,000.[39] They excluded participants who reported drinking more than 2 alcoholic drinks on one occasion, reported using any other drug 30 days prior to admission, or were referred from a drug or alcohol treatment program. The remaining participants were grouped into "never-users," "stoppers" who used cannabis prior to but not after admission, "continuing users," and "starters" who did not use cannabis prior to admission but started after admission. After balancing sample sizes across groups, they compared 4-month post-baseline outcomes for 2,276 Veterans. They included demographic covariates associated with cannabis use and found that continuing users and starters had significantly worse PTSD symptoms and greater drug abuse than never-users and stoppers at 4 months post-baseline. Starters also experienced significantly greater alcohol abuse than the other groups, and continuing users experienced significantly greater alcohol abuse than continuing users after 4 months. Starters experienced significantly more violent behavior at 4 months post-baseline compared to the other groups. There were no significant differences among the groups on employment status.

Johnson et al (2016) examined data at a single time point from Veterans entering a VA-based primary care and mental health integration program.[40] This study included 350 Veterans who used cannabis and 350 non-user controls who were matched on age and gender; all cases and controls had PTSD. Compared to cannabis users, controls were significantly more likely to be married, White, employed, and financially stable. There were no significant differences between cannabis users versus controls on PTSD symptom severity or depression symptom severity. The cannabis users were significantly more likely to experience suicidal ideation and reported significantly more alcohol use (reporting on average approximately 6 alcoholic drinks per week compared to approximately 3 drinks per week in the control sample).

**Table 3. Studies of the Effects of Cannabis on PTSD Symptoms**

| Study, setting, study design (N patients) Risk of bias (ROB) | Sample description Mean age % male | Description and duration of cannabis use and comparators | Primary findings | Other findings |
|---|---|---|---|---|
| Wilkinson 2015[39]<br>VA retrospective cohort study<br>(N=2276)<br>Medium ROB | All Veterans referred for intensive PTSD treatment. Excluded those with prior drug or alcohol use.<br>Mean age 51.7<br>96.7% male | Self-reported cannabis use during 4-month follow-up period:<br>850 never users<br>299 stoppers (use at admission but not at 4 months post-baseline)<br>296 continuing users (use at admission and 4 months post-baseline)<br>831 starters (no use at admission but use at 4 months post-baseline<br>Concomitant medications: Usual medical care including psychotropic medications and psychotherapy provided to all participants. | Continuing users and starters had significantly worse PTSD symptoms than never users and stoppers:<br>*F*=21.47, *P*<.0001 | Violent behavior: Starters significantly more violence than continuing users, never users, and stoppers.<br>*F*=21.28, *P*<.0001.<br>Alcohol abuse: Starters significantly more drug abuse than continuing users, never users, and stoppers; continuing users significantly more drug abuse than stoppers. *F*=88.51, *P*<.0001.<br>Drug abuse: Continuing users and starters significantly worse symptoms than never users and stoppers.<br>*F*=176.26, *P*<.0001.<br>Employment status: No significant differences among groups. *F*=0.66, *P*=.58. |
| Johnson 2016[40]<br>VA matched case-control cross-sectional study<br>(N=700)<br>High ROB | All Veterans with a probable PTSD diagnosis, who were referred for a primary care/mental health integration program based on clinical need following depression, PTSD, and alcohol use screening, or clinical judgment.<br>Mean age 47.1<br>91.0% male | Self-reported cannabis use within 3 months of the assessment (n=350)<br>Compared to no lifetime cannabis use reported at the time of assessment (n=350)<br><br>Users were matched to non-users on age and gender. | Users had significantly worse PTSD symptoms than non-users:<br>t (349) = 0.11, *P*=.91 | Users vs non-users (%):<br>Employed: 23 vs 40, $\chi^2$ (1) = 21.38, *P*<.0001<br>Financially stable: 61 vs 71, $\chi^2$ (1) = 8.15, *P*<.0001<br>Depression symptoms: No significant differences between groups. t (349) = 1.85, *P*=.07<br>Suicidal ideation: 33 vs 26, $\chi^2$ (1) = 12.18, *P*=.04<br>Alcohol use: Users had significantly more alcoholic drinks per day than non-users: 6.3 vs 3.1, t (349) = 4.65, *P*<.0001 |

Abbreviations: N = number; PTSD = post-traumatic stress disorder; ROB = risk of bias; VA = Department of Veterans Affairs

## KEY QUESTION 3: What are the harms associated with cannabis use in adults?

### KEY QUESTION 3A: Do the harms differ by patient subgroup, such as patient medical and mental health comorbidities?

We searched broadly for harms and describe the evidence base for each harm category below. We found no evidence which directly compared risk across different patient subgroups, but we describe relevant information about patient characteristics below as applicable.

### General Adverse Events

In the 2 systematic reviews examining cannabis for chronic pain, cannabis was overall associated with a higher risk of short-term adverse effects.[14,15] Across all indications (not just chronic pain or PTSD) and treatment formulations (including synthetic cannabinoids), treatment was associated with an increased risk of: any adverse event (OR 3.03; 95% CI, 2.42 to 3.80), serious adverse event (OR 1.41; 95% CI, 1.04 to 1.92), and withdrawal due to adverse event (OR 2.94; 95% CI, 2.18 to 3.96).[14] In the review focused on only chronic pain, cannabis was similarly associated with a higher risk of adverse events. While most adverse events were mild, there were possible treatment-related adverse events such as suicide attempts, paranoia, and agitation. In the additional trials that we reviewed, the rates of adverse events did not significantly differ between groups. Side effects were rated as minor and may be considered common effects of cannabis, such as dizziness, relaxation, short-term memory impairment, and mental clouding (Table 2).

One prospective cohort study of 431 patients study assessed the incidence of serious adverse events and adverse events over one year among patients using cannabis for chronic non-cancer pain and found no statistically significant group differences between the cannabis-using group and non-using group on serious adverse events. However, cannabis users were at higher risk for non-serious adverse events.[29] The limitations of this study were that the majority (66%) of the cannabis users were experienced, making the generalizability to cannabis-naïve users difficult, and more frequent follow-up times among the exposure group may have artificially inflated the number of adverse events reported by cannabis users.

In addition, Notcutt and colleagues (2004) had 2 participants withdraw or break blinding due to the inability to tolerate cannabis.[31] The investigators also had to increase the time interval of the initial dosing titration from 15 minutes to 30 minutes between sprays due to 2 participants experiencing dysphoria and lightheadedness.

### Medical Harms

#### *Pulmonary Effects*

*Overview*

One systematic review published in 2007,[47] and 2 more recent prospective cohort studies[48,49] provide data relevant to the short- and long-term pulmonary effects of cannabis smoking.

Taken as a whole, the literature provides low-strength evidence 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 are no studies in older users, or in those with medical comorbidities such as chronic obstructive pulmonary disease (COPD) or heart disease.

*Detailed Results*

There were 12 studies included in the review that directly assessed the short-term effects of inhaled cannabis.[47] Most studies found that smoking cannabis was associated with bronchodilation up to about an hour after exposure. One study found that nearly daily cannabis use in a controlled environment was associated with increased airway resistance over 2 months. In general, it is difficult to draw firm conclusions from these short-term, small (N < 35) studies published over 2 decades ago, 4 of which did not control for concomitant tobacco use.

The best evidence examining the long-term effects of cannabis smoking on pulmonary function comes from 2 more recently published prospective cohort studies with low risk of bias (Table 4). In one US study, pulmonary function testing was conducted at baseline and 4 more times over a 20-year follow-up in a cohort of healthy young adults (N=5,016).[49] While a similar proportion of participants smoked cannabis or tobacco cigarettes, most cannabis users smoked infrequently (about twice monthly on average). Higher cumulative tobacco exposure was associated with a significant decline in forced expiratory volume (FEV1) and forced vital capacity (FVC), but cannabis exposure was actually associated with an increase in both measures over 20 years. Of note, the trends in lung function were non-linear: FEV1 levels were flat or downtrending among those with substantial levels of cannabis exposure (the equivalent of one joint daily for 7 years or more).

A birth cohort study (N=1,037) from New Zealand similarly found that FEV1 and FVC increased over time, though the change was small and not statistically significant. Most cannabis users had relatively low rates of cumulative exposure.[48] Of note, higher rates of cumulative exposure were associated with a small increase in measures of airway resistance.

The prior systematic review also examined long-term pulmonary effects of cannabis. There were 3 cohort studies; the rest were cross-sectional. One of the cohort studies was an earlier interim follow-up from the New Zealand birth cohort study. Another older study examined the effects of "nontobacco" cigarette smoking, but did not have detailed information about cannabis exposure specifically and did not have pulmonary function data for many participants. A third study followed a convenience sample of healthy young adults (mean age 33 years) over up to 8 years of follow-up.[50] About one-third of the participants were heavy habitual cannabis smokers (3.5 joints per day on average), 28% smoked cannabis and tobacco, 17% smoked tobacco only, and 22% smoked neither. About two-thirds of participants had 2 or more FEV1 measures over time, and there was a similar mix of baseline smoking status in those lost to follow-up and those followed longitudinally. The authors found that, while there was a significant decline in FEV1 among tobacco users, cannabis smoking was not associated with a greater decline in FEV1 than nonsmoking.

### *Cardiovascular Events*

Overall, there was insufficient evidence from 2 studies about the effect of cannabis use on the risk of cardiovascular events. Two publications reported analyses from the Myocardial Infarction Onset Study in which nearly 4,000 patients were interviewed just after suffering a myocardial infarction (Table 4). One study assessed the relationship between cannabis use at the time of this baseline interview and subsequent mortality over an average of 12.7 years of follow-up.[51] There was no information about longitudinal exposure to either cannabis or tobacco use which makes it very difficult to assess the relationship between cannabis exposure and long-term mortality. The other analysis was a case-crossover study which compared the risk of myocardial infarction within one hour of cannabis use compared to periods of non-use based on one's pattern of use over the prior year.[52] This study had a high risk of bias because recall bias was a significant issue with this study and it was not clear how the authors accounted for tobacco use.

### Table 4. Observational Studies of Cannabis Use and Cardiopulmonary Outcomes

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age % male | Description and duration of cannabis use and comparators | Primary findings | Comments/other findings |
|---|---|---|---|---|
| ***Pulmonary effects*** | | | | |
| Hancox 2010[48]<br>New Zealand<br>Community-based birth cohort (N=1037)<br>Low ROB | Birth cohort of all individuals in Dunedin, New Zealand, enrolled 1972-1973 | Cannabis use only: 25%<br>Lifetime cannabis use, joint-years: 16% > 1, 84% ≤ 1<br><br>Comparators:<br>Non-users: 23%<br>Tobacco only: 6%<br>Tobacco + cannabis users: 46% | 32 years follow-up.<br>**FEV1**<br>Change with each joint-year cannabis in non-tobacco smokers: 5.4 mL (95% CI, -7.1 to 18.0).<br>Change with each pack-year tobacco: -3.9 mL (95% CI, -8.7 to 0.9).<br>**FVC**<br>Change with each joint-year cannabis in non-tobacco smokers: 13.4 mL (95% CI, -0.8 to 27.6).<br>Change with each pack-year tobacco: 3.6 mL (95% CI, -2.0 to 9.1). | Each joint-year cannabis use also associated with a small but significant increase in airway resistance (0.029 cm $H^2O$, *P*=.042), and alveolar volume (28.5 mL, *P*=.021) |
| Pletcher 2012[49]<br>US, 4 cities<br>Community-based cohort (N=5016)<br>CARDIA<br>Low ROB | Healthy 18-30 year olds enrolled in 1985<br>Mean age 25<br>45% male | Cannabis users: 16%<br>Lifetime use, median joint-years: 0.9<br>2 median episodes in last 30 days<br><br>Comparators:<br>Non-users: 46%<br>Tobacco only: 17%<br>Tobacco + cannabis users: 21% | 20 years follow-up.<br>**FEV1**<br>Highest (> 10 joint-years) vs lowest quartile lifetime cannabis exposure: +36 ml (95% CI, -6.5 to 79).<br>Highest (> 20 pack-years) vs lowest quartile tobacco exposure: -101ml (95% CI, -136 to -65)<br>**FVC**<br>Highest (> 10 joint-years) vs lowest quartile lifetime cannabis exposure: +59 ml (95% CI, 12 to 107).<br>Highest (> 20 pack-years) vs lowest quartile tobacco exposure: -35 mL (95% CI, -76 to 5.0). | Association between cannabis use and pulmonary function tests were nonlinear. Within low lifetime exposure group, increasing use was associated with an increase in FEV1 while the slope was level or downtrending in group with higher levels of exposure (> 7 joint-years) |
| ***Cardiovascular events*** | | | | |
| Frost 2013[51]<br>US, multicenter<br>Hospital-based cohort (N=2097)<br>Determinants of Myocardial Infarction Onset Study<br>High ROB | Patients interviewed just after MI.<br>Users vs non-users:<br>Mean age: 44 vs 52<br>% male: 94 vs 77 | Cannabis smoking within year prior to MI: 109/2097 (5%)<br><br>Comparator: No cannabis use within prior year (95%) | 12.7 years follow-up.<br>Adjusted HR death, compared to no use:<br>Any use: 1.29 (95% CI, 0.81 to 2.05)<br>< weekly: 1.31 (95% CI, 0.74 to 2.35)<br>≥ once weekly: 1.27 (95 % CI 0.63 to 2.56) | --- |

| Study, setting, design (N patients) Risk of bias (ROB) | Sample description Mean age % male | Description and duration of cannabis use and comparators | Primary findings | Comments/other findings |
|---|---|---|---|---|
| Mittleman 2001[52]<br>US, multicenter<br>Hospital-based case-crossover (N=3882)<br>Determinants of Myocardial Infarction Onset Study<br>High ROB | Patients interviewed just after MI.<br>Mean age 44 years (cannabis users)<br>94% male<br>68% current tobacco smokers | Exposure: cannabis smoking within one hour prior to onset of MI: 9/124 (7%)<br>Comparator: Self as control; expected frequency of cannabis use based on pattern over prior year | Risk of MI within one hour of cannabis use, compared to periods of non-use:<br>OR 4.8 (95% CI, 2.9 to -9.5) | Sensitivity analysis without 3 patients with other triggers in hour prior: OR 3.2 (95% CI, 1.4 to 7.3) |

Abbreviations: CARDIA = Coronary Artery Risk Development in Young Adults study; CI = confidence interval; FEV1 = forced expiratory volume; FVC = forced vital capacity; HR = hazard ratio; MI = myocardial infarction; N = number; OR = odds ratio; ROB = risk of bias; US = United States.

## Cancer

There was low-strength evidence mainly from case-control studies that cannabis use does not appear to be associated with a higher risk of head and neck or lung cancer (Table 5). There was insufficient evidence from a smaller number of methodologically limited studies about the effects of cannabis on testicular or transitional cell cancer. We found no evidence examining the effects of cannabis on other types of cancer.

### *Head and Neck Cancer*

A meta-analysis of 9 case-control studies (n=5,732 cases) showed that cannabis use was not associated with head and neck cancer (OR 1.02; 95% CI, 0.91 to 1.14).[53] Results were generally consistent across studies and there was no evidence of dose-response effect. The analyses are inherently limited by recall bias and there was a very wide range of ever cannabis use across studies, though results were consistent across different study populations.

### *Lung Cancer*

One international IPD meta-analysis of 6 case-control studies (n=2,159 cases) found no association between habitual cannabis use (≥ 1 joint-year) and lung cancer among middle-aged patients (OR 0.96; 95% CI, 0.66 to 1.38).[54] The results were consistent across different analyses, intensity of use, age of first use, and after excluding patients who had used cannabis within 2 years of diagnosis. Though the study was generally well-conducted, recall bias is an inherent limitation. The results apply most closely to persons with relatively light cannabis use as there were very few patients with a history of intense use. While this was a large study, there were few patients who were both habitual cannabis users and who had never smoked tobacco.

A large 40-year cohort study (N=49,231; n=189 lung cancer cases) from Sweden had a high risk of bias because of significant methodologic flaws including lack of long-term data on cannabis and tobacco exposure that make it difficult to interpret findings.[55] Cannabis and tobacco use were assessed only at the time of military conscription, and these exposures were related to subsequent risk of lung cancer over 40 years of follow-up.

### *Testicular Cancer*

A meta-analysis of 3 case-control studies (n=719 cases) found a small increase in the risk of testicular cancer among weekly cannabis users compared to those who never used (OR 1.92; 95% CI, 1.35 to 2.72).[56] In sensitivity analyses, the increased risk was only seen among those with non-seminoma cancers and not in those with seminoma cancers. While the meta-analysis itself was methodologically strong, there were substantial methodologic weaknesses in each of the 3 included studies rendering the meta-analysis at high risk of bias. The smallest study did not control for all important confounders including tobacco use. Results were consistent in the 2 larger and methodologically stronger studies, but response rates were very low which may exacerbate issues with recall bias.

### *Transitional Cell Cancer*

One small case-control study (n=52 cases) from 2 VA urology clinics assessed the risk of transitional cell carcinoma.[57] While there was an increased risk of cancer seen with heavier cannabis use, the results are difficult to interpret because of significant methodologic flaws placing the study at high risk of bias.

**Table 5. Observational Studies of Cannabis Use and Cancer Risk**

| ***Cancer type***<br>**Study, setting, design (N patients)**<br>**Risk of bias (ROB)** | **Sample description**<br>**Mean age**<br>**% male** | **Description and duration of cannabis use** | **Primary findings** | **Comments/other findings** |
|---|---|---|---|---|
| *Head and neck cancer*<br>Carvalho 2015[53]<br>US, Africa, South America<br>Meta-analysis of 13 case-control studies<br>Hospital-based (6) and cancer-registry (5) studies<br>Medium ROB | Patients with definitive diagnosis of head-neck cancer (in studies of moderate to high methodologic quality).<br>Mean age NR<br>% male NR | <u>% ever cannabis smokers:</u><br>Cases: range 2.4 to 83; overall 12.6<br>Controls: range 0.4 to 83; overall 14.3 | 9 studies contributed data to meta-analysis<br>OR (95% CI) for head neck cancer among cannabis users:<br>1.02 (0.91 to 1.14); adjusted for age, gender, race, tobacco use | |
| *Lung cancer*<br>Zhang 2015[54]<br>International Lung Cancer Consortium<br>North America, New Zealand, Europe<br>Individual-level meta-analysis of 6 case-control studies (2,159 cases, 2,985 controls, combined)<br>Medium ROB | Patients with histologically confirmed lung cancer.<br>Cases vs controls:<br>Median age: 57.3 vs 53.0<br>% male: 50 vs 53 | <u>Cannabis and tobacco use:</u><br>Cases:<br>≥ 1 joint-year: 10%<br>≥ 1 joint-year, non-tobacco users: 3.0%<br>Never smoked tobacco: 17%<br><br>Controls:<br>≥ 1 joint-year: 11%<br>≥ 1 joint-year, non-tobacco users: 4.7%<br>Never smoked tobacco: 46% | OR (95% CI) for lung cancer among habitual (≥ 1 joint-year) users compared to non-habitual or never users: 0.96 (0.66 to 1.38); adjusted for age, sex, race, education, tobacco pack-years and status | OR among never tobacco smokers: 1.03 (0.51-2.08) |
| *Lung cancer*<br>Callaghan 2013[55]<br>Sweden<br>Community-based cohort study (N=49,231)<br>High ROB | Military conscripts born between 1949-1951 and inducted between 1969 and 1970<br>100% male | <u>Lifetime cannabis use at time of conscription:</u><br>Cases:<br>Once (2.5%)<br>2-4 times (3.0%)<br>5-10 times (1.7%)<br>11-50 times (1.5%)<br>> 50 times/"heavy" (1.7%)<br>Controls:<br>Never (82.5%)<br>Tobacco only: 55.2%<br>Tobacco + cannabis: 9.1%<br>Cannabis with no tobacco use: 13.4% | 40 years follow-up.<br>189 incident cases of lung cancer (by ICD-9 codes).<br>HR (95% CI) for lung cancer among self-reported heavy users:<br>2.12 (1.08 to 4.14); adjusted for alcohol, COPD/asthma, socioeconomic status, occupation, tobacco | No significant association between other levels of cannabis use and lung cancer, no dose-response relationship. |

| ***Cancer type***<br>**Study, setting, design (N patients)**<br>**Risk of bias (ROB)** | **Sample description**<br>**Mean age**<br>**% male** | **Description and duration of cannabis use** | **Primary findings** | **Comments/other findings** |
|---|---|---|---|---|
| *Testicular cancer*<br>Gurney 2015[56]<br>US<br>Meta-analysis of 3 case-control studies (719 cases, 1419 controls combined)<br>High ROB | Young adults with histologically confirmed testicular cancer<br>Mean age NR; range 18 to 50<br>100% male | Overall proportion with ever, never, weekly, and current cannabis use NR | Cancer risk OR (95% CI), compared with never use:<br>Weekly use: 1.92 (1.35 to 2.72), all studies adjusted for age and cryptorchidism; 2 largest studies adjusted for alcohol and tobacco use.<br><br>≥ 10 year use: 1.50 (1.08 to 2.09).<br>Ever-use: 1.19 (0.72 to 1.95). | The association between cannabis use and cancer was only seen among non-seminoma cancers and not in seminoma cancers |
| *Transitional cell cancer*<br>Chacko 2006[57]<br>US, 2 VA sites<br>Case-control (52 cases 104 controls)<br>High ROB | Patients under age 60 with transitional call cancer presenting to urology clinic.<br>Mean age 51<br>100% male | Cases:<br>Smoked > 40 joint-years: 40.4%<br>Ever smoked cannabis: 88.5%<br>Smoked tobacco and cannabis: 76.9%<br>Smoked tobacco only: 17.3%<br>Smoked cannabis only: 11.5%<br><br>Controls:<br>Smoked > 40 joint-years: 15.1%<br>Smoked cannabis: 69.2%<br>Smoked tobacco and cannabis: 65.4%<br>Smoked tobacco only: 27.9%<br>Smoked cannabis only: 3.9% | Joint-years cannabis use as continuous variable was significantly associated with transitional cell cancer: *P*-trend .01 (adjusted for tobacco use, smoked meat use, radiation, agent orange, and dye exposure)<br><br>Risk of cancer with > 40 joint-years cannabis use compared to none: OR 3.4 (unadjusted, *P*=.012) | |

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; NR = not reported; OR = odds ratio; ROB = risk of bias; US = United States; VA = Department of Veterans Affairs.

### *Motor Vehicle Accidents*

Overall, we found evidence suggesting an increased risk of collision associated with acute cannabis intoxication, but the magnitude and precision of increased risk are unclear.

A 2016 systematic review of cannabis intoxication and motor vehicle accidents pooled the findings of 21 multi-national observational studies that were published between 1982 and 2015, with a combined sample size of 239,739. The meta-analysis determined a statistically significant, moderate increase in collision risk associated with acute cannabis intoxication (OR 1.35; 95% CI, 1.15 to 1.61).[58] In assessing study quality, the review authors examined the methods used to measure drug use (*eg*, self-report, or lab values from blood versus urine or saliva), crash severity, adjustment for alcohol use and other confounders, and whether the study evaluated a dose-response effect. Sub-analyses that grouped studies based on quality, design (case-control versus culpability studies), degree of adjustment for confounders, and crash severity (whether fatalities were involved) found pooled effects in the range of 1.07 to 1.81 using a random effects model, and 1.08 to 1.90 using meta-regression.

The review authors suggested that the pooled estimate may be complicated by factors affecting a user's decision to drive under the influence of cannabis. Experimental studies using simulated driving have reported that alcohol increases driving speed and risk-taking, while cannabis users tend to be aware of their impairment and drive slower and more cautiously in an effort to compensate.[59,60] The pooled effect may underestimate the true risk of collision with acute cannabis intoxication, if users are more likely to drive when their level of impairment is low. Conversely, the pooled estimate may be inflated if cannabis users who choose to drive while intoxicated have a higher baseline risk independent of cannabis use, compared with cannabis users who choose not to drive after use.[58]

A study that sought to determine a threshold for serum concentration of THC associated with driving impairment found that serum concentrations below 10 ng/mL were not associated with elevated accident risk, based on limited epidemiological data.[61] The authors of the study reported that based on experimental studies, THC serum concentration in the range of 7 to 10 ng/mL is comparable to a blood alcohol concentration of 0.05% on degree of impairment.[61]

## Mental Health-Related Harms

### *Suicidal Behaviors*

We found no evidence examining the effects of cannabis use on suicide risk in patients with chronic pain or PTSD.

A review and meta-analysis of epidemiological research from 1995 to 2015 found few studies on the effect of cannabis use and suicidality (suicide death, ideation, and attempt) among the general population including both adolescents and adults.[62] Data were insufficient to comment on the effect of acute cannabis use and suicidality. However, the review found limited evidence suggesting significantly increased odds of suicide death (pooled OR 2.56; 95% CI, 1.25 to 5.27, 4 studies) with any cannabis use. In 6 studies each, any cannabis use was significantly associated with increased odds of suicide ideation (pooled OR 1.43; 95% CI, 1.13 to 1.83) and suicide attempt (pooled OR 2.23; 95% CI, 1.24 to 4.00). Further, heavy cannabis use was associated with significantly increased odds of suicide attempt (pooled OR 3.20; 95% CI, 1.72 to 5.94). Suicide ideation was noted to be increased among heavy cannabis users, though this was of borderline significance (OR 2.53; 95% CI, 1.00 to 6.39). Cannabis use was slightly more common among individuals who died from suicide who used non-overdose methods (11.6%) than among those who died from suicide related to overdose methods (9.2%) in general population studies. Limitations of this review included significant heterogeneity between studies with respect to measurement of cannabis exposure and control of risk factors, the use of observational studies (including case-series and cross-sectional), a small number of suicidality cases in studies, and research from a small number of geographical locations. An older review that included 7 studies on suicidal ideation or attempts (with 2 studies included in both reviews) found mixed results: 4 studies reported an association between cannabis use and increased risk of suicidal ideation, one study showed no association, and one school cohort study demonstrated reduced risk of attempts but increased risk of ideation.[63]

### *Mania*

We found no evidence examining the effects of cannabis on the risk of mania among persons with PTSD or chronic pain.

One systematic review that included 6 prospective studies of other populations (mean follow-up 3.9 years) found support for an association between cannabis use and exacerbation or incidence of manic symptoms.[64] Among patients with known bipolar disorder, 3 studies demonstrated significant associations between cannabis use and fraction of time with mania or mania score/symptoms during follow-up, though meta-analysis was not undertaken. Further, a meta-analysis of 2 prospective community studies demonstrated an association between cannabis use and new-onset mania symptoms among those without a diagnosis of bipolar disorder (pooled OR 2.97; 95% CI, 1.80 to 4.90) with low heterogeneity between studies. The strength of the findings is limited by the small number of included studies in this review.

### *Psychosis*

One systematic review[63] and 7 studies[65-71] provided evidence related to psychotic symptoms associated with cannabis use. Overall, studies consistently showed a relationship between cannabis use and the development of psychotic symptoms, though the magnitude of risk is uncertain. In addition, experimental studies have found acute, transient psychotic symptoms within hours of use. The Moore et al (2007) review also included studies that showed an increased risk of psychotic spectrum disorder among cannabis users. Given that many of the studies are observational, it is difficult to determine whether cannabis directly contributed to the development of psychotic symptoms or whether its use was simply more common among individuals with a preexisting tendency towards these symptoms. The possibility that cannabis contributes directly to symptom development is supported but not proven by biologic plausibility, evidence of a dose-response relationship, and the results of prospective cohort studies, described in the following sections.

#### *Psychotic Symptoms*

Four studies included only participants with no psychotic symptoms at baseline.[65-67,71] Time to follow-up ranged from 12 to 36 months; 2 of the 4 studies examined linear trends across frequencies, and the other 2 comparing higher to lower frequencies of use. All 4 studies found that participants who had ever used cannabis had an increased likelihood of any psychotic outcome (*eg*, symptoms, psychotic disorder) compared to participants who had never used. The studies also found that frequency of use correlated with the likelihood of a psychotic outcome.

Two articles provided data from the Early Developmental Stages of Psychopathology (EDSP) study, a prospective cohort study (medium risk of bias) of randomly selected adolescents and young adults aged 14 to 24 at baseline (N=3,021; mean age 18.3 years).[65,66] Findings from these studies indicate that at the second (T2) and third time point (T3), using cannabis more than 5 times since the previous assessment (3.5 years between baseline and T2, and 4.9 years between T2 and T3) was associated with positive symptoms (OR 2.10; 95% CI, 1.61 to 2.75) and the co-occurrence of both positive and negative symptoms (OR 2.05; 95% CI, 1.18 to 3.59), but not negative/disorganized symptoms alone (OR 1.12; 95% CI, 0.91 to 1.39).[66] Among those reporting no cannabis use at baseline, cannabis use between baseline and T2 increased the risk for psychotic symptoms between T2 and T3 (adjusted OR 1.9; 95% CI, 1.1 to 3.1; $P = .02$). Among those reporting cannabis use at baseline, continued use at T2 was associated with psychotic symptoms at both T2 and T3 (adjusted OR 2.0, 1.0 to 3.8; $P = .037$).[65] In addition, a case-control study of 280 individuals presenting with a first episode of psychosis and 174 healthy controls found that after adjusting for confounders, there was no significant difference between groups in ever having used cannabis, or the duration of use. However, those experiencing a first episode of psychosis were more likely to use cannabis daily (adjusted OR 6.4; 95% CI, 3.2 to 28.6), and were more likely to use sinsemilla (adjusted OR 6.8; 95% CI, 2.6 to 25.4).[71]

One cohort study (N=591) with a low risk of bias examined the relationship between frequency of use in adolescence and psychotic symptoms over a 30 year period. In the multivariate model, the frequency of use in adolescence (casual use: OR 1.80; 95% CI, 1.24 to 2.59; $P = .002$; regular use: OR 2.60; 95% CI, 1.59 to 4.23; $P < .001$) was a significant predictor of ‘schizotypal signs’ (*eg*, feeling lonely even when with people, never feeling close to another person). There was no significant relationship between cannabis use and schizophrenia nuclear symptoms (*eg*, thought insertion, thought broadcasting, thought control, hearing voices).[67]

*Acute Cannabis-induced Psychosis*

Three studies examined the relationship between cannabis use and acute psychotic symptoms.[68-70] In one (moderate risk of bias) study, a double-blind cross-over RCT of 16 healthy cannabis-naïve women (mean age 23.56 years), comparing oral cannabis extract to placebo, one participant experienced psychotic symptoms (*ie*, “severe” somatic concern, anxiety, tension, depressive mood, suspiciousness, hallucinatory behavior, motor retardation, and “extremely severe” unusual thought contents) 3 hours after cannabis intake. Symptoms decreased without pharmacological intervention.[68] The second (low risk of bias) study compared THC plus CBD to THC plus placebo (N=48). Clinically significant positive symptoms (*ie*, an increase in Positive and Negative Syndrome Scale [PANSS] positive scores of 3 or more points), were more common with THC plus placebo (11 of 26 cases) compared to THC plus CBD (3 of 22 cases), ($\chi^2=4.74$, $P < .05$), and individuals in the THC plus placebo group experienced greater paranoia ($t=2.28$, $P < .05$).[70] The third was a (high risk of bias) case-control study comparing 140 cannabis users to 144 non-users on psychotic symptoms (*ie*, delusory thinking, perceptual distortion, cognitive disorganization, anhedonia, mania, and paranoia). Cannabis users were evaluated immediately after use, as well as 3 to 4 days later. Univariate results indicate more psychotic symptoms in the cannabis group ($F_{1,282} = 80.1$, $P < .005$), with greater effects immediately after use.[69]

### Cognitive Effects

One systematic review provides moderate-strength evidence that active, long-term cannabis use is associated with small negative effects on all domains of cognitive function, but insufficient evidence of long-term cognitive effects in past users.[72] The review first synthesized the literature on non-acute (*ie*, residual and long-term combined) cognitive effects of cannabis use, reporting that the 33 included studies (with a combined total of 1,010 cannabis users compared to 839 controls) suggested that there is a small, non-acute effect of cannabis use on global cognitive functioning and on each of the 8 domains of cognitive functioning reported in the papers, which included abstraction/executive, attention, forgetting/retrieval, learning, motor, perceptual-motor, simple reaction time, and verbal/language domains. The authors then conducted a subgroup analysis of only 13 studies (with a combined total of 388 cannabis users and 387 controls) which examined cognitive functioning after at least 25 days of abstaining from cannabis use, described as long-term use. They reported that in this subgroup of studies examining long-term effects, there was not a statistically significant effect on global cognitive functioning, nor on any of the 8 reported cognitive domains.[72]

Schreiner and colleagues' systematic review[72] documents consistent evidence supporting non-acute (*ie*, combined findings from both residual and long-term effects studies) cognitive effects of cannabis from the 33 studies included in their review, though these data are not specific to chronic pain or PTSD populations. Therefore, the strength of evidence for residual effects of cannabis use is rated as moderate. The magnitude of these non-acute effects is small overall, but because the studies all reported average cognitive impairment and not the percent of study participants with clinically significant cognitive impairment, it is not possible to provide an estimate for the range of severity of cognitive impairment experienced by the cannabis users in these studies.

The long-term effects of cannabis use on cognitive functioning are less clear, and the systematic review by Schreiner and colleagues suggests that cannabis use might not result in long-term cognitive impairment. This sub-analysis, however, was based on a relatively small sample from 13 studies with a very broad range of time since last cannabis use (ranging from an average of 25 days to an average of over 3 years). The amount of prior cannabis use reported in these studies also varied greatly, ranging from an average of weekly use to an average of using cannabis multiple times per day. This heterogeneity among the 13 included studies makes generalizations about amount and frequency of cannabis use associated with cognitive impairment impossible and could be at least part of the reason for the lack of consistent findings across studies. Most of the cognitive domains reported in these studies had inconsistent results within or across studies or more consistent but non-significant trends indicating the presence of at least mild long-term cognitive impairment. This suggests that, in at least some cognitive domains, a larger sample might yield findings of significant associations between cannabis use and cognitive impairment that is present after at least 25 days after abstinence. The evidence for a lack of long-term cognitive impairment associated with cannabis use reported in the Schreiner et al review, therefore, is rated as insufficient strength of evidence.

### *Cannabis Use Disorder (CUD)*

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[73] and the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[74] both require multiple symptoms of significant psychiatric distress, social impairment, and adverse consequences associated with cannabis use for an individual to be diagnosed with CUD. While we did not find studies reporting prevalence estimates of CUD in the population of Veterans with PTSD, Bonn-Miller et al (2012) report that the prevalence of PTSD among Veterans with CUD was 29.05% in fiscal year 2012.[75]

We did not find any articles comparing rates of CUD in chronic pain or PTSD populations to other populations, or any studies examining the rate of CUD in a cannabis-using population. Other studies of CUD provide potentially relevant cross-sectional data. For example, one non-VA study using structured diagnostic interviews found that the prevalence of cannabis misuse and dependence were 2.4% and 0.9%, respectively, in a primary care sample (though the proportion of patients who used cannabis was unknown).[76] Another cross-sectional study by Hefner and colleagues (2015) examined rates of CUD in a sample of over 1.3 million Veterans with chronic non-cancer pain, comparing rates of CUD among groups of Veterans based on the number of opioid prescriptions for non-cancer pain.[77] They found that 1.98% of Veterans with chronic non-cancer pain who were not prescribed opioids had a CUD diagnosis compared to 2.83% of those with 1 to 2 opioid prescriptions in one year, 3.44% with 3 to 10 opioid prescriptions, 3.28% with 11 to 19 opioid prescriptions, and 3.92% of Veterans with 20 or more opioid prescriptions in one year who were diagnosed with CUD.

Bonn-Miller et al (2015) studied 104 Veterans who had CUD and were attempting to stop using cannabis.[78] They reported that PTSD was associated with higher baseline rates of cannabis use and a slower decrease in cannabis use during the first 4 weeks following a quit attempt. Walsh and colleagues (2014) found that cannabis dependence was not associated with trauma exposure, but was associated with a greater number of PTSD symptoms in a sample of 1317 Jewish Israeli individuals.[79] Finally, Kevorkian and colleagues (2015) examined data from the National Epidemiologic Survey on Alcohol and Related Conditions (N=34,396).[80] They reported that while trauma exposure during one's lifetime was only very minimally associated with CUD (OR 0.997; 95% CI, 0.996 to 0.999), among trauma-exposed, cannabis-using individuals, PTSD was significantly associated with increased likelihood of CUD (OR 1.217; 95% CI, 1.214 to 1.220).

CUD may also impact response to PTSD treatment, though CUD has not been well-studied in general in PTSD populations. Bonn-Miller et al reported in 2013 that among Veterans who were enrolling in a VA, all-male, inpatient, intensive PTSD treatment program, those who had CUD experienced less improvement in PTSD symptoms during the course of treatment than those who did not have CUD upon enrollment.[81] This relationship was observed for overall PTSD symptoms as well as avoidance/numbing and hyperarousal symptom clusters, though group differences were non-significant for re-experiencing symptoms. These analyses included statistical adjustment for covariates including age, combat exposure, and depression symptoms as well as alcohol, amphetamine, cocaine, opioid, and sedative use disorders.

## Emerging Harms

### *Infectious Diseases*

Several case reports have suggested an association between smoking cannabis and invasive pulmonary aspergillosis in immunocompromised individuals.[82-84] In an older study, investigators randomly selected 28 individuals with a history of cannabis smoking, 21 of whom were asymptomatic, 6 of whom had bronchitis symptoms after smoking, and 1 of whom was diagnosed with pulmonary aspergillosis.[85] Serum precipitins against Aspergillus antigens were significantly more common among individuals with a cannabis smoking history compared to age-matched controls. Most cannabis cigarette samples provided by the participants had Aspergillus species detected in culture, and there was passage of fungal spores demonstrated through most of the samples.

Cannabis has been implicated as a possible contributing factor in tuberculosis clusters through the shared use of a cannabis water pipe,[86 13841] or through the practice of "hotboxing."[87]

### Cannabinoid Hyperemesis Syndrome

Recently, a number of case series have described a syndrome of at times severe cyclic vomiting associated with chronic cannabis use called the cannabinoid hyperemesis syndrome.[88-94] The largest case series included 98 patients from a single institution.[95] The authors performed an institution-wide review of medical records of patients with recurrent vomiting, without an associated etiology, and known preceding cannabis use. All patients were younger than 50 years old and 95% had used at least once weekly; 68% of the patients had used cannabis for over 2 years. Most patients (86%) had abdominal pain as well. Information about the effect of hot water was available in 57 patients: 91% of these patients reported relief of symptoms with hot showers. Long-term follow-up was only available in 10 patients, so it is uncertain how many patients ultimately abstained from use and how often this resolved the symptoms. Earlier case series reported that most patients who discontinued use recovered.[90]

### Complications from Intravenous Use of Cannabis

The intravenous marijuana syndrome is an acute illness following the injection of boiled cannabis preparations. The syndrome was last described in a synthesis of 25 case reports in 1986. In most cases, patients had a febrile illness with tachycardia, hypotension, gastrointestinal symptoms, and myalgias.[96] The pathogenesis of the syndrome is unknown. A minority of patients had used cotton to strain the preparation prior to use suggesting some similarity to "cotton fever" that has been described in heroin users. Alternatively, it is possible that very high doses of cannabis itself could have contributed.

### Aggression and Violence

Two studies investigated the effect of cannabis use on aggression and found mixed results. A retrospective study of clinical files from 4 public psychiatric outpatient facilities in Italy that included patients treated for 6 months continuously (N=1,582; 49% male, 41% with mood disorder and 27% with psychotic disorder) found cannabis use to be a risk factor for violent behavior, regardless of psychiatric disorder, sex, and age.[97] The combination of a mental disorder and cannabis use was present in significantly more patients with violent behavior (3.9%) versus those with non-violent behavior (0.2%; OR 19.2; 95% CI, 4.4 to 118.6). Also, mental health patients who used cannabis were significantly more likely to engage in both violence towards others (OR 10.2; 95% CI, 3.8 to 27.5) and violence towards themselves (OR 5.7; 95% CI, 2.4 to 13.5). In particular, the probability of suicide increased more than 17 times (OR 17.6; 95% CI, 3.5 to 87.7) and the probability of attempted suicide tripled (OR 3.4; 95% CI, 1.5 to 9.4) among cannabis users versus non-users. Notably, cannabis use was significantly associated with being male, a family history of violent behavior, precarious employment, poor compliance with treatment, and undergoing psychotherapy, and there was a significant correlation between violent behavior and a positive family history for both substance misuse and violent behavior, suggesting that factors other than cannabis use are implicated in violent behavior.

A second study of 30 undergraduate males who received intense provocation following ingestion of either low (0.1 mg/kg), medium (0.25 mg/kg), or high (0.4 mg/kg) doses of THC found that the low-dose group tended to respond with more aggression than the high-dose group.[98] Participants in this study were randomly allocated to their THC dosing and asked to select a shock intensity to be administered to an opponent during a competition. In the absence of provocative stimulation, in which participants were not aware of their opponents' aggressive intentions (based on opponents' choice of shock level to be administered to the participant), there was no difference in shock intensity given by participants by THC dose. In the presence of provocative stimulation, participants in the low-dose group were significantly more likely to escalate shock intensity and use extremely high shock settings to retaliate against aggressive opponents compared with those in moderate and high THC dose groups ($P < .05$ for both). These findings suggest that aggression is not associated with cannabis use.

### *Miscellaneous*

There are emerging issues related to newer methods of cannabis use that clinicians may encounter. "Dabbing" refers to vaporization and inhalation of butane hash oil which has THC concentrations that typically far exceed that seen in the cannabis flower. In a survey study, "dab" users (N=357) reported more trouble with tolerance and withdrawal than what they had experienced using flower cannabis.[99] Edible cannabis use has become more common in recent years, especially in states in which cannabis has been legalized for recreational or medical purposes.[100] A recent case series described 5 patients hospitalized with acute psychosis after ingestion of edible cannabis.[101] The patients described ingesting multiple portions in part because of the delay in onset of effect seen with edible cannabis, thus ingesting a much larger dose of THC than recommended.

A recently published (after our search dates ended) follow-up to a New Zealand birth cohort study found that cannabis use was associated with the development of periodontal disease by early midlife after adjusting for tobacco use.[102] They found no association with intermediate health outcome measures such as lipids, hemoglobin A1c, and measures of inflammation. However, nearly two-thirds of cannabis users also used tobacco, and there were relatively few people who used cannabis heavily.

## 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?

### Summary of Findings

*Chronic Pain*

We identified 10 ongoing RCTs examining the effectiveness of cannabis for a variety of chronic pain conditions (Table 6), 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). While there are several ongoing observational studies on the benefits and/or harms of cannabis, we found no studies looking specifically at chronic pain populations that would meet our inclusion criteria.

Most of the ongoing trials are relatively small, with 6 including fewer than 100 patients (mean 46 participants). However, 2 industry-funded placebo-controlled trials investigating nabiximols include roughly 400 patients each, and another parallel RCT compares vaporized cannabis to dronabinol (synthetic THC) and placebo in 120 adults. In addition to assessing pain, 5 trials will assess quality of life and/or functional status outcomes, 5 trials will look for mental health outcomes such as mood and depression, and 4 trials will examine cognitive outcomes, a harm on which there is very little current evidence in chronic pain populations. The follow-up duration for these trials is relatively short, ranging from 1 to 10 weeks (median 5 weeks).

Similar to the published studies included in this report, the most commonly used cannabis products in these ongoing trials are vaporized (3 studies) or smoked (3 studies) cannabis with known THC and/or CBD content, or nabiximols oromucosal spray (2 studies). One of these trials is a crossover RCT investigating 6 different vaporized cannabis products with varying THC and CBD content in 40 adults with painful osteoarthritis of the knee (NCT02324777). This trial may provide some evidence as to the most effective cannabis formulations or potencies; however, as a relatively small trial (40 patients) with only one day of exposure for each of the formulations, conclusions about their effectiveness will be limited. We found only one other study planning to compare different potencies of cannabis (NIH project number 5R01DA030424-03).

**Table 6. Ongoing Studies[a] of Cannabis for Chronic Pain**

| PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion | Study Title | Purpose of Study | Participants; Intervention(s)/ Comparator | Outcomes and Timing |
|---|---|---|---|---|
| Abrams, DI (NCT01771731)<br>· Crossover RCT<br>· Sponsored by the University of California, San Francisco; National Heart, Lung, and Blood Institute (NHLBI); University of Minnesota - Clinical and Translational Science Institute<br>· March 2016 | Vaporized Cannabis for Chronic Pain Associated With Sickle Cell Disease (Cannabis-SCD) | To assess whether inhaling vaporized cannabis ameliorates chronic pain in patients with sickle cell disease; assess the possible synergistic affect between inhaled cannabis and opioids; assess the clinical safety of the concomitant use of cannabinoids and these opioids; evaluate the short-term effects of inhaled cannabis on markers of inflammation and disease progression in patients with sickle cell disease. | 35 adults with sickle cell disease with ongoing opioid analgesic therapy for chronic sickle cell disease-associated pain.<br><br>In a controlled inpatient setting, the contents of 1 cigarette is vaporized and inhaled at 12pm on day 1; 8am, 2pm, and 8pm on days 2-4; and 8am on day 5.<br>1. Cannabis cigarette: 4.7% THC and 5.1% CBD<br>2. Placebo cigarette: 0% THC and 0% CBD<br>Participants to receive both treatments in random order for 5 days (2-week washout). | Pain VAS evaluated during the 5-day inpatient exposure.<br><br>Other outcomes: mood; QOL assessments; inflammation markers and disease progression from blood samples. |
| Dayan, L (NCT02560545)<br>· Crossover RCT<br>· Sponsored by the Tel-Aviv Sourasky Medical Center<br>· September 2016 | Cannabinoids Effects on the Pain Modulation System | NR | 40 adults with at least moderate neuropathic pain (> 30 out of 100 on VAS) for ≥ 3 months, who have not responded to other painkillers or for whom they are contraindicated due to side effects.<br>1. Cannabis oil: 20% THC, 40 mg per 70 kg weight; route of administration not specified<br>2. Placebo oil | Evaluation of pain using a questionnaire at 1 month.<br><br>Other outcomes: testing of the pain-modulation system using TSA Neurosensory Analyzer. |
| GW Pharmaceuticals Ltd. (NCT01262651)<br>· Parallel RCT<br>· Sponsored by the GW Pharmaceuticals Ltd.; Otsuka Pharmaceutical Development & Commercialization, Inc. | A Study of Sativex® for Relieving Persistent Pain in Patients With Advanced Cancer | To determine the efficacy, safety and tolerability of nabiximols (Sativex) as an adjunctive treatment, compared with placebo, in relieving uncontrolled persistent chronic pain in patients with advanced cancer. | 397 adults with an advanced cancer for which there is no known curative therapy, and a clinical diagnosis of cancer-related pain which is not alleviated with their current optimized opioid treatment.<br><br>100 µl oromucosal spray administered twice daily up to a maximum of 10 sprays | Percent improvement from baseline to the end of treatment in NRS average pain score (5 weeks).<br><br>Other outcomes: change in NRS average pain; change in mean NRS worst pain; change in |

| PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion | Study Title | Purpose of Study | Participants; Intervention(s)/ Comparator | Outcomes and Timing |
|---|---|---|---|---|
| · July 2015 | | | per day:<br>1. Nabiximols (oromucosal spray delivering 2.7 mg THC/2.5 mg CBD)<br>2. Placebo | mean sleep disruption. |
| GW Pharmaceuticals Ltd. (NCT01424566)<br>· Crossover RCT<br>· Sponsored by the GW Pharmaceuticals Ltd.; Otsuka Pharmaceutical Development & Commercialization, Inc.<br>· December 2015 | A Two-Part Study of Sativex® Oromucosal Spray for Relieving Uncontrolled Persistent Pain in Patients With Advanced Cancer | To determine the efficacy of nabiximols (Sativex) as an adjunctive medication in relieving persistent chronic pain (not breakthrough pain) in patients with advanced cancer, who have this pain even when they are on optimized/maximized chronic opioid therapy. | 406 adults with an advanced cancer for which there is no known curative therapy, and a clinical diagnosis of cancer-related pain which is not alleviated with their current optimized opioid treatment.<br><br>100 µl oromucosal spray administered twice daily up to a maximum of 10 sprays per day:<br>1. Nabiximols (oromucosal spray delivering 2.7 mg THC/2.5 mg CBD)<br>2. Placebo | Mean 11-point NRS average pain score over the last 4 days of treatment period (7 weeks).<br><br>Other outcomes: percentage improvement in NRS average pain score; mean NRS worst pain score; mean sleep disruption. |
| Irving, P (NCT01562314)<br>· Parallel RCT<br>· Sponsored by GW Research Ltd<br>· June 2015 | A Pilot Study of GWP42003 in the Symptomatic Treatment of Ulcerative Colitis (GWID10160) | To determine the efficacy and safety of GWP42003 compared with placebo, by the percentage of participants achieving remission. | 60 adults with mild to moderate ulcerative colitis on a fixed dose of 5-aminosalicylic acid treatment and a with a Mayo assessment score 4-10.<br><br>One of the following twice daily for 10 weeks:<br>1. GWP42003 (oral capsule that contains both CBD and THC) up to 250 mg twice daily<br>2. Placebo | Percentage of participants achieving remission, quantified as a Mayo score of ≤ 2 (with no sub-score > 1).<br><br>Other outcomes: NRS pain, Mayo total score, health-related QOL, Subject Global Impression of Change, Global Assessment of Illness Severity. |
| Martinez, D (NCT02675842)<br>· Parallel RCT<br>· Sponsored by the New York State Psychiatric Institute<br>· December 2021 | Investigation of Cannabis for Pain and Inflammation in Lung Cancer | To investigate the efficacy of cannabis, compared to placebo, in participants undergoing radiation therapy for lung cancer. | 30 adults with lung cancer receiving radiation therapy.<br><br>Smoked cannabis (1 to 2 cigarettes over the course of 2 to 3 hours) administered 3 to 5 days/week in the research laboratory for 6 weeks:<br>1. High CBD/low THC: 15.76% CBD and | Change in pain ratings using the McGill Pain Questionnaire and the 9 item BPI at 6 weeks.<br><br>Other outcomes: sickness-related impairment; physical and emotional wellbeing; QOL; tiredness; mood; appetite/eating; |

| PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion | Study Title | Purpose of Study | Participants; Intervention(s)/ Comparator | Outcomes and Timing |
|---|---|---|---|---|
| | | | 3.11% THC<br>2. Placebo: 0.0% CBD and 0.01% THC | subjective effects; cognitive status; physiological state; opioid use. |
| Martinez, D (NCT02683018)<br>· Crossover RCT<br>· Sponsored by the New York State Psychiatric Institute<br>· March 2021 | Investigation of Cannabis for Chronic Pain and Palliative Care | To investigate the effects of high CBD/low THC cannabis on symptoms such as pain, nausea/vomiting, and QOL in seriously ill participants. | 70 adults with one of the following medical diagnoses whose pain remains (score ≥ 3 on item 3 of the 9-item BPI) despite their current medical treatment: cancer, amyotrophic lateral sclerosis, Parkinson's disease, spinal cord injury, neuropathy, phantom limb pain, thalamic pain, pain related to injury of nerve plexus/plexi, and neuropathic facial pain.<br><br>Smoked cannabis (1 to 2 cigarettes over the course of 2 to 3 hours) administered 3 to 5 days/week in the research laboratory for 4 weeks:<br>1. High CBD/low THC: 15.76% CBD and 3.11% THC<br>2. Placebo: 0.0% CBD and 0.01% THC | Change in pain ratings using the McGill Pain Questionnaire and the 9 item BPI at 4 weeks.<br><br>Other outcomes: sickness-related impairment; physical and emotional wellbeing; QOL; cognitive status; symptom prevalence, characteristics and degree of stress; psychological state and psychological wellbeing; mood; appetite. |
| Ware, M & Lynch, M (NCT02324777)<br>· Crossover RCT<br>· Sponsored by Prairie Plant Systems Inc., McGill University Health Center, Dalhousie University, Algorithme Pharma Inc., Research Institute of the McGill University Health Center<br>· May 2016 | Cannabinoid Profile Investigation of Vapourized Cannabis in Patients With Osteoarthritis of the Knee (CAPRI) | To determine the analgesic dose-response characteristics of vaporized cannabinoids with varying degrees of THC/CBD ratios. | 40 adults with painful osteoarthritis of the knee (NRS Pain intensity score ≥ 4 out of 10).<br><br>100 mg of finely ground herbal cannabis drug product formulation administered via the Volcano® Medic Vapourizer (percentages are mass fractions):<br>1. 21.9% THC and 0.8% CBD<br>2. 15.0% THC and 5.0% CBD<br>3. 9.0% THC and 9.5% CBD<br>4. 3.8% THC and 10.0% CBD<br>5. 0.6% THC and 13.0% CBD<br>6. Placebo: < 0.3% THC and < 0.3% CBD<br>Participants to be randomly assigned to | Change in VAS pain intensity at 3 hours post-dose (measured every 15 minutes).<br><br>Other outcomes: Stiffness; physical, social and emotional functional outcomes; psychoactive adverse events; global rating of preference; VAS of drug effect; change in blood pressure and heart rate; hematocrit, liver, and renal function (1 week after final exposure) |

| PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion | Study Title | Purpose of Study | Participants; Intervention(s)/ Comparator | Outcomes and Timing |
|---|---|---|---|---|
| | | | receive all 6 formulations in random order for one day of exposure (6-days washout) | |
| Wilsey, BL (NCT02460692)<br>· Parallel RCT<br>· Sponsored by the University of California, San Diego & National Institute on Drug Abuse (NIDA)<br>· May 2020 | Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain | To assess whether treatment with vaporized cannabis or dronabinol reduces spontaneous and evoked pain more than placebo, whether there are any differences between the 2 active treatments in terms of interference with activities of daily living, mood, neuropsychological function, and psychomimetic side-effects (high, stoned, *etc*). | 120 adults with chronic low back pain (painDETECT questionnaire score ≥ 19, and daily NRS Pain intensity ≥ 3 out of 10).<br><br>One of the following for 8 weeks:<br>1. Vaporized cannabis: 3.5% THC<br>2. Dronabinol<br>3. Placebo | 11-point pain intensity NRS.<br><br>Other outcomes: mood; depression; psychoactive effects; withdrawal; marijuana subscale of the Addiction Research Center Inventory; Cold Pressor Test; Hopkins Verbal Learning Test; Grooved Pegboard Test; Wechsler Adult Intelligence Scale-III Digit Symbol Test; and driving simulation. |
| Zhao, H (5R01DA030424-03)<br>· Crossover RCT<br>· Sponsored by National Institute on Drug Abuse (NIDA)<br>· May 2016 | The effect of vaporized cannabis on neuropathic pain in spinal cord injury | To evaluate the analgesic effects of vaporized cannabis in patients with neuropathic pain due to spinal cord injury, as well as evaluate other potential benefits and side effects, including the effect of different strengths of cannabis on mood, cognition, and psychomotor performance. | Patients with neuropathic pain due to spinal cord injury.<br><br>1. Vaporized cannabis: 3.5% THC<br>2. Vaporized cannabis: 7.0% THC<br>3. Placebo | Pain intensity and pain unpleasantness (timing NR).<br><br>Other outcomes: neuropsychological functioning (attention, learning and memory, and psychomotor performance), emotional response/mood. |

Abbreviations: BPI = Brief Pain Inventory; CBD = cannabidiol; NR = not reported; NRS = Numeric Rating Scale; QOL = quality of life; RCT = randomized controlled trial; THC = tetrahydrocannabinol; VAS = Visual Analog Scale.

[a] Unpublished studies completed in June 2015 or later are included in the table in order to allow time for publication.

### *PTSD*

There are 2 recently initiated studies on the benefits and harms of cannabis for PTSD using an RCT design that should add to the body of evidence (Table 7). The Colorado Department of Public Health and Environment has funded a "triple-blind cross-over placebo-controlled" trial to determine the effects of smoking 4 different types of cannabis with varying THC and CBD content on PTSD symptoms in Veterans (Bonn-Miller, NCT02759185). The anticipated completion date of the trial is April 2019. Second, Eades et al are conducting a study sponsored by Tilray and the University of British Columbia (NCT02517424). This study is a cross-over RCT of 42 adults with PTSD who will be administered differing amounts of THC and CBD (High/Low, High/High, and Low/Low) to compare PTSD outcomes as well as other mental and physical health outcomes.

There are also multiple ongoing studies of cannabis and PTSD that are not RCTs, or that investigate cannabis-related outcomes but do not specifically test the effectiveness of cannabis for reducing PTSD symptoms. For example, a VA-funded trial is described as investigating the impact of cognitive behavioral therapy for insomnia on cannabis cessation. Bonn-Miller and colleagues are investigating how cannabis use impacts PTSD and sleep in an unfunded observational study of 150 Veterans. Finally, another study funded by The Colorado Department of Public Health and Environment is assessing 150 individuals with PTSD to determine if recent medical or recreational cannabis use versus no cannabis use in the past 6 months is associated with differential trajectories of PTSD symptoms over the course of a year. Table 7 provides a summary of ongoing studies related to benefits and harms of cannabis for PTSD.

**Table 7. Ongoing Studies[a] of Cannabis for PTSD**

| PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion | Study Title | Purpose of Study | Participants; Intervention(s)/ Comparator | Primary Outcome and Timing |
|---|---|---|---|---|
| Babson, K (NCT02102230)<br>· Double-blind RCT<br>· Funded by VA Clinical Science Research and Development CDA-2<br>· August 2019 | The Impact of CBT-I on Cannabis Cessation Outcomes | To examine the role of a behavioral intervention for sleep on cannabis use frequency and insomnia symptoms among Veterans with CUD and insomnia. | 200 Veterans with CUD and insomnia. Randomly assigned to of the following conditions:<br>1. CBT for insomnia<br>2. CBT for insomnia + CBT-I coach (mobile app)<br>3. Placebo control (quasi-desensitization) | Change in cannabis use frequency, point prevalence abstinence, and change is sleep quality post-treatment and 6 months post-treatment. |
| Bedard-Gilligan, M (NCT02874898)<br>· Single Group Assignment<br>· Funded by the National Institute on Drug Abuse (NIDA)<br>· April 2019 | Marijuana Use, Extinction Learning, and Exposure Therapy in Individuals with PTSD | To examine the effects of cannabis use on extinction learning using both a standard discriminative conditioning and extinction task at pre-treatment and response to an exposure treatment protocol. To also examine ability of a brief protocol to decrease PTSD and retain individuals in treatment for patients with and without cannabis use. | 72 men and women (ages 18-65) with chronic PTSD (≥ 3 months); half are heavy cannabis smokers (≥ 5 days per week) and half are non- cannabis users (no use in last 3 months).<br><br>Brief imaginal exposure protocol (6 daily sessions) for PTSD is provided to all participants. | PTSD severity (PSS-I severity) at post-treatment and 12-week follow-up; treatment drop-out (completion of less than 5 imaginal exposure sessions).<br><br>Other Outcomes: Depression symptoms (QIDS), cannabis use and problems (MPS, Marijuana Frequency and Quantity Scale) assessed at post-treatment and 12-week follow-up. |
| Bonn-Miller, M (NCT02759185)<br>· Crossover RCT<br>· Funded by The Colorado Department of Public Health and Environment<br>· April 2019 | Placebo-Controlled, Triple Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress | To evaluate the safety and efficacy of smoked cannabis of 4 different concentrations among participants with chronic, treatment-resistant combat-related PTSD. | 76 Veterans with service-related PTSD (≥ 6 months duration, moderate severity at baseline)<br><br>Smoked cannabis up to 1.8 g/day for 3 weeks:<br>1. High THC (more THC than CBD)<br>2. High CBD (more CBD than THC)<br>3. High THC/High CBD (equal amounts)<br>4. Placebo cannabis (low levels THC/CBD) | Change in CAPS Global Severity Score at 3 weeks and 8 weeks after randomization.<br><br>Other outcomes: depression and anxiety symptoms; general and psychosocial functioning; sleep quality; suicidal ideation; responses to cannabis; withdrawal; blood and urine tests. |

| PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion | Study Title | Purpose of Study | Participants; Intervention(s)/ Comparator | Primary Outcome and Timing |
|---|---|---|---|---|
| | Disorder (PTSD) | | Participants to receive 2 of the 4 types of cannabis during 2 stages, each lasting 3 weeks (2-week washout). | |
| Bonn-Miller, M<br>· Observational Study<br>· Unfunded<br>· June 2017 | Evaluation of Veteran Cannabis Use and Impact on Sleep and PTSD | The present study aims to fill a large gap in the literature by providing an a priori test of the impact of cannabis, including variations in cannabinoids, on individual sleep, PTSD, and psychosocial functioning. | 150 Veterans currently using cannabis and are members of the Santa Cruz Veterans Alliance.<br><br>Data are collected through repeated survey assessments every other week. In addition, all product provided to Veterans by the Santa Cruz Veterans Alliance is tested for cannabinoid content by an independent laboratory. | The association between cannabinoid concentration and symptoms of PTSD, sleep, and psychosocial functioning over time among cannabis-using Veterans. |
| Bonn-Miller, M<br>· Observational Study<br>· Funded by The Colorado Department of Public Health and Environment<br>· September 2018 | Treating PTSD with Marijuana: Clinical and Functional Outcomes | The proposed study aims to determine whether, among a sample of Colorado residents (Veterans and non-Veterans), individuals with PTSD who obtain and use cannabis from a medical or recreational dispensary, compared to a matched sample of individuals with PTSD who report no current cannabis use at study baseline (control), will exhibit lower PTSD symptom severity. | 150 adult Colorado residents with PTSD, half using cannabis from a medical or recreational dispensary in Colorado and half reporting no recent (past 6 month) cannabis use.<br><br>Assessment at baseline and 3-, 6-, 9-, and 12-months following baseline. Measures include interview (MINI, CAPS-5, TLFB), self-report, computerized neuro-psych assessments, and actigraphy for 1 week following each assessment point, and urine tests for objective verification of use status. Further, those using cannabis will report on the cannabis used and the dispensary from which it is obtained, and a sample will be procured and tested for cannabinoid and terpene content. | PTSD symptom severity, as indexed by: (1) Self-reported overall symptom severity at each time point as assessed by the CAPS-5; (2) Self-reported and objective sleep quality at each time point as assessed by the PSQI and actigraphy; (3) Interview-based diagnosis at 12-month follow-up as assessed by the CAPS-5.<br><br>Secondary Outcomes (assessed at each timepoint): (1) self-reported and objective psychosocial functioning; (2) suicidal ideation; (3) engagement in medical and psychological services. |
| Browne, K<br>· Mixed Methods | Characterizing Cannabis Use in | The objective of this study is to build our | Veterans diagnosed with PTSD who report at least weekly cannabis use will be | · Conduct an online survey in order to characterize cannabis use patterns |

| PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion | Study Title | Purpose of Study | Participants; Intervention(s)/ Comparator | Primary Outcome and Timing |
|---|---|---|---|---|
| Observational Study<br>· University of Washington Alcohol and Drug Abuse Institute<br>· VA Puget Sound Health Care System Research & Development<br>· September 2017 | Veterans with PTSD | understanding of cannabis use in Veterans with PTSD by: 1) characterizing cannabis use patterns and motives in Veterans with PTSD symptoms, 2) conducting a prospective examination of the day-to-day relations between PTSD symptoms and cannabis use, and 3) conducting the first effort to qualitatively describe the perspective of Veterans with PTSD who use cannabis. | invited to participate in:<br>1. Anonymous online survey (n=200)<br>2. Daily symptom and use monitoring (*ie*, IVR; n=48)<br>3. In-depth qualitative interviews (n=30)<br>4. Blood draw for cannabis biomarkers (n=48) | and replicate previous findings related to PTSD symptoms, cannabis use, motives for use, and craving.<br>· Examine (via IVR) day-to-day relations between cannabis use and PTSD symptoms along with a one-time assessment of cannabis use motives.<br>· To conduct key informant interviews in order to characterize Veterans' beliefs about the relations between cannabis use and mental health symptoms and treatment, including the role of cannabis in PTSD symptom management, treatment for cannabis use, and PTSD treatment. |
| Eades, J (NCT02517424)<br>· Crossover RCT<br>· Sponsored by Tilray and the University of British Columbia<br>· December 2018 | Placebo-Controlled, Triple-Blind, Crossover Study of the Safety and Efficacy of Three Different Potencies of Vaporized Cannabis in 42 Participants with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD) | To evaluate the safety and efficacy of vaporized cannabis of 3 different concentrations among participants with chronic, treatment-resistant PTSD. | 42 adults with PTSD (≥ 6 months duration, PCL-5 ≥ 40 at baseline). Approximately 50% police/military Veterans, 33-50% female, and 8-12% Aboriginal (First Nations, Metis, Inuit).<br><br>Cannabis administered via vaporization up to 2.0 g/day as needed:<br>1. High THC/Low CBD cannabis<br>2. High THC/High CBD cannabis<br>3. Low THC/Low CBD cannabis | Change in CAPS Global Severity Score at 3 weeks and 8 weeks after randomization.<br><br>Other outcomes: anxiety and depression symptoms; psychosocial functioning; preference; sleep quality; problems associated with cannabis use; suicidal thoughts or behaviors. |

Abbreviations: CAPS = Clinician-Administered PTSD Scale; CBD = cannabidiol; CBT = cognitive behavioral therapy; CDA-2 = VA Career Development Award 2; CUD = cannabis use disorder; IVR = interactive voice response; MINI = Mini International Neuropsychiatric Interview; MPS = Marijuana Problems Scale; TLFB = Timeline Followback interview; PCL = Post-traumatic Stress Disorder Checklist; PSQI = Pittsburgh Sleep Quality Index; PSS = Posttraumatic Stress Disorder Symptom Scale-Interview Version; PTSD = post-traumatic stress disorder; QIDS = Quick Inventory of Depressive Symptomatology; RCT = randomized controlled trial; THC = tetrahydrocannabinol; VA = Department of Veterans Affairs.

[a] Unpublished studies completed in June 2015 or later are included in the table in order to allow time for publication.

# SUMMARY AND DISCUSSION

We reviewed the literature examining the benefits of cannabis in chronic pain and PTSD populations, as well as literature examining potential harms relevant to these populations. Table 9 summarizes the evidence on the benefits and harms of cannabis use. Overall, we found an evidence base limited by a paucity of trials, methodologic deficiencies, and poor applicability to current general medical practice. There is 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 pain, spasticity, and sleep in populations with MS. However, the results are inconsistent across studies, the long-term benefits and harms are unclear given the brief follow-up duration of most studies, and there is insufficient evidence of effects on quality of life or functional status. The applicability 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.[103] There is insufficient evidence to determine the effects of cannabis in populations other than MS.

We found no trials 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.

Even though we did not find strong evidence of benefit, clinicians will still need to counsel patients with chronic pain or PTSD who are using or requesting to use cannabis for therapeutic or recreational purposes. Therefore, understanding what is known and not known about potential harms of cannabis is also important.

There is moderate-strength evidence that at least light to moderate cannabis smoking does not adversely impact lung function over about 20 years. However, there is no evidence examining the effects in older patients, or those with multiple medical comorbidities. Moreover, the limited evidence examining the effects of heavy use (the equivalent of one joint daily for 7 years or more) suggests a possible deleterious effect on lung function over time.

There is low-strength evidence that light to moderate cannabis use is not associated with lung cancer or head and neck cancer diagnoses independent of tobacco use, but the data are limited to case-control studies and do not address heavy use. However, there is at least biologic plausibility that cannabis smoking has the potential to increase the risk of lung cancer based on data showing that cannabis use is associated with macrophage dysfunction, tar deposition, and cytologic abnormalities.[104] There is insufficient evidence about effects on other cancers.

While there is a biologically plausible link between cannabis use and cardiovascular risk given data showing adverse effects on hemodynamic parameters and anginal threshold,[52] we found insufficient evidence examining whether cannabis use is associated with cardiovascular events over the long-term.

There are potentially serious mental health and adverse cognitive effects of cannabis, though there is not enough data to characterize the magnitude of risk or in whom the risk is highest. Cannabis appears to be associated with at least small, short-term deleterious effects on cognition in active users, but long-term effects in past users are uncertain. We found no data on the risk of mania or suicidality in chronic pain or PTSD populations specifically, but cannabis has been associated with these risks in other populations.

We found stronger data suggesting an association between cannabis use and the development of psychotic symptoms over the long-term and limited data suggesting a risk of acute psychosis immediately following cannabis use. There is no data to directly assess whether the risk of psychotic symptoms is related specifically to the THC content of the formulation used, but this is biologically plausible, there are case reports of severe acute psychosis after ingestion of edibles with very high THC concentrations,[101] and CBD may in fact have antipsychotic effects.[105,106]

Intuitively, patients with PTSD or patients with serious mental illness, especially those already suffering with hypervigilance, agitation, and anger management issues, might be at higher risk of suffering serious consequences should they experience any adverse effects, especially psychotic symptoms. Observational studies in PTSD populations suggest a signal for harm, though the studies are inconclusive.[39,40] While clinicians do not have adequate data to quantify risks and benefits for PTSD patients, they might consider discussing potentially serious mental health adverse effects during shared decision-making discussions. They also might consider discussing other evidence-based interventions recommended by the 2010 VA/Department of Defense (DoD) Clinical Practice Guideline for PTSD.[107] Specifically, “A” level interventions with “strong recommendations” for use include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and “trauma-focused psychotherapy that includes components of exposure and/or cognitive restructuring, or stress inoculation training.” Similar recommendations based on research synthesized through 2013 were made by the Institute of Medicine (IOM).[108] This IOM report noted, “A 2013 meta-analysis of treatment efficacy for PTSD was consistent with the VA/DoD guideline in finding that cognitive therapy including cognitive processing therapy (CPT); exposure therapy, such as prolonged exposure (PE) therapy; and eye movement desensitization and reprocessing (EMDR) were effective psychotherapies, and SSRIs were the most effective pharmacotherapies.”

Finally, 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 are reviewed above in the emerging harms section and include infectious disease complications, cannabis hyperemesis syndrome, inadvertent overingestion of THC and associated psychosis related to edible cannabis, and violent behavior.

Currently, the Centers for Disease Control and Prevention recommends the use of evidence-based non-pharmacologic therapy – such as physical therapy, exercise therapy, and psychologic interventions – and non-opioid pharmacologic therapy as the preferred modalities to treat chronic pain.[109] After trying first-line options, clinicians may continue to struggle with the often difficult treatment of chronic pain in patients who have not responded. Cannabis may be perceived as a safer strategy in these patients.[110] Indeed, the scale and severity of adverse events, including death, seen with opioids have not been described with cannabis use in the literature (though there is also simply less research available on cannabis than opioids).[110] However, there are no studies directly comparing cannabis to opioids, and there is no good-quality data examining what impact cannabis use actually has on opioid use and opioid-related adverse effects. We found no observational studies that met inclusion criteria, but a growing body of cross-sectional literature suggests negative opioid-related correlates among individuals who use cannabis and opioids concurrently. These include opioid misuse;[9,10,77,111] a greater number of opioid refills;[77] a longer duration of opioid use; a higher dose of opioid medication prescribed;[9] and endorsement of using opioids and other pain medications without a prescription.[112] By contrast, one recent open-label study found that pain scores and opioid use decreased over 6 months in a chronic pain population who initiated cannabis treatment, though confidence in the findings is limited by the lack of a control group and the large number of participants lost to follow-up.[113]

## LIMITATIONS

There are a number of limitations to this body of evidence beyond the paucity of well-conducted trials of treatment efficacy. The methodologic issues with each particular trial and observational study are detailed in the quality assessment tables (Appendix C). Applying available data to clinical practice is challenging for several reasons. The data on effectiveness largely comes from studies examining cannabis formulations with known THC and CBD content (most with 1:1 to 2:1 ratio). While dispensaries are increasingly labeling the content of offered products, there are often important discrepancies between labeled and measured content.[103]

While trials were often able to standardize the dosing of the active ingredients in cannabis (THC and CBD), most of the observational studies were not able to characterize the amount of cannabis consumed beyond rough measures such as the average number of joints smoked per day. No observational studies were able to account for the potency of cannabis consumed. In a sense, this lack of precise dosing information reflects the reality of clinical practice and, therefore, the crude approximations of exposure in most studies may still provide useful information. Nevertheless, the evidence base is limited in providing very exact dose-response information beyond the relative distinctions between very heavy and infrequent use. Moreover, the evidence base on harms is limited because there are relatively few patients included in studies with a history of heavy and prolonged cannabis use.

There are also limitations in our approach to synthesizing this literature. Given the broad scope of our review, we relied on existing systematic reviews when available to identify the best available evidence. We believe we are unlikely to have missed important studies both because we only used systematic reviews meeting key quality criteria and because we searched the primary literature for more recent studies not captured by the reviews. As our intention was to provide an overview of evidence that would be important for clinicians to know in counseling patients, we included studies of harms in general populations when we thought it unlikely that the conditions of chronic pain or PTSD would independently contribute to risk (*eg*, pulmonary or cardiovascular harms when concurrent tobacco use was accounted for). Though we made these determinations through group discussion and in conjunction with a panel of experts, we acknowledge that the choices are inherently subjective to some degree and that there is still the possibility that there are residual confounders relevant to chronic pain or PTSD accounting for observed effects.

## FUTURE RESEARCH

There is virtually no conclusive information about the benefits of cannabis in chronic pain or PTSD populations and limited information on harms, so methodologically strong research in almost any area of inquiry is likely to add to the strength of evidence. Fortunately, it appears that the US government is poised to lift restrictions on access to cannabis for research which should help speed the development of this evidence base which has lagged far behind policy changes regarding the use of cannabis for medical purposes in many states.[114] Also, there are studies currently being done which should also add to the evidence base in the near future (and are summarized in Key Question 4). Table 8 lists opportunities for future research in each of the areas we reviewed.

**Table 8. Suggestions for Future Research**

| Area of Inquiry | Research Suggestions |
|---|---|
| Efficacy of cannabis for treating chronic pain | · Populations other than MS or neuropathic pain<br>· Studies with longer follow-up duration<br>· Studies with cannabis-naïve patients<br>· Compare cannabis to other active treatments for pain, including opioids<br>· Use cannabis preparations that are routinely available to consumers in the US, especially given legalization in more states<br>· Examine the effects of different THC:CBD ratio preparations, and more study of CBD preparations<br>· Obtain blood levels of THC and CBD to assess actual level of drug exposure |
| Efficacy of cannabis for treating PTSD | · RCT of treatment<br>· Trials comparing to cognitive behavioral therapy, other standard treatments |
| CUD | · Studies assessing risk of CUD in patients using cannabis |
| Pulmonary harms | · Observational studies in older and multimorbidity populations |
| Cardiovascular harms | · Observational studies with more comprehensive information about exposure history |
| Cancer | · Larger scale observational studies of lung cancer reflecting patterns of use in the US<br>· More studies to investigate the insufficient evidence of a possible link with testicular and transitional cell cancers |
| Mental health harms | · Studies on acute psychosis in chronic pain and PTSD populations<br>· Identification of non-schizophrenic patients at high risk for psychosis<br>· Risk mitigation strategies for cannabis-induced psychosis<br>· Studies on mania and suicidality in PTSD populations<br>· Effects on sleep |
| Cognitive function | · Studies in chronic pain and PTSD populations |
| Emerging harms | · Studies characterizing cannabis hyperemesis syndrome in a larger number of patients<br>· Studies examining treatment and follow-up of patients with cannabis hyperemesis syndrome |

## 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 that cannabis may be helpful in improving pain and spasticity in selected populations with MS, but there is insufficient evidence in other populations. There is insufficient evidence examining the effects of cannabis in PTSD populations. Cannabis is associated with an increased risk of short-term adverse effects, but data on its effects on long-term physical health vary; harms in older patients or those with multiple comorbidities have not been studied. Cannabis has been associated with short-term cognitive impairment 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.

**Table 9. Summary of Evidence for the Benefits and Harms of Cannabis in Chronic Pain or PTSD Populations**

| | N studies | Findings | Strength of Evidence[a] | Comments |
|---|---|---|---|---|
| ***Chronic Pain*** | | | | |
| · Multiple sclerosis (MS) | 4 Low ROB studies (combined N=1017; 24 to 424 per study):<br>- 2 of THC/CBD capsules<br>- 1 of nabiximols<br>- 1 of sublingual spray delivering THC, CBD, or THC/CBD combined<br><br>3 Unclear ROB studies of nabiximols (combined N=562; 36 to 337 per study)<br><br>7 High ROB studies (combined N=430; 13 to 160 per study):<br>- 3 of nabiximols<br>- 2 of THC/CBD capsules<br>- 1 of smoked THC<br>- 1 of oral THC | **Favorable effect on pain and spasticity:**<br>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.<br>A 12-week study of nabiximols (2.7 mg THC/2.5 mg CBD oromucosal spray) reported significant improvement in spasticity.<br>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):<br>- 2 of THC/CBD capsules<br>- 1 of nabiximols<br>- 1 of sublingual spray delivering THC, CBD, or THC/CBD combined | **Other outcomes:**<br>**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.<br>**Other:**<br>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)<br><br>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<br><br>Only one study of nabiximols – not tested otherwise |

| | N studies | Findings | Strength of Evidence[a] | Comments |
|---|---|---|---|---|
| · Neuropathic pain | 2 Low ROB studies (combined N=62):<br>- 1 of vaporized (N=39)<br>- 1 of smoked THC (N=23)<br><br>4 Unclear ROB studies of nabiximols (combined N=681; 30 to 339 per study)<br><br>12 High ROB studies (combined N=1304; 16 to 380 per study):<br>- 9 of nabiximols<br>- 3 of smoked cannabis | **Small, inconsistent improvements in pain:**<br>A study in which 25 mg of cannabis containing 9.4% THC was delivered by a single smoked inhalation 3 times daily reported significant improvements in average daily pain intensity.<br>Another study reported short-term pain relief with inhaled cannabis at doses of 3.53% and 1.29% THC administered using a vaporizer. Peak pain relief appeared to occur after the second dosing at 180 minutes, then dropped off 1 to 2 hours later. | Insufficient | Few patients enrolled in the low ROB studies; statistically significant results but likely below clinical significance thresholds; marked differences among studies in dosing and delivery mechanism |
| | 1 Low ROB study of smoked THC (N=23) | **Other outcomes reported in low ROB studies:**<br>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:<br>- 1 trial of sublingual spray delivering THC, CBD, or THC/CBD combined (N=34)<br>- 1 observational study of cannabis containing 12.5% THC (smoked, oral, or vaporized) (N=431)<br><br>3 Unclear ROB studies of nabiximols (combined N=428; 10 to 360 per study)<br><br>3 High ROB studies (combined N=265; 18 to 177 per study):<br>- 2 of nabiximols<br>- 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:<br>- 1 Medium ROB (N=2276)<br>- 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 | 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<br>Ø Pulmonary function | 2 Low ROB prospective cohort studies with 20-32 years follow-up (combined N=6053)<br><br>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.<br>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<br>*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:<br>- 1 case-crossover (N=3882)<br>- 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.<br>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)<br><br>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 | 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<br>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<br><br>7 studies including patients without psychotic symptoms at baseline:<br>- 3 Low ROB studies<br>- 3 Medium ROB studies<br>- 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 |

| | N studies | Findings | Strength of Evidence[a] | Comments |
|---|---|---|---|---|
| Ø Cognitive effects | 1 systematic review of 33 studies | Active long-term cannabis use associated with small negative effects on all aspects of cognition.<br>Mixed, inconsistent findings on long-term effects in past users. | Moderate<br>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 |
| Ø CUD | No studies examining risk of CUD over time, or rates in cannabis-using populations | --- | No evidence | In cross-sectional studies, the prevalence of CUD in chronic pain populations was about 2%, though the rate among a group of cannabis-using patients is unclear |

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.

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# APPENDIX A. SEARCH STRATEGIES

## Databases/Websites

- Ovid Medline
- PubMed (non-Medline materials)
- Elsevier EMBASE
- Ovid PsycINFO
- PILOTS Database (PTSD search only)
- EBM Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*)
- Conference Papers Index

- Clinicaltrials.gov
- International Clinical Trials Registry Platform (WHO ICTRP)
- ISRCTN

- NIH Reporter
- AHRQ Gold

- American Cancer Society Database of Studies

## Search Strategies

**Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to December Week 5 2015,

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** January 11, 2016

Date Searched: Tuesday January 12, 2016

| # | Searches | Results |
|---|---|---|
| 1 | medical marijuana/ or cannabis/ or marijuana smoking/ or exp Cannabinoids/ or Cannabaceae/ | 18682 |
| 2 | (cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw. | 38570 |
| 3 | 1 or 2 | 41269 |
| 4 | pain/ or acute pain/ or breakthrough pain/ or mastodynia/ or exp musculoskeletal pain/ or exp back pain/ or chronic pain/ or facial pain/ or headache/ or metatarsalgia/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or pain, referred/ | 205083 |
| 5 | (pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*).tw. | 770253 |
| 6 | 4 or 5 | 823437 |
| 7 | 3 and 6 | 2868 |
| 8 | 7 and (humans/ not animals/) | 1331 |
| 9 | 7 not (humans/ or animals/) | 312 |
| 10 | 8 or 9 | 1643 |
| 11 | limit 10 to (case reports or comment or editorial or letter or news) | 293 |

| | | |
|---|---|---|
| 12 | cross-section*.tw. | 243912 |
| 13 | 10 not (11 or 12) | 1313 |
| 14 | limit 13 to english language | 1211 |
| 15 | stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ | 26019 |
| 16 | (PTSD or post-traumatic stress or posttraumatic stress).ti,ab. | 23732 |
| 17 | 15 or 16 | 32767 |
| 18 | 3 and 17 | 210 |
| 19 | 18 and (humans/ not animals/) | 131 |
| 20 | 18 not (humans/ or animals/) | 31 |
| 21 | 19 or 20 | 162 |
| 22 | limit 21 to (case reports or comment or editorial or letter or news) | 9 |
| 23 | cross-section*.tw. | 243912 |
| 24 | 21 not (22 or 23) | 140 |
| 25 | limit 24 to english language | 132 |
| 26 | medical marijuana/ or cannabis/ or marijuana smoking/ or marijuana abuse/ or exp Cannabinoids/ or Cannabaceae/ | 22185 |
| 27 | (cannabis* or canabis* or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana* or marihuana* or hashish* or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw. | 38598 |
| 28 | 26 or 27 | 41948 |
| 29 | (ae or co or de).fs. | 5311331 |
| 30 | (harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw. | 3065069 |
| 31 | 29 or 30 | 7263273 |
| 32 | 28 and 31 | 25510 |
| 33 | limit 32 to (meta analysis or systematic reviews) | 422 |
| 34 | 32 not 33 | 25088 |
| 35 | 34 and (humans/ not animals/) | 13847 |
| 36 | 34 not (humans/ or animals/) | 1758 |
| 37 | 35 or 36 | 15605 |
| 38 | limit 37 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") | 8086 |
| 39 | limit 38 to (case reports or comment or editorial or letter or news) | 1030 |
| 40 | cross-section*.tw. | 243912 |
| 41 | 38 not (39 or 40) | 6701 |
| 42 | limit 41 to english language | 6238 |

**PubMed**

Date searched: Friday May 6, 2016

| # | Searches | Results |
|---|---|---|
| #10 | Search (#7 OR #8 OR #9) | 444 |
| #9 | Search ((((((cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab]))))) AND (((harm[tiab] OR harms[tiab] OR harmful[tiab] OR safe[tiab] OR safety[tiab] OR side effect*[tiab] OR undesirable effect*[tiab] OR treatment emergent[tiab] OR tolerability[tiab] OR toxic*[tiab] OR adrs[tiab] OR damag*[tiab] OR impair*[tiab] OR disorder*[tiab] OR abuse*[tiab] OR addict*[tiab] OR withdrawal*[tiab] OR adverse effect[tiab] OR adverse effects[tiab] OR adverse reaction[tiab] OR adverse reactions[tiab] OR adverse event[tiab] OR adverse events[tiab] OR adverse outcome[tiab] OR adverse outcomes[tiab])))) AND (((pubmednotmedline[sb] OR inprocess[sb] OR [publisher[sb]))))) AND (((((meta-review*[tiab] OR meta-epidemiolog*[tiab] OR metaepidemiolog*[tiab] OR horizon scan*[tiab] OR systematic* review*[tiab] OR systematic effectiveness review*[tiab] OR comparative effectiveness review*[tiab] OR evidence review*[tiab] OR landscape review*[tiab] OR quantitative review*[tiab] OR qualitative review*or integrative review*or mixed-method* review*or mixed method* review*[tiab] OR research review*or scoping review*[tiab] OR umbrella review*or review of review*[tiab] OR updat* review*[tiab] OR cochrane review*or campbell review*[tiab])) OR (research* aggregat*[tiab] OR evidence aggregat*[tiab] OR evidence map*[tiab] OR evidence brief*[tiab] OR evidence summar*[tiab] OR rapid review*or mini* review*or pragmatic review*or targeted review*or focused review*or brief review*or short review*[tiab])) OR (meta-analy*[tiab] OR metaanaly*[tiab] OR meta-meta-analy*[tiab] OR evidence synthes*[tiab] OR knowledge synthes*[tiab] OR quantitative synthes*[tiab] OR research synthes*[tiab] OR pooled analy*[tiab] OR indirect* comparison*[tiab] OR mixed* comparison*[tiab])) OR (HTA[tiab] OR health technology assessment*[tiab] OR mini-HTA*[tiab] OR relative effectiveness assessment*[tiab])) | 16 |
| #8 | Search (((((cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab]))))) AND (((PTSD[tiab] OR post-traumatic stress[tiab] OR posttraumatic stress[tiab])))) AND (((pubmednotmedline[sb] OR inprocess[sb] OR [publisher[sb])))) | 39 |
| #7 | Search (((((cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab]))))) AND (((pain[tiab] OR pains[tiab] OR painful*[tiab] OR migraine*[tiab] OR headache*[tiab] OR neuropath*[tiab] OR neuralgia*[tiab] OR arthriti*[tiab] OR fibromyalg*[tiab])))) AND (((pubmednotmedline[sb] OR inprocess[sb] OR [publisher[sb])))) | 392 |
| #6 | Search ((meta-review*[tiab] OR meta-epidemiolog*[tiab] OR metaepidemiolog*[tiab] OR horizon scan*[tiab] OR systematic* review*[tiab] OR systematic effectiveness review*[tiab] OR comparative effectiveness review*[tiab] OR evidence review*[tiab] OR | 78086 |

| | | |
|---|---|---|
| | landscape review*[tiab] OR quantitative review*[tiab] OR qualitative review*or integrative review*or mixed-method* review*or mixed method* review*[tiab] OR research review*or scoping review*[tiab] OR umbrella review*or review of review*[tiab] OR updat* review*[tiab] OR cochrane review*or campbell review*[tiab])) OR (research* aggregat*[tiab] OR evidence aggregat*[tiab] OR evidence map*[tiab] OR evidence brief*[tiab] OR evidence summar*[tiab] OR rapid review*or mini* review*or pragmatic review*or targeted review*or focused review*or brief review*or short review*[tiab]) OR (meta-analy*[tiab] OR metaanaly*[tiab] OR meta-meta-analy*[tiab] OR evidence synthes*[tiab] OR knowledge synthes*[tiab] OR quantitative synthes*[tiab] OR research synthes*[tiab] OR pooled analy*[tiab] OR indirect* comparison*[tiab] OR mixed* comparison*[tiab]) OR (HTA[tiab] OR health technology assessment*[tiab] OR mini-HTA*[tiab] OR relative effectiveness assessment*[tiab])) | |
| #5 | Search (pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb]) | 2833028 |
| #4 | Search (harm[tiab] OR harms[tiab] OR harmful[tiab] OR safe[tiab] OR safety[tiab] OR side effect*[tiab] OR undesirable effect*[tiab] OR treatment emergent[tiab] OR tolerability[tiab] OR toxic*[tiab] OR adrs[tiab] OR damag*[tiab] OR impair*[tiab] OR disorder*[tiab] OR abuse*[tiab] OR addict*[tiab] OR withdrawal*[tiab] OR adverse effect[tiab] OR adverse effects[tiab] OR adverse reaction[tiab] OR adverse reactions[tiab] OR adverse event[tiab] OR adverse events[tiab] OR adverse outcome[tiab] OR adverse outcomes[tiab]) | 3137250 |
| #3 | Search (PTSD[tiab] OR post-traumatic stress[tiab] OR posttraumatic stress[tiab]) | 24584 |
| #2 | Search (pain[tiab] OR pains[tiab] OR painful*[tiab] OR migraine*[tiab] OR headache*[tiab] OR neuropath*[tiab] OR neuralgia*[tiab] OR arthriti*[tiab] OR fibromyalg*[tiab]) | 788713 |
| #1 | Search (cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab]) | 39258 |

## EMBASE.COM

Date Searched: Tuesday May 10, 2016

| # | Searches | Results |
|---|---|---|
| #1 | 'medical cannabis'/mj OR 'cannabis'/mj OR 'cannabis smoking'/mj OR 'cannabinoid'/exp/mj OR 'cannabaceae'/mj | 28,447 |
| #2 | cannabis:ab,ti OR canabis:ab,ti OR cannabinoid*:ab,ti OR cannabidiol*:ab,ti OR cbd:ab,ti OR cannabacae:ab,ti OR marijuana:ab,ti OR marihuana:ab,ti OR hashish:ab,ti OR hash:ab,ti OR ganja:ab,ti OR ganjah:ab,ti OR hemp:ab,ti OR bhang:ab,ti OR charas:ab,ti OR thc:ab,ti OR tetrahydrocannabinol*:ab,ti OR 'tetra hydrocannabinol*':ab,ti OR '9 tetrahydrocannabinol*':ab,ti OR 9tetrahydrocannabinol*:ab,ti OR 'delta*9*tetrahydrocannabinol 11carboxylic acid':ab,ti | 52,180 |
| #3 | #1 OR #2 | 57,164 |
| #4 | 'pain'/mj OR 'breakthrough pain'/mj OR 'mastalgia'/mj OR 'musculoskeletal pain'/mj OR 'low back pain'/mj OR 'backache'/exp/mj OR 'chronic pain'/mj OR 'face pain'/mj OR 'headache and facial pain'/exp/mj OR 'metatarsalgia'/mj OR 'neck pain'/mj OR 'neuralgia'/exp/mj OR 'nociceptive pain'/mj OR 'intractable pain'/mj OR 'referred pain'/mj | 243,955 |
| #5 | pain:ab,ti OR pains:ab,ti OR painful*:ab,ti OR migraine*:ab,ti OR headache*:ab,ti OR neuropath*:ab,ti OR neuralgia*:ab,ti OR arthriti*:ab,ti OR fibromyalg*:ab,ti | 1,079,039 |
| #6 | #4 OR #5 | 1,130,556 |
| #7 | #3 AND #6 | 4,553 |

| | | |
|---|---|---|
| #8 | #7 AND 'human'/de NOT 'nonhuman'/de | 2,655 |
| #9 | #8 AND ('editorial'/it OR 'letter'/it OR 'note'/it) | 80 |
| #10 | 'cross-section*':ab,ti | 297,421 |
| #11 | #8 NOT (#9 OR #10) | 2,516 |
| #12 | #8 NOT (#9 OR #10) AND [english]/lim | 2,308 |
| #13 | #8 NOT (#9 OR #10) AND [english]/lim AND [embase]/lim | 2,088 |
| #14 | 'posttraumatic stress disorder'/mj | 23,335 |
| #15 | ptsd:ab,ti OR 'post-traumatic stress':ab,ti OR 'posttraumatic stress':ab,ti | 29,813 |
| #16 | #14 OR #15 | 34,693 |
| #17 | #3 AND #16 | 314 |
| #18 | #17 AND 'human'/de NOT 'nonhuman'/de | 227 |
| #19 | #18 AND 'editorial'/it | 1 |
| #20 | 'cross-section*':ab,ti | 297,421 |
| #21 | #17 NOT (#19 OR #20) | 295 |
| #22 | #17 NOT (#19 OR #20) AND [english]/lim | 286 |
| #23 | #17 NOT (#19 OR #20) AND [english]/lim AND [embase]/lim | 267 |
| #24 | 'medical cannabis'/mj OR 'cannabis'/mj OR 'cannabis smoking'/mj OR 'cannabinoid'/exp/mj OR 'cannabaceae'/mj OR 'cannabis addiction'/mj | 30,213 |
| #25 | #2 OR #24 | 57,324 |
| #26 | #25 AND ('adverse drug reaction'/lnk OR 'complication'/lnk OR 'drug interaction'/lnk OR 'drug toxicity'/lnk OR 'side effect'/lnk) | 7,995 |
| #27 | harm:ab,ti OR harms:ab,ti OR harmful:ab,ti OR safe:ab,ti OR safety:ab,ti OR 'side effect*':ab,ti OR 'undesirable effect*':ab,ti OR 'treatment emergent':ab,ti OR tolerability:ab,ti OR toxic*:ab,ti OR adrs:ab,ti OR damag*:ab,ti OR impair*:ab,ti OR disorder*:ab,ti OR abuse*:ab,ti OR addict*:ab,ti OR withdrawal*:ab,ti OR 'adverse effect':ab,ti OR 'adverse effects':ab,ti OR 'adverse reaction':ab,ti OR 'adverse reactions':ab,ti OR 'adverse event':ab,ti OR 'adverse events':ab,ti OR 'adverse outcome':ab,ti OR 'adverse outcomes':ab,ti | 4,055,060 |
| #28 | #26 OR #27 | 4,059,085 |
| #29 | #25 AND #28 | 25,939 |
| #30 | #25 AND #28 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) | 373 |
| #31 | #25 AND #28 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [embase]/lim | 335 |
| #32 | #25 AND #28 ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [embase]/lim AND [english]/lim | 319 |
| #33 | #14 OR #24 OR #33 | 2,616 |
| #34 | #33 NOT [medline]/lim | 1,592 |

**PSYCINFO** 1806 to May Week 1 2016

Date Searched: Tuesday May 10, 2016

| # | Searches | Results |
|---|---|---|
| 1 | cannabis/ or hashish/ or marijuana/ or exp cannabinoids/ or tetrahydrocannabinol/ or cannabinoids/ or tetrahydrocannabinol/ or marijuana usage/ or marijuana/ | 11208 |
| 2 | (cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw. | 19269 |
| 3 | 1 or 2 | 19585 |
| 4 | pain/ or aphagia/ or back pain/ or chronic pain/ or headache/ or myofascial pain/ or neuralgia/ or neuropathic pain/ or somatoform pain disorder/ or headache/ or migraine headache/ or muscle contraction headache/ or neuralgia/ or trigeminal neuralgia/ or pain management/ | 50895 |

| | | |
|---|---|---|
| 5 | (pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*).tw. | 116341 |
| 6 | 4 or 5 | 117164 |
| 7 | 3 and 6 | 915 |
| 8 | limit 7 to human | 599 |
| 9 | limit 7 to animal | 346 |
| 10 | 7 not (8 or 9) | 35 |
| 11 | 8 or 10 | 634 |
| 12 | limit 11 to english language | 582 |
| 13 | limit 12 to ("column/opinion" or "comment/reply" or editorial or "erratum/correction" or letter) | 54 |
| 14 | 12 not 13 | 528 |
| 15 | cross-section*.tw. | 54490 |
| 16 | 14 not 15 | 505 |
| 17 | posttraumatic stress disorder/ or complex ptsd/ or desnos/ | 25127 |
| 18 | (PTSD or post-traumatic stress or posttraumatic stress).tw. | 33843 |
| 19 | 17 or 18 | 35163 |
| 20 | 3 and 19 | 209 |
| 21 | limit 20 to human | 178 |
| 22 | limit 20 to animal | 33 |
| 23 | 20 not (21 or 22) | 12 |
| 24 | 21 or 23 | 190 |
| 25 | limit 24 to english language | 173 |
| 26 | limit 25 to ("column/opinion" or "comment/reply" or editorial or letter) | 9 |
| 27 | 25 not 26 | 164 |
| 28 | cross-section*.tw. | 54490 |
| 29 | 27 not 28 | 155 |
| 30 | (harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw. | 816214 |
| 31 | 3 and 30 | 10099 |
| 32 | limit 31 to ("0830 systematic review" or 1200 meta analysis) | 111 |
| 33 | 16 or 29 or 32 | 750 |

**EBM Reviews Databases**

- Cochrane Central Register of Controlled Trials April 2016,
- Cochrane Database of Systematic Reviews 2005 to May 05, 2016,
- Database of Abstracts of Reviews of Effects 1st Quarter 2016,
- Health Technology Assessment 2nd Quarter 2016,
- NHS Economic Evaluation Database 1st Quarter 2016

Date Searched: Tuesday May 10, 2016

| # | Searches | Results |
|---|---|---|
| 1 | (cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw. | 2318 |
| 2 | (pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*).tw. | 100259 |
| 3 | 1 and 2 | 262 |
| 4 | (PTSD or post-traumatic stress or posttraumatic stress).tw. | 2401 |
| 5 | 1 and 4 | 20 |
| 6 | (harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw. | 274193 |
| 7 | 1 and 6 | 1227 |
| 8 | (meta-review* or meta-epidemiolog* or metaepidemiolog* or "horizon scan*" or ((systematic* or "systematic effectiveness" or "comparative effectiveness" or evidence or landscape or methodologic or methodological or quantitative or qualitative or integrative or mixed-method* or "mixed method*" or research or scoping or umbrella or "review* of" or updat* or cochrane or campbell) adj review*) or ((research* or evidence) adj2 aggregat*) or "evidence map*" or "evidence brief*" or "evidence summar*" or ((rapid or mini* or pragmatic or targeted or focused or brief or short*) adj2 (systematic or evidence or knowledge or review* or synthes*)) or meta-analy* or metaanaly* or "meta-meta-analy*" or "evidence synthes*" or "knowledge synthes*" or "quantitative synthes*" or "qualitative synthes*" or "research synthes*" or "integrat* data analys*" or (integrative adj1 analys?s) or "pooled analy*" or (indirect* adj2 comparison*) or (mixed* adj2 comparison*) or ((reliability or validity) adj generali?ation*) or meta-aggregat* or metaaggregat* or meta-ethnograph* or metaethnograph* or meta-interpret* or metainterpret* or meta-narrative* or metanarrative* or meta-review* or metareview* or meta-stud* or metastud* or meta-summar* or metasummar* or meta-synth* or metasynth* or "narrative synth*" or "narrative review*" or "qualitative comparative analy*" or "qualitative cross-case" or realist-synth* or "realist synth*" or "realist review*" or "thematic synth*" or "summary receiver operating characteristic*" or "comparative case study" or "comparative case studies").ti,ab. | 41555 |
| 9 | 7 and 8 | 116 |
| 10 | 3 or 5 or 9 | 343 |
| 11 | remove duplicates from 10 | 334 |
| 12 | limit 11 to english language | 308 |

**PILOTS: Published International Literature On Traumatic Stress Database**
(http://www.ptsd.va.gov/professional/pilots-database/)

Date Searched: Tuesday May 10, 2016

ab(cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9?tetrahydrocannabinol* OR DELTA?9?-tetrahydrocannabinol*)
AND
(PTSD OR posttraumatic stress OR post-traumatic stress)

| |
|---|
| = 177 results |

## COS Conference Papers Index

Date Searched: Tuesday May 17, 2016

| Set | Search | Results |
|---|---|---|
| **S4** | S1 or S2 or S3 | **711°** |
| **S3** | (cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9?tetrahydrocannabinol* OR DELTA?9?-tetrahydrocannabinol*) AND (harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse NEAR/2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)))Limits applied | **532°** |
| **S2** | (cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9?tetrahydrocannabinol* OR DELTA?9?-tetrahydrocannabinol*) AND (PTSD or post-traumatic stress or posttraumatic stress)Limits applied | **4°** |
| **S1** | (cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*) AND (pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*)Limits applied | **176°** |

## ClinicalTrials.gov

Date Searched: Monday May 16, 2015

| **Chronic Pain Search** |
|---|
| ( pain OR pains OR painful* OR migraine* OR headache* OR neuropath* OR neuralgia* OR arthriti* OR fibromyalg* ) [DISEASE] AND ( cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol* OR Δ9-THC ) [TREATMENT] = 74 results |

| **Post-traumatic Stress Disorder (PTSD) Search** |
|---|
| ( PTSD OR post-traumatic stress OR posttraumatic stress ) [DISEASE] AND ( cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol* ) [TREATMENT] = 6 results |

| **Harms Search** |
|---|
| ( harm* OR safety OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR tolerability OR toxic* OR adrs OR damag* OR impair* OR abuse* OR addict* OR withdrawal* OR "adverse effect*" OR "adverse event*" OR "adverse outcome*" ) AND ( ( cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol* ) AND NOT ( sativex OR namisol OR POT-4 OR Levodopa OR Carbidopa ) ) [TREATMENT] = 65 results |

### WHO ICTRP Database

Date Searched: Wednesday May 18, 2016

*Due to the 256 character limit for searches, the following searches were edited to fit within the proscribed limits. All terms removed were searched separately and found to not change or add additional results compared to the searches below.

| **Chronic Pain Search** |
|---|
| CONDITION = (pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*)<br>AND<br>INTERVENTION=(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or hashish or hash or ganja or ganjah or hemp or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9-tetrahydrocannabinol* or DELTA-9-tetrahydrocannabinol*)<br>= 45 results [24 results were from ClinicalTrials.gov, therefore only 21 results were downloaded] |

| **Post-traumatic Stress Disorder (PTSD) Search** |
|---|
| CONDITION = (PTSD or post-traumatic stress or posttraumatic stress)<br>AND<br>INTERVENTION=(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or hashish or hash or ganja or ganjah or hemp or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9-tetrahydrocannabinol* or DELTA-9-tetrahydrocannabinol*)<br>= 4 results [all results were from ClinicalTrials.gov so no results were downloaded] |

| **Harms Search** |
|---|
| CONDITION = (harm* or safe or safety or side effect* or undesirable effect* or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or adverse effect* or adverse reaction* or adverse event* or adverse outcome*)<br>AND<br>INTERVENTION=(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or hashish or hash or ganja or ganjah or hemp or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9-tetrahydrocannabinol* or DELTA-9-tetrahydrocannabinol*)<br>= 203 results [108 results were from ClinicalTrials.gov, therefore only 95 results were downloaded] |

### ISRCTN Registry

Date Searched: Tuesday May 24, 2016

| |
|---|
| Text search: cannabis or canabis or cannabinoid or cannabidiol or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol or tetra-hydrocannabinol or 9-tetrahydrocannabinol or DELTA-9-tetrahydrocannabinol (each keyword searched individually and results reviewed)<br>= 8 results |

### NIH RePORTER

Date Searched: Monday May 16, 2016

| **Chronic Pain Search** |
|---|
| ((cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol) AND (pain OR pains OR painful OR migraine OR migraines OR headache OR headaches OR neuropathy OR neuropathies OR neuralgia OR arthritis OR fibromyalgia)) \| Search in: Projects \| Limit Project Search To: Project |

| |
|---|
| Title,Project Abstracts | Limit Publication Search To: 2015-2016 = 50 results |

| Post-traumatic Stress Disorder (PTSD) Search |
|---|
| ((cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol) AND (PTSD OR post-traumatic stress OR posttraumatic stress)) Search in: Projects | Limit Project Search To: Project Title,Project Abstracts | Limit Publication Search To: 2015-2016 = 5 results |

| Harms Search |
|---|
| ((cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol) AND (harm OR harms OR harmful OR safe OR safety OR "side effects" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR adrs OR damage OR impaired OR impairing OR abuse OR addicted OR addiction OR addictions OR withdrawal OR "adverse effects" OR "adverse events" OR "adverse outcomes")) (Advanced), Search in: Projects | Limit Project Search To: Project Title,Project Abstracts | Limit Publication Search To: 2015-2016 = 220 results |

## AHRQ Gold (Grants On-Line Database)

Date Searched: Monday May 16, 2016

| |
|---|
| cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol = 0 results |

# APPENDIX B. STUDY SELECTION

## Inclusion codes, code definitions, and criteria

******Please note:*** Important background/discussion papers may be coded "B" followed by an exclusion code, with notes or key words. For example: **B–X2, pearl for references**

1. Does the intervention or exposure consist of cannabis preparations including marijuana, hashish, tincture, hashish oil, infusion, and plant extract (*eg*, Sativex)?

   No " STOP. **Code X1** *(Not relevant to topic)*

   Yes " Proceed to 2.

2. Is the article any of the following study designs or publication types:

   · Non-systematic or narrative review
   · Opinion/editorial
   · Cross-sectional study
   · Individual case report

   No " Proceed to 3.

   Yes " STOP. **Code X2** *(Excluded study design or publication type)*

3. Does the population include adults with chronic pain or PTSD?

   No " Go to 10.

   Yes: Chronic pain " Go to 20.

   Yes: PTSD " Go to 30.

**X4** = lab/blood/imaging findings

**X5** = superseded by previous high-quality systematic review

Questions 10-13 deal with KQ3 (harms) in the general population

10. Are the majority of the study subjects either of the following:
    - Younger than age 18
    - Adults diagnosed with a psychotic disorder (*eg*, schizophrenia)

No " Proceed to 11.

Yes " STOP. **Code X10** (*Excluded pop for KQ3*)

11. Does the study report any of the following harms:
    - Fungal infections
    - Cannabinoid hyperemesis syndrome
    - Other emerging harms (potential example: sudden onset of violent behaviors)

No " Proceed to 12.

Yes " **Code I-11** *(Gen pop, rare harms, KQ3)*
Proceed with items 12 and 13. **Add Code I-13 if applicable.**

12. Does the study report any of the following harms:
    - Psychotic symptoms
    - Cardiovascular events
    - Pulmonary/FEV1 outcomes
    - Infectious disease complications
    - Traffic collisions
    - Mortality

No " STOP. **Code X12** *(Gen pop, no harms of interest reported)*

Yes " Proceed to 13.

13. Does the study design include a control group? The control group should differ from the primary group in dose or duration of cannabis use (including no use). However, a study comparing onset of cannabis use during adolescence vs adulthood would be excluded.

No " STOP. **Code X13** (G*en pop, no control group for specified harms*)

Yes " STOP. **Code I-13** *(Gen pop, has control group for specified harms)*

Questions 20-22 deal with chronic pain

20. Do the study outcomes include either of the following:
    - Cannabis use disorder
    - Withdrawal symptoms

    No " Proceed to 21.

    Yes " **Code I-20** *(Pain pop, no controls needed for specified harms)*
    Proceed with items 21 and 22. **Add Code I-22 if applicable.**

21. Does the study report any of the following outcomes? The list below includes effectiveness outcomes and specific adverse effects of interest:
    - Validated measures of pain intensity and pain-related function (including spasticity)
    - Validated measures of pain-related outcomes (mood, depression, anxiety)
    - Validated measures of sleep quality
    - Validated measures of quality of life
    - Utilization of health services
    - Reduction in opioid use or dosage
    - Social functioning/disability
    - Other substance use/substance use disorder
    - Mental health symptoms including depression, anxiety, *etc* (not psychotic symptoms)
    - Cognitive effects (*eg*, IQ, SLUMS, or measures of memory, processing speed, attention, learning, executive function, *etc*)
    - Employment
    - Weight gain
    - Diversion
    - Insomnia

    No " STOP. **Code X21** *(Pain pop, no outcomes of interest)*

    Yes " Proceed to 22.

22. Is the study design a controlled clinical trial, case-control, or cohort study with a comparison group?

    No " STOP. **Code X22** *(Pain pop, excluded study design)*

    Yes " STOP. **Code I-22** *(Pain pop, addresses KQ1 and/or KQ3)*

Questions 30-32 deal with PTSD

30. Do the study outcomes include either of the following:

    - Cannabis use disorder
    - Withdrawal symptoms

    No " Proceed to 31.

    Yes " **Code I-30** *(PTSD, no controls needed for specified harms)*
    Proceed with items 31 and 32. **Add Code I-32 if applicable.**

31. Does the study report any of the following outcomes? The list below includes effectiveness outcomes and specific adverse effects of interest:
    - Validated PTSD clinical interviews and symptom inventories, such as:
        - Clinician Administered PTSD Scale (CAPS)
        - PSTD Checklist (PCL)
        - PTSD Symptom Scale (PSS)
        - Posttraumatic Diagnostic Scale (PDS).
    - Validated measures of mental health symptoms commonly associated with PTSD (mood, depression, anxiety)
    - Validated measures of sleep quality
    - Validated measures of quality of life
    - Utilization of health services
    - Reduction in benzodiazepine use or dosage
    - Social functioning/disability
    - Other substance use/substance use disorder
    - Mental health symptoms including depression, anxiety, *etc* (not psychotic symptoms)
    - Cognitive effects (*eg*, IQ, SLUMS or measures of memory, processing speed, attention, learning, executive function)
    - Employment
    - Weight gain
    - Diversion
    - Insomnia

    No " STOP. **Code X31** *(PTSD, no outcomes of interest)*

    Yes " Proceed to 32.

32. Is the study design a controlled clinical trial, case-control, or cohort study with a comparison group?

    No " STOP. **Code X32** *(PTSD, excluded study design)*

    Yes " STOP. **Code I-32** *(PTSD, addresses KQ2 and/or KQ3)*

# APPENDIX C. QUALITY ASSESSMENT

## Cochrane Risk of Bias (ROB) Assessment Criteria for Trials[20]

| ***Domain*** | **Criteria** |
|---|---|
| *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 outcome data adequately addressed? Consider attrition, intention-to-treat analysis |
| *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 (ROB)? |
| *Overall assessment of potential for bias* | Low/Unclear/High |

## Trials in Patients with Chronic Pain – Risk of Bias (ROB) Assessment

| *Criteria* | Notcutt 2004[31] | Notcutt 2012[27] | Novotna 2011[25] | Ungerleider 1987[26] | Wade 2003[28] |
|---|---|---|---|---|---|
| *Sequence generation* | Unclear - "randomization was undertaken externally and the schedule supplied to GW Pharmaceuticals." However, participants were only randomized if they had shown "some benefit in one or more of their assessments" | Yes - independent statistician produced an allocation schedule using balanced permuted blocks of 4 with computer-based algorithm | Unclear - methods not described | Unclear - methods not described | Yes - sequence generated with Williams squares |
| *Allocation concealment* | Yes - randomization done externally | Yes - independent statistician | Unclear - methods not described | Unclear - methods not described | Yes - stated that participants and staff were blinded. |
| *Blinding* | Yes - trial stated as being double-blind and delivery of intervention and placebo were matched | Unclear - no methods described | Unclear - states that trial was double-blind but no details on methods; comment that inclusion into trial based on investigator assessment that patient remained blinded during initial phase of study | Unclear - states that trial was double-blind but no details on methods | Yes - identical sprays used with masking flavor; investigators were not aware of coding |
| *Incomplete outcome data* | Unclear - for the trial portion, 71% (24/34) patients were included in analysis due to withdrawal/use of rescue medications; however, each person was compared to self so unclear that this really matters | Yes - had high attrition (~50%) and only some subjects met treatment failure but based on disposition tree, all included subjects were analyzed | Yes; ITT though patients without post-randomization efficacy data were excluded, all patients who had received one dose of medication included in safety analyses; attrition reported (12% for nabiximols group and 2% for placebo). | No - there was > 80% attrition, no comment on the use of ITT, and efficacy analysis was based on only 8 patients | Yes - lost 4 patients who initially enrolled (< 80% attrition) but followed others and included them in analysis; also attempted to analyze those who took rescue medications vs entire sample |
| *Selective outcome reporting* | Yes | Yes - appeared to report on relevant outcomes | Yes - had clearly stated pre-specified primary outcome and included multiple secondary outcomes | Yes - had clearly stated pre-specified primary outcomes | Yes - looked at range of symptoms |

| ***Criteria*** | **Notcutt 2004[31]** | **Notcutt 2012[27]** | **Novotna 2011[25]** | **Ungerleider 1987[26]** | **Wade 2003[28]** |
|---|---|---|---|---|---|
| *Other sources of bias* | Yes - aside from excluding those who had to use rescue medications; pts who were randomized reported a positive response to medical cannabis prior to the initiation of the double-blind, crossover, randomized trial. | No - underpowered (though CI adjusted to help with this), some participants re-started on their own nabiximols prior to final assessment (likely to reduce the effect of the drug) | Yes - no major issues identified aside from lack of clarity around the methods used for allocation, randomization | No - it is unclear how researchers chose to increase dose of study medication. Use of self-report for spasticity and side effects can lead to concern about bias, though spasticity was also measured by physicians, side effects were not. | No - small sample size |
| *Overall assessment of potential for bias* | Low - generally well done; there are some areas that are unclear | Unclear - multiple areas of uncertainty; study was under powered and patients could have restarted nabiximols prior to assessment | Low - though limited data on methodology around allocation and blinding, authors state that study was double-blind and had low attrition with ITT analyses and pre-specified outcomes | High - poor description of methods for randomization and allocation, unclear analyses and high attrition with risk of bias from self-report, though do have outcomes specified | Low - aside from small sample size, discuss aims generally with scales to measure them, give analysis of those with and without use of rescue medication, reported on all outcomes |

## Trials Assessing the Risk of Psychotic Symptoms with Cannabis Use – Risk of Bias (ROB) Assessment

| ***Criteria*** | **Englund 2013[70]** | **Kaufmann 2010[68]** |
|---|---|---|
| *Sequence generation* | Unclear - methods not described | Unclear - methods not described |
| *Allocation concealment* | Unclear - methods not described | Unclear - methods not described |
| *Blinding* | Yes - double blind, randomly allocated | Unclear - double blind. No details provided. |
| *Incomplete outcome data* | NA - all participants completed study | No - One participant developed acute psychotic symptoms and was not included in the statistical analysis, but was qualitatively described. |
| *Selective outcome reporting* | Yes - All relevant outcomes appear to be reported | Yes - appear to report all outcomes. |
| *Other sources of bias* | Yes - no major issues identified aside from lack of clarity around the methods used for sequence generation and allocation. | No - small sample/under powered. |
| *Overall assessment of potential for bias* | Low - despite lack of clarity about sequence generation and allocation concealment. | Moderate - due to lack of clarity about sequence generation and allocation concealment and small sample size. |

## Quality Assessment Criteria for Observational Studies, Based on the Newcastle-Ottawa Scale[21]

| |
|---|
| **Representativeness of the exposed cohort**<br>*Enter 0 or 1:*<br>1 = truly representative of the average patient in the community<br>1 = somewhat representative of the average patient in the community<br>0 = selected group of users (*eg*, nurses, volunteers)<br>0 = no description of the derivation of the cohort |
| **Selection of the non-exposed cohort**<br>*Enter 0 or 1:*<br>1 = drawn from the same community as the exposed cohort<br>0 = drawn from a different source<br>0 = no description of the derivation of the non-exposed cohort |
| **Ascertainment of exposure**<br>*Enter 0 or 1:*<br>1 = biological test (*eg*, blood/urine)<br>1 = structured interview<br>1 = written self-report that characterizes dose (current or cumulative)<br>0 = written self-report without quantification of exposure<br>0 = no description |
| **Precision of Exposure Dose Ascertainment**<br>*Enter 0 or 1:*<br>1 = amount and time<br>0 = no information about amount and time |
| **Ascertainment of exposure done prospectively or retrospectively**<br>*Enter 0 or 1:*<br>1 = Prospectively<br>0 = Retrospectively |
| **Demonstration that outcome of interest was not present at start of study, OR baseline assessment**<br>*Enter 0 or 1:*<br>1= yes<br>0 = no |
| **Adjustment for confounding (rendering comparability of cohorts on the basis of the design or analysis)**<br>*Add points: Minimum 0, Maximum 2*<br>1 = study accounts/controls for other substance use<br>1 = study controls for any additional factor (mental health comorbidity; medication use; severity of PTSD; mental health comorbidity and treatment; socioeconomic status)<br>0 = no adjustment for potential confounders |
| **Assessment of outcome**<br>*Enter 0 or 1:*<br>1 = objective measure<br>1 = validated self-report measures<br>0 = no information or non-validated measures |
| **Was follow-up long enough for outcomes to occur?**<br>*Enter 0 or 1:*<br>1 = yes (need to define adequate follow-up period for outcome of interest)<br>0 = no |
| **Adequacy of follow-up of cohorts**<br>*Enter 0 or 1:*<br>1 = complete follow-up; all subjects accounted for.<br>1 = subjects lost to follow-up unlikely to introduce bias; small number (less than 20 %) lost, or description was provided of those lost.<br>0 = follow-up rate < 80% and no description of those lost.<br>0 = no statement |

## Observational Studies in Patients with Chronic Pain – Risk of Bias (ROB) Assessment

| *Criteria* | Ware 2015[29] | Storr 2014[30] | Fiz 2011[32] |
|---|---|---|---|
| *Representativeness of the exposed cohort* | 1 - included patients with non-cancer pain but had to be moderate/severe and refractory | 1 - exposed cohort was equal for males and females although IBS impacts females at a slightly higher base rate | 1 - somewhat; these are treatment resistant patients in particular |
| *Selection of the non-exposed cohort* | 1 - all drawn from same clinical centers | 1 - drawn from same source | 0 - 2 of the recruitment sites were the same (FM associations and outpatient rheumatology) but cannabis group also recruited from cannabis association. |
| *Ascertainment of exposure* | 1 - pharmacy dispensed and recorded use | 0 - self-report; only method of administration (*ie*, smoking) recorded | 0 - information reported about duration of cannabis use (*ie*, 1 year) and administration modality, but no info provided about dose or cannabinoid concentration. |
| *Precision of Exposure Dose Ascertainment* | 1 - dosing described | 0 - no dosing information provided | 0 - method of administration varied among users (smoking 54%; oral 46%; combined 43%), duration and frequency of use varied among users. Dosage varied among users ("1-2 cigarettes each time when smoked or 1 spoonful each time when eating"). No info on THC/CBD content given. 39% used daily, 18% used 2-5 days per week. |
| *Ascertainment of exposure done prospectively or retrospectively* | 1 - prospectively | 0 - cross-sectional so ascertainment based on one timepoint | 0 - exposure groups established by use status |
| *Demonstration that outcome of interest was not present at start of study, OR baseline assessment* | 1 - all results compared to baseline | 0 - no baseline | 1 - baseline data gathered 2 hours prior to exposure |
| *Adjustment for confounding* | 2 - cohort significantly different on age, gender, disability status, tobacco status, past cannabis use, drug abuse screening, average pain intensity (cannabis users higher) and medications – however, these group differences were controlled for in the inferential statistics. | 2 - study adjusts for demographic variables, tobacco smoking status, time since diagnosis, and biological use | 0 - no adjustments made |

| ***Criteria*** | **Ware 2015[29]** | **Storr 2014[30]** | **Fiz 2011[32]** |
|---|---|---|---|
| *Assessment of outcome* | 1 - objective/validated measures used | 0 - surgical history gleaned from medical chart (only measure of utilization provided) no other validated measures reported for our PICOTS. Side effects and perceived utility of cannabis for treatment of IBD symptoms all subjective and only descriptive data is provided for users. | 1 - validated self-report measures for outcomes (*eg*, VAS, SF-36) |
| *Was follow-up long enough for outcomes to occur?* | 1 - (12 months follow-up) | 0 - no follow-up | 0 - difficult to ascertain sustainability of outcomes, only 2 hours of follow-up |
| *Adequacy of follow-up of cohorts* | 1 - > 20% loss to follow-up in the cannabis group but all subjects are accounted for and all subjects included in the primary safety analysis | 0 | 1 - appears to be complete follow-up |
| *Comments on study quality* | Low ROB - there are some concerns as noted below but what is measurable by scale appears to be properly done - Study's primary outcomes were adverse events, other outcomes were secondary; Study notes that protocol changes were made but no details provided; Study did not recruit pre-specified sample size for power; Multiple adjustments and subgroup analyses were undertaken; Also, strange that inclusion into cannabis group relied on use of cannabis but there are persons included there who are cannabis naïve and who were ex-users; baseline demographics/ population details differed by group, though adjustments made in analyses...the majority (66%) of the cannabis users were experienced, making the generalizability to cannabis-naïve users difficult, and differences in the follow-up times between the control and exposure group may have artificially inflated the number of AEs reported by cannabis users. | High ROB - dosing information was not provided or consistent for users, data collection only at one time point so no f/u data provided. Minimal outcomes of interest. | High ROB - dosing information was not provided or consistent for users, participants gathered from different sources introducing selection bias; groups were established by exposure status and those using cannabis are likely to differ from others not using cannabis (although baseline characteristics are not different per study authors and this is the only way to conduct a cohort study), also concern that there were no adjustments made for other medications used, small sample size, use of self-reported measures, very limited follow-up with a pre-, post-design rather than between group comparison for primary outcome |
| *Notes on Applicability* | Patients had treatment moderate/severe, refractory chronic pain but otherwise applicable, especially since drawn from clinical centers | | Patients had treatment resistant FM |

## Observational Studies in Patients with PTSD – Risk of Bias (ROB) Assessment

| ***Criteria*** | **Wilkinson 2015[39]** | **Johnson 2016[40]** |
|---|---|---|
| *Representativeness of the exposed cohort* | 1 | 1 |
| *Selection of the non-exposed cohort* | 1 | 1 |
| *Ascertainment of exposure* | 0 (self-report) | 0 (self-report) |
| *Precision of Exposure Dose Ascertainment* | 0 (not specific) | 0 (not specific) |
| *Ascertainment of exposure done prospectively or retrospectively* | 1 | 0 |
| *Demonstration that outcome of interest was not present at start of study, OR baseline assessment* | 1 | n/a |
| *Adjustment for confounding* | 1 (included all assessed confounders related to cannabis use) | 0 |
| *Assessment of outcome* | 1 (validated self-report measures) | 1 (validated self-report measures) |
| *Was follow-up long enough for outcomes to occur?* | 1 (4 months) | n/a |
| *Adequacy of follow-up of cohorts* | 1 | n/a |
| *Comments on study quality* | Medium ROB | High ROB |
| *Notes on Applicability* | VA population with PTSD | VA population with PTSD |

## Observational Studies of Medical Harms Associated with Cannabis Use – Risk of Bias (ROB) Assessment

| *Criteria* | Pletcher 2012[49] | Hancox 2010[48] | Mittleman 2001[52] | Frost 2013[51] | Carvalho 2015[53] |
|---|---|---|---|---|---|
| *Representative-ness of the exposed cohort* | 1 - truly representative Community based study in 4 cities representing different parts of country, ethnically diverse group. | 1 - somewhat representative (birth cohort, but for that reason does not represent older patients in the community) | 1 - somewhat representative of MI patients - not community, but most MI patients would get cared for in hospital and this was multisite hospital study | 1 - somewhat representative of MI patients - not community, but most MI patients would get cared for in hospital and this was multisite hospital study | 1 - in half the studies, these were hospital patients, half the studies used cancer registry data |
| *Selection of the non-exposed cohort* | 1 - drawn from same community | 1 - same community | 1 - self-control | 1 - same community | 1 - most studies found general population controls (*eg*, electoral rolls, random digit dialing) |
| *Ascertainment of exposure* | 1 - structured interview | 1 - interview | 0 - risk of recall bias, not clear how accurate recalled pattern of use over prior year was - since this formed basis for control (expected frequency of hourly use) there is some potential for bias. | 1 - interview | 1 - most studies used structured interview |
| *Precision of Exposure Dose Ascertainment* | 1 - amount and time | 1 - amount and time | 0 - not enough information about amount and time | 0 - time only, and only at baseline | 1 - most gathered information about amount and time |
| *Ascertainment of exposure done prospectively or retrospectively* | 1 - prospectively | 1 - prospectively | 0 - retrospectively | 0 - retrospectively | 0 - retrospectively |
| *Demonstration that outcome of interest was not present at start of study, OR baseline assessment* | 1 - yes - PFTs were longitudinally collected - baseline PFT data were available and outcomes were reported as change from baseline | 1 - yes, serial PFT measures, and they adjusted for spirometry at age 15 | n/a | 1 - yes (inception cohort) | 0 - no |

| *Criteria* | Pletcher 2012[49] | Hancox 2010[48] | Mittleman 2001[52] | Frost 2013[51] | Carvalho 2015[53] |
|---|---|---|---|---|---|
| *Adjustment for confounding* | 1 - for PFT outcomes, most important covariate is tobacco exposure along with gender, age, race all of which were well accounted for. | 1 - accounts for tobacco exposure, age, gender which are probably most relevant for the PFT outcomes - did not account for race, SES, second hand smoke exposure, *etc* | 0 - not clear that they account for tobacco use in hour prior to MI | 1 - propensity score matching - adjusted for tobacco, other substance use, SES other factors | 1 - most studies adjusted for tobacco use and alcohol use |
| *Assessment of outcome* | 1 - PFTs, objective measure | 1 - PFTs | 1- objective assessment of MI outcome | 1 - national death index | 1 - only included studies of patients with definitive HNC |
| *Was follow-up long enough for outcomes to occur?* | 1 - yes | 1 - yes | n/a | 1 - yes, partly - the exposed group was younger and the number of mortality events therefore relatively small, but 18 year f/u | n/a |
| *Adequacy of follow-up of cohorts* | 1 - data from 98% of participants, 95% of all visits had complete data | 1 - data from 96% of original cohort at 32 years | n/a | 1 - national death index | n/a |
| *Comments on study quality* | Low ROB. Well-conducted, prospective cohort study. Should be one of the better sources of data for this outcome. | Low ROB. Well-conducted, prospective cohort study. Similar to Pletcher study, but did not have data on linear trends. | High ROB. Case-crossover study with several potential sources of bias including recall bias, small # patients with exposure of interest, and lack of clarity re: accounting for tobacco use. | High ROB. Information on exposure (both cannabis and tobacco) only available at baseline interview. Assess long-term mortality, but no information on total use over the period of follow-up, making it difficult to assess relationship between exposure and outcome. Moreover, cannabis users were different than non-users - confounders were adjusted for, but strong possibility of residual confounding. | Medium ROB. Ascertainment of exposure is necessarily limited by retrospective nature and issues of recall bias. |

| ***Criteria*** | **Pletcher 2012**[49] | **Hancox 2010**[48] | **Mittleman 2001**[52] | **Frost 2013**[51] | **Carvalho 2015**[53] |
|---|---|---|---|---|---|
| *Notes on Applicability* | Applicable to younger populations (< 30) | Applicable to younger populations | Most cannabis users were male | Most cannabis users were male, younger than nonusers | Very wide range of ever cannabis use - some of the studies with very low rates of use may not be applicable, but the consistency of results across different study populations is reassuring. |

**Medical Harms Observational Studies – Risk of Bias (ROB), Continued**

| ***Criteria*** | **Zhang 2015[54]** | **Callaghan 2013[55]** | **Gurney 2015[56]** | **Chacko 2006[57]** |
|---|---|---|---|---|
| *Representative-ness of the exposed cohort* | 1 - international, mix of hospital-based and community studies | 1 - nearly all (98%) 18-20 year old males | 1 - cancer registry cases with community-based controls | 1 - representative of transitional cell ca population, at least in VA |
| *Selection of the non-exposed cohort* | 1 - all drew controls either from same hospital/clinic, or the community | 1 - drawn from same population | 1 - drawn from same population (random general population in 2 studies and friends of cases in one study which is a potential source of selection bias) | 0 - drawn from urology clinic, presenting for different reason - not representative of community |
| *Ascertainment of exposure* | 1 - written self-report with information on duration and frequency | 0 - self-report without adequate quantification | 0 - interview in 2 studies and written self-report with quantification in other, but not clear that interviewers were blinded to case/control status of participant | 1 - written self-report with information on duration and frequency |
| *Precision of Exposure Dose Ascertainment* | 1 - amount and time | 0 - minimal information about exposure over time | 1 - amount and time | 1 - amount and time |
| *Ascertainment of exposure done prospectively or retrospectively* | 0 - retrospectively | 0 - retrospectively, and only at time of conscription | 0 - retrospectively | 0 - retrospectively |
| *Demonstration that outcome of interest was not present at start of study, OR baseline assessment* | 1 - performed additional analyses excluding patients who had used within 2 years of cancer diagnosis (to evaluate possibility of reverse causality) | 0 - no, but very unlikely that outcome was present in young age group | 1 - (case-control) | n/a |
| *Adjustment for confounding* | 1 - adjusted for tobacco use and some other sociodemographic factors | 0 - adjusted for multiple factors, but did not have a way of quantifying tobacco exposure after conscription which is likely to have been heaviest amongst those with heavier cannabis use | 1 - adjusted for major confounders relevant to disease (including cryptorchidism), but one study did not adjust for alcohol or tobacco use (but was also the smallest of the studies) | 0 - important confounders considered, but they did not report adequately the adjusted analyses |
| *Assessment of outcome* | 1 - only histologically confirmed lung cancer | 1 - based on national medical records, claims - fair validation | 1 - histologically confirmed cancers | 1 - confirmed cancers |
| *Was follow-up long enough for outcomes to occur?* | n/a | 1 - yes | n/a | n/a |
| *Adequacy of follow-up of cohorts* | n/a | 1 - 1.9% lost to f/u due to emigration | n/a | n/a |

| ***Criteria*** | **Zhang 2015[54]** | **Callaghan 2013[55]** | **Gurney 2015[56]** | **Chacko 2006[57]** |
|---|---|---|---|---|
| *Comments on study quality* | Medium ROB - ascertainment of exposure is necessarily limited by retrospective nature and issues of recall bias. | High ROB - biggest issue was that the main exposure and main confounder (tobacco use) were only determined at time of conscription. High risk of residual confounding due to ongoing tobacco exposure for finding of heavy cannabis use association with lung cancer. | High ROB - the meta-analysis itself was well done, but there were methodologic deficiencies in all 3 included studies. The smallest study did not control for important confounders such as tobacco. Low response rates among controls or cases in the 2 bigger studies. There was a potential for ascertainment bias, and recall bias is also an issue. Use of friends as controls in one study is a potential source of bias. The largest and methodologically strongest study showed results consistent with overall findings, direction of effect was consistent across studies, there was a dose-response relationship, and the authors do highlight some biologic plausibility to findings. | High ROB - small study, 2 VA sites, very little information on adjusted analyses, control group were symptomatic patients in urology clinic so not representative of community, reverse causality a real concern (*ie*, cancer patients may have been using cannabis to palliate symptoms - no information on timing of use and diagnosis), recall bias |
| *Notes on Applicability* | Variety of settings, included squamous cell and adenocarcinoma patients but few patients with other types of lung cancer. | -- | -- | VA only - 2 sites. One of the sites located in a town with prominent textile industry (and, thus, dye exposure). Small number of patients. |

**Observational Studies of Adverse Mental Health Effects Associated with Cannabis Use – Risk of Bias (ROB) Assessment**

| ***Criteria*** | **Di Forti 2009**[71] | **Dominguez 2010**[66] | **Kuepper 2011**[65] | **Mason 2008**[69] | **Rossler 2011**[67] | **van Nierop 2013**[115] |
|---|---|---|---|---|---|---|
| *Representative-ness of the exposed cohort* | 1 - first episode psychosis (presenting to the hospital) | 1 - representative population study. | 1 - representative population study. | 0 - No information about the population from which the sample was recruited. Recreational cannabis smokers who used cannabis at least once a month. No personal history of diagnosed mental illness. Lifetime drug usage of other illicit drugs in the cannabis group commonly included amphetamines, benzodiazepines, cocaine, ketamine, LSD, and heroin. | 1 - representative population based sample. Males identified from a military screening test, and females from an electoral roster. | 1 - somewhat representative (siblings of individuals with psychotic disorders and healthy controls in the same geographical areas) |
| *Selection of the non-exposed cohort* | 0 - No description of source. Control group was individuals with no psychotic episodes. | 1 - same population | 1 - same population | 0 - No description of source | 1 - same population | 1 - same community |
| *Ascertainment of exposure* | 1 - Cannabis Experience Questionnaire | 1 - Munich composite international diagnostic interview (DIA-X/M-CIDI) | 1 - Munich composite international diagnostic interview (DIA-X/M-CIDI) | 1 - self-report and urinalysis | 1 - Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology (SPIKE) | 1 - urinalysis and CIDI |

| ***Criteria*** | **Di Forti 2009**[71] | **Dominguez 2010**[66] | **Kuepper 2011**[65] | **Mason 2008**[69] | **Rossler 2011**[67] | **van Nierop 2013**[115] |
|---|---|---|---|---|---|---|
| *Precision of Exposure Dose Ascertainment* | 1 - Assessed type and frequency, as well as potency | 0 - > or < 5 times since last exposure | 0 - > or < 5 times since last exposure | 0.5 - Participants contacted researchers when they were using cannabis recreationally. The study team went to meet them for testing. Dose not ascertained. | 1 - frequency of use | 0.5 - used interviews to determine lifetime use and urinalysis to determine current use. No information re: dose, frequency, *etc* |
| *Ascertainment of exposure done prospectively or retrospectively* | 0 - retrospectively | 0 - retrospectively | 0 - retrospectively | 1 - prospectively | 0 - retrospectively | 0 - retrospectively |
| *Demonstration that outcome of interest was not present at start of study, OR baseline assessment* | 1 - first psychotic episode | 0 - not excluded | 0 - not excluded | 0 - not excluded, and no baseline assessment. | 1 - although clinical diagnoses of psychotic disorders were not assessed with the SPIKE at baseline through 1999, two-thirds of the sample were at "high risk" for subclinical psychosis symptoms based on Symptom Checklist 90—Revised (SCL-90-R) scores. | 1 - healthy siblings of individuals with a psychotic disorder (high risk) and healthy controls. |
| *Adjustment for confounding* | 2 - adjusted for age, gender, ethnicity, other stimulant use, education, and employment status. | 1 - controls for depression but not other substance use | 2 - Adjusted for age at baseline, sex, baseline SES, use of other drugs at baseline and T2, trauma before the age of 14 as assessed at baseline, and urban/rural environment. | 1 - performed sensitivity analysis for other drug/alcohol use | 2 - adjusted for sex, familial background, socio- economic status, family history of mental disorders, other family problems, and school problems, and used step wise multivariate analysis with each substance entered individually. | 0 - adjusts only for age, sex, high-risk sibling status |

| *Criteria* | **Di Forti 2009**[71] | **Dominguez 2010**[66] | **Kuepper 2011**[65] | **Mason 2008**[69] | **Rossler 2011**[67] | **van Nierop 2013**[115] |
|---|---|---|---|---|---|---|
| *Assessment of outcome* | 1 - hospital admission | 1 - Munich composite international diagnostic interview (DIA-X/M-CIDI) | 1 - Munich composite international diagnostic interview (DIA-X/M-CIDI) | 0 - Psychotomimetic States Inventory (PSI) - the study is a validation study. | 1 - SPIKE and SCL-90-R | 1 - Community Assessment of Psychic Experience (CAPE) |
| *Was follow-up long enough for outcomes to occur?* | NA | 1 - Mean T1 1.6, T2 3.5, and T3 8.4 years (range=7.3-10.5) | 1 - Mean T1 1.6, T2 3.5, and T3 8.4 years (range=7.3-10.5) | 1 - interested in acute symptoms. Assessed at time of exposure, then 3 to 4 days later. | 1 - 30 years | 0 - Mean 3.3 years |
| *Adequacy of follow-up of cohorts* | NA | 0 - 84% at T2 and 73% at T3. No description provided. | 0 - 84% at T2 and 73% at T3. No description provided. | NA - no follow-up other than 3-4 days post use. | 1 - 57% assessed at 30 year follow-up. Description of lost provided. | 1 - 78% assessed at follow-up. Description of participants lost provided. |
| *Comments on study quality* | Low ROB study despite lack of detail on ascertainment of control group. Nicely conducted retrospective study. | Moderate ROB study. Included participants with negative/disorganized symptoms at baseline. | Moderate ROB study. Included participants with negative/disorganized symptoms at baseline. | High ROB study. No information about the source of the exposed or non-exposed sample. Exposed sample used drugs in addition to cannabis, and there was no baseline assessment. No information about dose ascertained. | Low ROB study. Well-conducted, good description of follow-up and loss to follow-up, description of methods, *etc* | High ROB due to lack of controlling for important confounders, short follow-up |

# APPENDIX D. PEER REVIEWER COMMENTS AND AUTHOR RESPONSES

| Rev # | Comment | Response |
|---|---|---|
| ***Are the objectives, scope, and methods for this review clearly described?*** | | |
| 1-7 | Yes | Noted. |
| 9 | No - page 4, line 35: please add risk of cannabis use disorder to the list of adverse events in this phrase- "assess the impact of short- and long-term marijuana use on the risk of adverse effects such as pulmonary diseases, cardiovascular diseases, cancer, and psychosis in the general adult population" | This change has been made. |
| ***Are there any published or unpublished studies that we may have overlooked?*** | | |
| 1, 2, 4, 7 | No | Noted. |
| 3 | Yes - There is a recently published systematic review of medical marijuana in psychiatric indications (Wilkinson et al., 2016) that wasn't included. This may have been a timing issue. But now that it is published, it should be included - especially since it informs the PTSD literature. | We have added information from this recent systematic review to our report. |
| 5 | Yes - A couple of studies regarding harms have come out since your February 2016 deadline. Considering that the review is not likely to be formally published much before 2017. I uploaded the pdfs of these papers.<br>· One is a new analysis of the Dunedin study showing that cannabis users are more likely to develop periodontal disease.<br>· The second one is an epidemiologic study from Sweden that shows an association between early, heavy cannabis use and mortality. | We added the new Dunedin analysis to the emerging harms section. We had assessed another analysis from the Swedish military conscript study – there was no data on ongoing tobacco or cannabis use after conscription and, since the outcomes were many decades later, the lack of exposure information made the study results very difficult to interpret. |
| 6 | Yes - See Review. | We have reviewed the studies you suggested and included them in our report if they met our inclusion criteria or if they were relevant for background and discussion sections. |
| 9 | Yes - In assessing risk of harm, it would be more appropriate to include studies assessing harm among daily marijuana users (whether or not they have pain or PTSD) than to assess risk of harm amongst pain or PTSD patients who do not use or who occasionally use marijuana. | We broadly included studies with varying levels of use (including heavy use) and in broad patient populations. We have clarified throughout the summary table and manuscript whether the results apply to light or heavy use and we have clearly noted when there is a lack of data on heavy (daily) use. |
| ***Is there any indication of bias in our synthesis of the evidence?*** | | |
| 1-5, 7 | No | Noted. |
| 6 | Yes - The choice of only including plant-based and not synthetic cannabinoid studies seems biased, given that they have the same molecular structure. | We have rewritten the methods and the KQ1 results section to better clarify the rationale for this decision and we note how the exclusion of synthetic cannabinoid studies would likely not have affected our overall findings (since there were no large, good quality studies of synthetics in the populations of interest for this report). |
| 9 | Yes - There appears to be a bias in favor of state- | We agree. We have added language to the results |

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| | approved retail marijuana products for treatment of pain and PTSD. The executive summary introduction states that the purpose of the paper is to examine health effects of marijuana use because of increased state legalization of marijuana plant products for the indications of pain and PTSD, but the review of the literature conflates studies of plant-based pharmaceutical grade products (i.e. Sativex) with those of retail smoked marijuana and other marijuana products. As written, the two types of cannabis products are conflated in the summaries of the evidence and in the recommendations. The differences between the two types of products need to be clearly explained and then considered separately in all of the analyses. While Sativex is not currently FDA-approved, it is approved as a pharmaceutical in other countries, is manufactured to known standards of purity and potency and is therefore distinct from retail marijuana products.<br>I recommend a clear explanation in the introduction of the differences between pharmaceutical products manufactured to specific potency and purity versus retail marijuana products. THC and cannabidiol concentrations vary widely in retail marijuana. The trend toward higher THC and lower cannabidiol in retail marijuana renders studies of lower THC/higher cannabidiol pharmaceuticals and plant products irrelevant or only indirectly relevant to many currently marketed marijuana products. Given these differences, the level of evidence should be appropriately downgraded for "indirectness" when citing studies of cannabinoid pharmaceuticals, as these do not directly address the benefits and harms of smoked marijuana or other retail marijuana products. | clarifying that most studies examined preparations with precisely defined THC/CBD content. We also added to the applicability section in the Executive Summary and main report that preparations studied may not reflect what is widely available in dispensaries, and we added a reference to a study that suggested measured content differed from labeled content in dispensaries. Finally, we added the issue of applicability to the rationale for strength of evidence in the summary of evidence table. |
| 9 | In assessing potential risks, studies of "low to moderate use" are not appropriate for inclusion. When used for medical purposes, the usual pattern is daily consumption. Therefore, in order to evaluate potential risk, only studies that systematically assess for risk among daily users would be relevant to the question of potential harm from medical use. At least one cited study includes cannabis non-users in the denominator when reporting rates of cannabis use disorder among patients with pain, and is therefore implies a much lower risk of cannabis use disorder than would be expected among daily "medical marijuana" users. | With regard to the cannabis use disorder studies, we agree that we did not clearly describe the cited study and the limitations in the overall evidence base. We revised this section to clearly state that there were no studies in cannabis users. We also de-emphasized the cross-sectional data in chronic pain users in the summary of evidence section since these were not studies in a cannabis-using population.<br><br>With regard to the other harms, we were broadly inclusive in part because clinicians may encounter a broad range of use among patients. We were careful to describe the evidence as being applicable to low levels of use (as with effects on pulmonary function) when appropriate, and added clarification on the lack of data (or even potential for harm in case of pulmonary function) with heavy use. |
| ***Additional suggestions or comments.*** | | |
| 1 | Excellent review.<br>Clarify on page 4 and in methods the reasons for choice in key exposure (e.g., what is typically found at dispensaries, and not synthetic forms that have been | See above. |

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| | systematically reviewed already) | |
| 2 | My comments are all fairly minor.<br><br>1. A brand name, "Sativex," is used many times in tables and intermittently throughout the text. I believe the generic name (nabiximols) should be used instead in all text and tables. | We agree and have made this change. |
| 2 | 2. Page 6, line 18 (also page 18, line 39): "and an estimated 6.2%-39% of chronic pain patients are utilizing cannabis in addition to opioid medication for pain management." The denominator is unclear in this sentence. Should it be "among patients on opioid medication for chronic pain, 6-39% also use cannabis"? | This language was clarified. |
| 2 | 3. Page 6: The introduction alternates between "marijuana" and "cannabis." Is there any distinction? If not, I suggest selecting a preferred term and using it consistently for clarity. | We agree and have changed it to "cannabis" throughout. |
| 2 | 4. Page 6, Methods: A brief rationale for the decision to exclude synthetic cannabinoids would be helpful. | This has been added. |
| 2 | 5. Page 66, last paragraph of discussion: When considering implications for pain management, it seems appropriate to mention that multiple pharmacological and nonpharmacological therapies have stronger evidence for chronic pain than either cannabis or opioids. Given the state of the science on cannabis and the existence of many efficacious medical and complementary therapies for pain, I am aware of no scientific rationale for singling out cannabis as an important "opioid sparing" therapeutic option. (This is a common line of argument for increasing cannabis availability, so I don't fault the authors for mentioning it.) The first recommendation from CDC guidelines on opioid prescribing, as well as treatment guidelines for common conditions such as back pain and arthritis, could be cited here. | We added language from the 1st recommendation in the CDC guidelines. We also added references and language about other evidence based pharmacologic and non-pharmacologic therapies. |
| 3 | Overall this is a very thorough review.<br><br>The risks of psychosis are underestimated and understated. There is a body of evidence that exposure to cannabis is associated with a risk for a psychotic disorder. There is an entire special issue of Biological Psychiatry (April, 2016) dedicated to cannabinoids and psychosis. The authors are strongly urged to review this special issue.<br><br>There is robust evidence (unlike what the review states) of direct experimental evidence that cannabinoids at certain doses can induce psychosis-like effects in healthy individuals and that cannabinoids can exacerbate psychosis in individuals at risk for or with an established, psychotic disorder. Restating the risk of psychosis is important because of the numbers of veterans with SMI who seek out certification for medical marijuana. I see a number of veterans diagnosed with chronic psychotic disorders | We generally agree, though we have to stick to the strength of evidence grading approach we have used throughout the report – we did include mention of experimental studies, though they were small and had some methodologic flaws. However, we had not incorporated these into the summary statement – we have changed this and clarified the extent of evidence. The SOE rating is low because much of the evidence is observational (though not entirely), it is difficult to know the magnitude of effect, and there is little data specific to chronic pain and PTSD populations – we have clarified this rationale throughout. |

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| | who have asked for medical marijuana certification from VA doctors. They go to non-VA providers get a card, start using marijuana and end up in the hospital. While this is anecdotal, stating that the link to psychosis is "low" or "entirely observational" is not without risk. | |
| 5 | Obviously, compiling all the papers need to generate this review took a lot of effort. Overall, the review seems comprehensive and generally accurate. When fully refined, it will make an important contribution to our knowledge base.<br><br>There is some sloppiness in the preparation as though the draft did not undergo careful and extensive proofreading before being sent out for review. In certain presentations of various studies there is a lack of needed detail and occasionally lack of rigor in interpretation. Most of the examples of these concerns that I could find are detailed below, but I cannot confirm that this list is exhaustive of all miscues. | Thank you for the suggestions – we have detailed our responses below and additionally went through the entire report and did an additional round of copyediting. |
| 5 | Page 5, lines 12-13: The assumption that rates of pulmonary effects or cancer would not be influenced by presence of PTSD or pain seems flawed at least on the basis that individuals with these disorders use tobacco at higher rates than the general population, and tobacco and cannabis might have additive or synergistic effects. In addition, it seems likely that both PTSD and pain might have subtle hormonal or immune system effects that could interact negatively with cannabis use. | We agree that there is some risk in considering studies in broader populations. We did so after considering likely important confounding factors as related to chronic pain or PTSD. We agree tobacco use is an important confounder and levels might be higher in chronic pain or PTSD populations, but the studies that contributed findings all accounted for tobacco use (and usually conducted analyses among never smokers *etc*) – studies that did not adequately control for tobacco use were downgraded in quality and did not contribute to findings. There are certainly other factors that might theoretically confound findings – we have added to the limitations section this issue (and, in general, this is one of the reasons why bodies of evidence based only on observational data typically start with a lower strength of evidence rating). |
| 5 | Page 5, line 45: Change “size” to “sizes.” | We have made this change. |
| 5 | Page 6, lines 4-13: Given the nature of the uncontrolled studies reviewed, it would probably be better to say that “cannabis is potentially associated with either harmful or neutral effects” rather than is potentially harmful. | We have made this change. |
| 5 | Page 8, line 36: Change “is” to “are.” | Done |
| 5 | Table (Page 9): Calls medication Sativex when text calls it nabiximols. Should use generic name throughout document to be consistent.<br>Acronym ROB should be footnoted to explain it to anyone perusing the table. | Done |
| 5 | PTSD: It seems incorrect to say that marijuana is potentially harmful since these studies were observational. Is it likely the marijuana is causing more violence and use of other substances? Possibly, but it seems more intuitively probable that patients who are more violent and certainly who use other | We changed the executive summary paragraph accordingly. There is more detail in the main body of the report, but the strength of evidence related to bias and small number of studies is clearly indicated. |

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| | substances are more likely to use marijuana. It is more credible to say that there is no evidence that it is helpful. | |
| 5 | Page 21, lines 54-57: This sentence does not make sense. If they inhaled a 25 mg dose, the per cent THC is irrelevant because the dose would be the same. What is the preparation here? It does not sound like herbal marijuana. | Language regarding the preparation was clarified; it was indeed an herbal preparation obtained from Prairie Plant Systems Inc. (Saskatoon, Sask.). Regarding dose and potency, this is the language that the authors use to describe the potency and dose. The 0% THC was prepared using "ethanolic extraction of cannabinoids" (see Ware 2010 pg. E695). Concentrations/potencies (percent THC) were varied, but were delivered in the same dose (25 mg). |
| 5 | Page 22, lines 42-59: This study is very poorly described. The reader needs to know more about the cannabis product used. If the study was observational, how was assignment to condition determined? The word "native" should be "naïve." | Cannabis product described in more detail. Assignment to conditions described in more detail. Native changed to naïve. |
| 5 | Page 23, lines 7-21: These studies are also exceedingly poorly described. What were the basic study methodologies? | Designs for both studies were described in more detail. |
| 5 | Table 3: How can the Wilkinson study be medium risk of bias? Shouldn't it be high risk of bias? Obviously, the participants self-selected into their groups. We know that people who use marijuana are more likely to use alcohol and vice-versa. Most likely individuals with PTSD and a propensity to violence are more likely impulsive and more likely to use marijuana. The marijuana may not be causing the violence. The p-value given for primary outcome of Johnson study is inconsistent with what the text says. | We used a standard risk of bias tool to evaluate the observational studies (Newcastle-Ottawa Scale), and using this tool classified the study as medium risk of bias (individual item scores are included in the Appendix C PTSD risk of bias table). This particular study adjusted for confounders which contributed to the medium rating. We agree that causation is very difficult to assume here and this is part of what contributes to rating the body of evidence as insufficient.<br><br>Regarding the Johnson et al. paper, we have checked the values and confirmed that those reported in our table correspond to those reported in the paper. |
| 5 | Page 26, lines 21-23: Serious adverse events mentioned twice with different ORs. | Thanks – this was a typo and was corrected (last should have been withdrawal due to AE). |
| 5 | Page 26, lines 25-26: Information on specific serious adverse events should be provided in more detail. It is hard to see how paranoia or agitation by themselves would meet the FDA definition of serious adverse event unless they resulted in hospital admission. | We believe the section provides the detail we have available, while remaining circumspect about the seriousness of most of the short-term adverse events reported. The definition of serious adverse event is not provided in the Whiting review or its review protocol. We do clarify that many of the side effects were minor and common effects of cannabis. We have rewritten the sentence and taken out the modifier "serious". The definition of serious adverse events includes medical events for which an intervention might be necessary to prevent something like hospitalization – this is obviously somewhat at the discretion of the monitoring board and investigators and we simply report what the review authors reported. |
| 5 | Page 26, line 34: add "and" between "pain" and "found." | This change has been made. |
| 5 | Page 34, line 13: Change "was" to "were." | This change has been made. |

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| 5 | Page 36, line 8: Describe dose and route of administration of cannabis in this study. | This change has been made. |
| 5 | Page 37, line 42: Delete "…who were diagnosed with CUD." | We have left this statement in the text for clarification. |
| 5 | Page 38, lines 4-15: An apparent issue with the Bonn-Miller study described here which may warrant mention is that the Veterans who had CUD and checked into an inpatient unit presumably had to undergo cannabis withdrawal absent any treatment for it. Was it their CUD per se or the withdrawal symptoms (or both) that interfered with their treatment improvement? It would be good to know also if their PTSD severity at treatment entry was equivalent to that of the non-CUD group. | Our summary describes the results and adjustments for confounders, but we have not included a discussion about whether or not withdrawal symptoms vs. CUD was responsible for the findings because it is not possible to determine based on the methods. |
| 5 | Page 40, line 7: Change "abuse" to "misuse." | This change has been made. |
| 5 | Page 41, line 4: Remove "is." | This change has been made. |
| 5 | Page 42, line 47: Need route of administration of cannabis oil. | This was not specified in the ClinicalTrials.gov entry; we have clarified this in table. |
| 5 | Page 43, line 42: 0 mg does not make sense. | This is what was reported in the ClinicalTrials.gov entry, but we have clarified (it was a titration up to 250 mg). |
| 5 | Page 52, Table 8: Additional suggestions: All clinical trials of cannabis should obtain blood levels of THC and CBD so that there is some objective measure of how much drug exposure has occurred. Almost all studies done thus far have been quite low dose. Thus, higher doses must be tested. CBD should be much better studied acutely and longitudinally to determine whether it is reinforcing and whether tolerance and withdrawal occur with chronic use. | Thanks, this has been added. |
| 6 | Excellent work! Remaining points to consider are highlighted below...<br><br>Major Issues:<br><br>1. One of the larger issues with the report, as written, is the choice to exclude "synthesized, pharmaceutically prepared cannabinoids (e.g., dronabinol, nabilone)." The authors chose to include studies of whole-plant or plant-derived cannabinoid preparations, but synthetic preparations with the same exact molecular structure and delivery method were excluded. There are very few organizations that produce plant-derived cannabinoids (e.g., NIDA, GW Pharmaceuticals), whereas synthetic cannabinoids (e.g., dronabinol, nabilone) are not only more widely available to researchers, but have been produced and used in research for quite some time.<br><br>Without a clear rationale, which I think would be difficult to make, the choice of excluding synthetics appears to introduce bias particularly as a number of studies on pain and PTSD have utilized synthetic preparations. For example, Jetly et al., 2015 conducted a pilot RCT of nabilone for PTSD and nightmares, Fraser (2009) conducted a chart review | We added rationale in methods section. We also added information to both the chronic pain and PTSD section regarding the findings from recent systematic reviews on synthetics as they relate to our populations of interest. There was an SR published that included PTSD data very recently – while it was published after our search dates ended, we did include a description of the review and the studies relevant to PTSD. We added discussion of the applicability of the synthetic studies to our questions of interest – there was only one trial of nabilone with very few patients – the other studies would not have met inclusion criteria. Regardless, even after considering all the additional studies, the authors of the recent SR came to the same conclusion re: insufficient evidence. |

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| | of 47 patients diagnosed with PTSD who received nabilone, and Roitman et al., 2014 conducted an open-label trial of oral THC for PTSD symptoms. While there is currently debate regarding the necessity of using plant-derived versus synthetic cannabinoids in research and treatment, the heart of this debate lies in the importance of secondary cannabinoids and terpenes, which are present in plant-derived products and not in synthetic ones. As it is unlikely that the role of these secondary compounds informed the selection criteria, given that secondary cannabinoids and terpenes are not even reported in the studies discussed in this review, it seems as though it would be difficult to provide a compelling case for this choice. | |
| 6 | 2. An additional consideration for the section entitled "Emerging Harms" could be the recent proliferation of new methods of cannabinoid delivery and the resulting risks of adverse events. For example, the use of "dabs" appears to be associated with particularly heightened risk of tolerance and withdrawal (e.g., Loflin & Earleywine, 2014), and the use of edibles with a number of more acute consequences (e.g., Hudak et al., 2015; Lamy et al., 2016). | We added this information to the emerging harms section. |
| 6 | 3. While the authors are correct in stating that the majority of the literature describes the effects of "cannabis" or "marijuana" without a clear definition of the cannabinoid profile of the product tested or used, the authors similarly make broad comments about consequences of "cannabis," where a more nuanced understanding is emerging. For example, the authors discuss a negative consequence of cannabis use as being psychosis. While this is indeed a finding that has been described in-depth within the literature, and even tied to a genetic vulnerability (i.e., catechol-O-methyltransferase), emerging evidence suggests that the association between cannabis and psychosis is specific to THC and that CBD can actually provide anti-psychotic effects (e.g., Leweke et al., 2012). This level of nuance is not currently provided in the review. | We agree. We have added clarification that it is the THC component that is most likely to be associated with psychotic symptoms and we added a statement to the discussion that CBD has actually been studied as an antipsychotic agent. |
| 6 | 4. Somewhat related to the inclusion and selection of studies for the review, it is puzzling that the Bonn-Miller, Boden, Vujanovic, & Drescher, 2013 study was not included in the list of studies of the effects of cannabis on PTSD symptoms. That study appears to meet inclusion criteria as it was prospective, involved validated measures of PTSD (i.e., PCL), and included a comparison group (CUD diagnosis was compared to those without CUD diagnosis). The sample was adults and there is no indication that they used synthetics. While the study did use data from medical records, so did the administrative study by Wilkinson et al., 2015. This is just confusing. | Although this study included a control group, the controls didn't have CUD, but might have used cannabis; therefore, it did not meet our criteria because we were comparing studies with a non-cannabis using control group. |
| 6 | 5. On page 7, the authors note that they "…did not find any literature comparing rates of CUD among individuals with chronic pain or PTSD to rates in other | Although these studies don't meet inclusion criteria, we have added the 2012 data on prevalence to the background paragraph of our CUD section. |

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| | populations…" While this may be true, a study by Bonn-Miller, Harris, & Trafton (2012) documented the prevalence of PTSD among Veterans with CUD (29.05% in FY12), and a VA fact-sheet by Bonn-Miller & Rousseau utilized VA PERC data to document the percentage of Veterans with PTSD-SUD who had a CUD diagnosis (22.7% in FY14). These data seem to provide information close to what the authors note as being missing from the literature. | |
| 6 | Minor Issues:<br>1. The authors switch between using the terms "cannabis" and "marijuana." The manuscript may flow more nicely if consistent terminology was used throughout. Indeed, the term "cannabis" is generally preferable over "marijuana." | We agree and have made this change. |
| 6 | 2. p. 7: "…found that about 2% if Veterans with non-cancer…" should be "…found that about 2% of Veterans with non-cancer…" | This change has been made. |
| 6 | 3. p. 46: The description of the study by Eades et al. within the text is not consistent with the table. The table is correct and the text is inaccurate. The text should note that the three groups are "High/Low, High/High, and Low/Low". | This change has been made. |
| 6 | 4. p. 46: "…marijuana use versus no marijuana use in the past 6 months is associated with PTSD symptoms and sleep" should be "…marijuana use versus no marijuana use in the past 6 months is associated with differential trajectories of PTSD symptoms over the course of a year." | This change has been made. |
| 6 | 5. p. 48: Replace "In addition, we obtain lab analysis results of the cannabis donated through the Santa Cruz Veterans Alliance to the Veterans. This includes lab analysis results of percent cannabinoids within each product." with "In addition, all product provided to Veterans by the Santa Cruz Veterans Alliance is tested for cannabinoid content by an independent laboratory." | This change has been made. |
| 6 | 6. The authors cite one of the two epidemiological studies of cannabis and PTSD (i.e., Kevorkian et al., 2015), but not the earlier study conducted among the NCS-R (i.e., Cougle et al., 2011). | The Cougle et al. study only reports data on cannabis use, not CUD, and therefore is not included in this section. |
| 7 | I was primarily interested/knowledgeable of the evidence for its use in PTSD and think that you did an excellent job reviewing that sparse literature and mentioning the fact that there are two current RCTs in progress that will add to the literature. Overall, very nice job and I have no further suggestions. | Noted. |
| 9 | Page 6-line 20. "There is low strength evidence that low levels of marijuana smoking do not adversely impact lung function over about 20 years in young adults." Low levels of marijuana smoking are irrelevant to the question of possible harm associated with "medical" that is, frequent/daily use. | We included any data regarding harms from studies that met inclusion criteria. We clearly state that these data apply to low level users and not daily users. We feel that the breadth of evidence will be useful to clinicians who can assess patients' frequency of use and decide whether or not the available data apply to an individual patient. While it is likely that many patients using medical marijuana do so daily, we do not know this to be universally true and there may be |

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| | | substantial proportion of patients who use less frequently. In any case, the lack of information in older or multimorbid populations (which we clearly state) is perhaps an even bigger issue in applying the data in VA clinical settings – again, we attempted to present our broadest look at harms with clarification on generalizability issues. |
| 9 | Page 7-line 38. Recommend deleting this sentence: "One large cross-sectional study of Veterans found that about 2% if (sic) Veterans with non-cancer pain had a diagnosis of CUD, and that this increased to 4%..." This is irrelevant to the question of the risk of cannabis use disorder among patients using marijuana for chronic pain treatment who would more likely use it multiple times daily. If it is possible to discern from the paper the prevalence of CUD among those with pain who used marijuana to treat pain, that would be worth mentioning. THC concentration would also be important to note, as more potent varieties (10 - 20+%) currently marketed would pose a greater risk for CUD than the more common low potency (3%) of a decade ago. | We have corrected this sentence and provided this information (as well as some additional, new information) on prevalence as part of our background. |
| 9 | Page 8-line 30. Ibid. "Light to moderate use" is irrelevant to the question of harm among daily users. | We have clarified that the data does not apply to heavy (daily) users. |
| 9 | Page 8 line 34- also needs to include cannabis use disorder among the serious mental health adverse events. Including indirect evidence about the risk of cannabis use disorder among daily users would better inform decision-making than the indirect study of pain patients who have not used marijuana. | We rewrote the sections on CUD to clarify that there was no evidence with which to assess rates of CUD, and we mention cross-sectional data. |