



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

August 2017

Prepared for:

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

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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; 2017.

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

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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

Key Question (KQ)	<p>KQ 1. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have chronic pain?</p> <p>KQ 1A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</p>	<p>KQ 2. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have PTSD?</p> <p>KQ 2A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</p>	<p>KQ 3. What are the harms associated with cannabis use in adults?</p> <p>KQ 3A: Do the harms differ by patient subgroup, such as patient medical and mental health comorbidities?</p>	<p>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?</p>									
Population	Adults with chronic pain	Adults with PTSD	Adults (not otherwise specified)	Adults with chronic pain or PTSD									
Intervention	Cannabis preparations, including marijuana, hashish, tincture, hashish oil, infusion, and plant extract. <u>Exclude:</u> Synthesized, pharmaceutically prepared cannabinoids (eg, dronabinol, nabilone).												
Comparator	Any comparator												
Outcomes	<ul style="list-style-type: none"> § 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/employment 	<ul style="list-style-type: none"> § Validated PTSD clinical interviews and symptom inventories, such as: Clinician Administered PTSD Scale (CAPS), PTSD Checklist (PCL), PTSD Symptom Scale (PSS), Posttraumatic Diagnostic Scale (PDS), etc § 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/employment 	<table border="1"> <thead> <tr> <th></th> <th>Control group required</th> <th>No control group required (case series accepted)</th> </tr> </thead> <tbody> <tr> <td>General Population</td> <td> <ul style="list-style-type: none"> § Psychotic symptoms (in previously non-psychotic population) § Cardiovascular events § Pulmonary outcomes (eg, forced expiratory volume [FEV1]) § Infectious disease complications § Mortality § Cognitive effects (eg, intelligence quotient [IQ], SLUMS Saint Louis University Mental Status [SLUMS]) </td> <td> <ul style="list-style-type: none"> § Fungal infections § Cannabinoid hyperemesis syndrome § Other emerging harms </td> </tr> <tr> <td>Chronic</td> <td>§ Other substance</td> <td>§ CUD</td> </tr> </tbody> </table>		Control group required	No control group required (case series accepted)	General Population	<ul style="list-style-type: none"> § Psychotic symptoms (in previously non-psychotic population) § Cardiovascular events § Pulmonary outcomes (eg, forced expiratory volume [FEV1]) § Infectious disease complications § Mortality § Cognitive effects (eg, intelligence quotient [IQ], SLUMS Saint Louis University Mental Status [SLUMS]) 	<ul style="list-style-type: none"> § Fungal infections § Cannabinoid hyperemesis syndrome § Other emerging harms 	Chronic	§ Other substance	§ CUD	Not applicable
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<p>Key Question (KQ)</p>	<p>KQ 1. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have chronic pain? KQ 1A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</p>	<p>KQ 2. What are the effects of cannabis on health outcomes and healthcare utilization for adults who have PTSD? KQ 2A: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?</p>	<p>KQ 3. What are the harms associated with cannabis use in adults? KQ 3A: Do the harms differ by patient subgroup, such as patient medical and mental health comorbidities?</p>		<p>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?</p>	
			<p>Pain or PTSD patients</p>	<ul style="list-style-type: none"> use/substance use disorder § Mental health symptoms (not including psychotic symptoms) including depression, anxiety, <i>etc</i> § Employment § Weight gain § Diversion § Utilization of health services § Insomnia 	<ul style="list-style-type: none"> § Withdrawal symptoms 	
<p>Timing</p>	<p>Short- and long-term outcomes</p>					
<p>Study design</p>	<p>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. <u>Exclude:</u> Non-systematic or narrative reviews, opinions, case studies, case series, and cross-sectional studies.</p>	<p>Study designs included for KQ1 and KQ2, plus case series for certain harms (see Outcomes box). <u>Exclude:</u> Non-systematic or narrative reviews, opinions, cross-sectional studies, and individual case reports.</p>		<p>Not applicable</p>		



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. For the subgroup of neuropathic pain studies, we conducted a study-level meta-analysis of the proportion of patients experiencing clinically significant ($\geq 30\%$) pain relief (Appendix D) using the profile-likelihood random-effects model²³ to combine risk ratios (RRs). We assessed the magnitude of statistical heterogeneity among the studies using the standard Cochran's chi-square test the I^2 statistic.²⁴ All analyses were done using Stata/IC, version 13.1 (StataCorp).

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).²⁵ 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.²⁶ 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

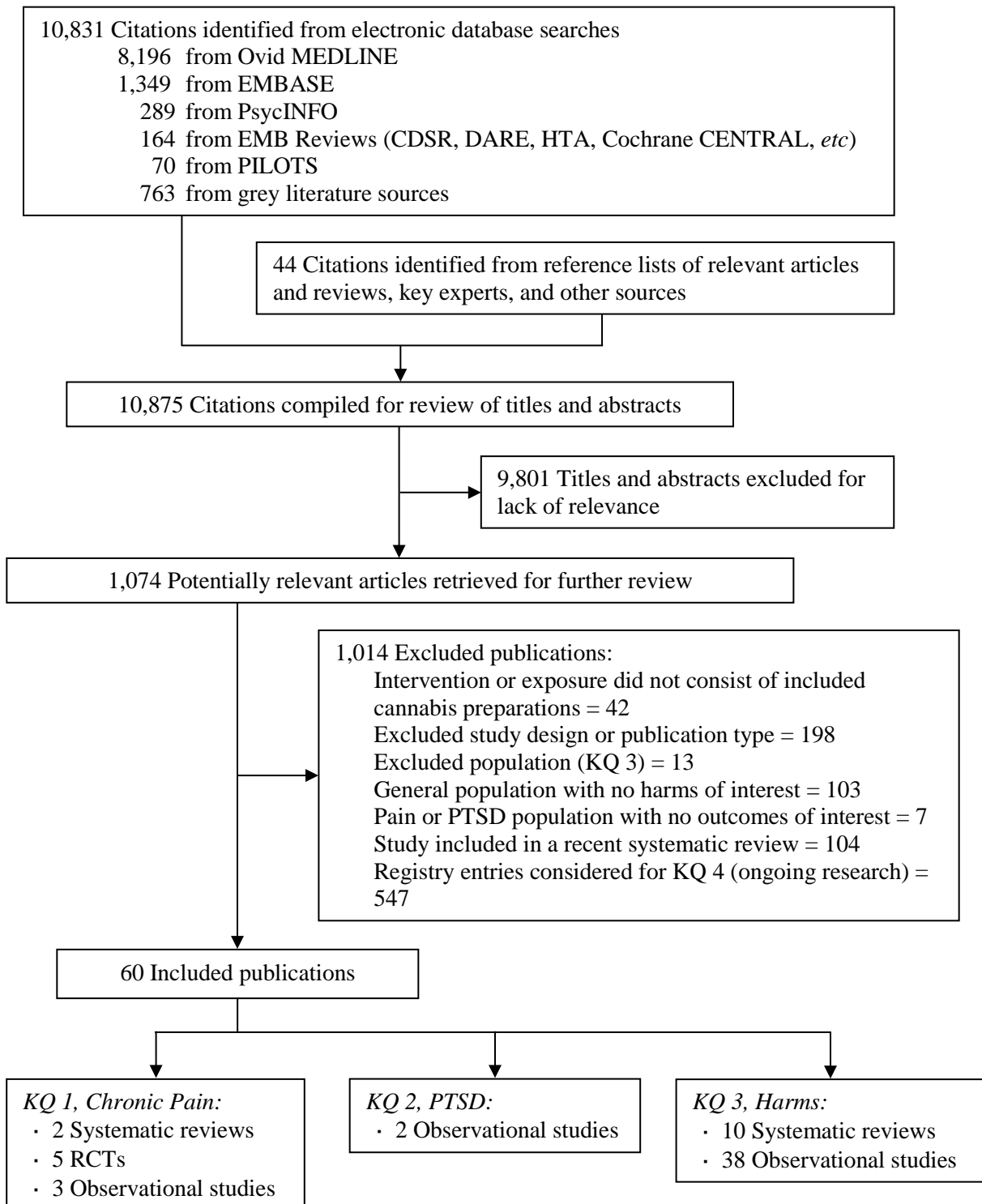
A draft version of this report was reviewed by 8 individuals with technical expertise and clinical leadership. Their comments and our responses are presented in Appendix D.

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

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

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 included eligible trials identified by the prior reviews, and found an additional 8 studies²⁷⁻³⁴ 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). Table 2 presents the overall findings of studies that examined pain and other outcomes in patients with chronic pain. Table 3 presents the findings of RCTs that reported pain outcomes.

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

Table 2. Studies of the Overall 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 ²⁹ UK, 5 sites RCT (N=36) Unclear ROB	Age 57 100% Caucasian 41.7% male MS: 16.4 years Spasticity: 12.7 years Nabiximols use: 3.6 years; Subjects experienced ongoing benefit with nabiximols. Mean daily dose of nabiximols: 8.25 sprays Mean baseline scores, Treatment vs placebo: Spasticity score on NRS: 3.6 (SD=1.7) vs 4.13 (SD=2.2), 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. C: Placebo, mean daily dose 9.0 sprays	4-week treatment period Pain: NR 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). 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 ²⁷ Europe, 51 sites RCT (N=241) Low ROB	Age 48.6 40% male 100% white/Caucasian, 18% with previous cannabis use in last year, MS years: 12.6 Spasticity years: 7.7 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). C = Placebo oromucosal spray. Maximum permitted dose was 12 sprays in any 24 hour period.	Pain: NR Spasticity: Change in mean NRS score at 12 weeks: -0.84 (95% CI, -1.29 to -0.40), <i>P</i> =.0002 % with at least 30% improvement, T vs C: 74% vs 51%; OR 2.73 (95% CI, 1.59-4.69), <i>P</i> =.0003. Other: Nabiximols were significantly superior (<i>P</i> <.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 ²⁸ US, single site Double-blind, placebo-controlled, crossover clinical trial (N=13) High ROB	Age 48.3 39% male 53% wheelchair bound 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. Patients were initiated at varying oral doses of THC (range: 2.5 to 7.5 mg in first paired trial). 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 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), <i>P</i> =.03; improvement started at 7.5 mg dose. No change from baseline on physician ratings on all measures (limb weakness, limb spasticity, limb coordination, gait impairment, reflexes; all <i>P</i> -values > 0.05).	No difference in AEs for 7.5 mg THC vs C. AEs were more frequent and less tolerable with higher doses of THC. 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 ³⁰ UK, single site outpatient clinic Pilot study: double-blind, placebo-controlled single-patient cross-over RCT (N=24) Low ROB	Age 48 50% male Types of pain: MS (n=14) Spinal cord injury (n=4) Brachial plexus damage (n=1) Limb amputation due to neurofibromatosis (n=1) Target symptoms: 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 T1: CBD T2: THC T3: Both THC and CBD, 1:1 ratio C: Placebo Maximum permitted dose was 120 mg every 24 hours.	Mean (SD) daily VAS (0-100) over last 7 days of each 2-week period, <i>P</i> -value vs C: Pain: baseline 30.1 (17.8) to T1: 54.8 (22.6), <i>P</i> <.05 T2: 54.6 (27.4), <i>P</i> <.05 T3: 51.3 (27.0), <i>P</i> =NS C: 44.5 (22.7) Spasm: baseline 40.9 (18.5) to T1: 54.6 (19.1), <i>P</i> =NS T2: 58.4 (22.3), <i>P</i> <.05 T3: 55.8 (24.4), <i>P</i> <.05 C: 47.3 (22.6) Spasticity: baseline 29.0 (16.1) to T1: 47.8 (18.5), <i>P</i> =NS T2: 57.3 (22.2), <i>P</i> <.05 T3: 43.8 (15.6), <i>P</i> =NS C: 42.3 (18.1)	AEs reported by 33% in CBD, 55% in THC, 30% in CBD:THC, and 48% in placebo; 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 ³⁴ Spain, single site Retrospective cohort study (N=56) High ROB	Adults with fibromyalgia, with moderate to severe symptoms, and who were resistant to pharmacological treatment. Age 50 years 5% male (users 7%, non-users 4%) 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%. C: non-users (for QOL comparison) Duration of use: 40% < 1 year 32% 1 to 3 years 29% ≥ 3 years THC/CBD content NR.	Pain: 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), $P<.001$. Other: 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). 68% of patients reported reduction in pharmacological treatment (not otherwise specified) when they started using cannabis. Increased perception of well-being (40.0 mm increase); relaxation (27.6 mm increase), and somnolence scores (20.0 mm increase) were significantly increased from baseline, $P<.05$; 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: Somnolence (64%) Dry mouth (61%) Sedation (43%) Dizziness (36%) High (32%) Tachycardia (29%) Conjunctival irritation (25%) Hypotension (21%) 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 ³³ Canada Single site "N of 1" double-blind, placebo-controlled, crossover RCT (N=34) Low ROB	Age 46.7 32% male 100% with chronic pain (mostly neuropathic) 47% with MS	Sublingual spray that delivered 2.5 mg each of: T1: THC T2: CBD T3: both CBD and THC (1:1 ratio), C: 0.1 mL matching placebo; 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 Symptom 1 score (median [IQR]) pain reduction: T1: 4.63 (1.74-6.06) T2: 5.45 (3.6-7.4) T3: 4.4 (2.6-5.8) C: 5.9 (2.8-7.3) T1 and T3 both significantly better than C ($P<.05$, $P<.01$, respectively) Symptom 2 score (median [IQR]) pain reduction: C: 4.98 (2.61-7.50) T1: 4.08 (1.33-5.43) T2: 5.03 (3.16-6.88) T3: 4.28 (2.33-5.51) T1 and T3 significantly better than placebo ($P=.054$, $P<.001$, respectively) 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 patients also had reduction with CBD. Other: Sleep Quality: Percentage of "good" nights during trial period, median (IQR): T1: 42.9% (57.2-35.7) T2: 36.9% (47.9-28.6) T3: 55.4% (78-34.5) C: 17.0% (35.7-3.6) 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 ³² Canada, outpatient GI clinic Retrospective cohort study (N=313) High ROB	<p>Adults with IBD Age 39.6 years (non-users 40.2, users 36.6 years) 31% male (27.4% non-users; 50.0% users) Note: Significant between group differences in race, household income, and education level ($P < .05$)</p> <p>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.</p> <p>Note: Significant between-group difference in type of disease ($P = .035$)</p>	Patients self-reported cannabis use; varied between smoking (95%), oral (9%) and drinking (5%); no info provided about dose or frequency Comparator: non-users (<i>ie</i> , those who did not endorse cannabis use for treatment of IBD)	<p>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).</p> <p>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</p>	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 ³¹ Canada, 7 sites Prospective cohort (N=431) Low ROB	Age: 49.0 (cannabis vs control: 45.5 vs 52.4) 43.1% male (cannabis vs control: 51.2% vs 35.2%) Groups differed significantly for age and gender ($P<.001$) Type of pain, cannabis vs control: Nociceptive 16.3% vs 18.1% Neuropathic 38.6% vs 32.4% Both 45.1% vs 49.5% 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; median daily dosing was 2.5 g/day Patients used any delivery system that they were comfortable with (27% smoked, 61% combined smoking, oral, and vaporization, 8% consumed orally) 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): T: 5.54 (2.11) C: 6.10 (2.13) Difference = 1.10 (95% CI, 0.72-1.56) 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) Other: 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) 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: Serious AEs: no sig. difference, 13% vs 19%; 40 vs 56 events Adjusted IRR (95% CI) for event = 1.08 (0.57-2.04) Most common AEs: surgical/medical procedures 25% vs 20% GI disorders 25% vs 13% Most common serious AEs in cannabis group: -abdominal pain (n=3, 12%), -intestinal obstruction (n=3, 12%) -nephrolithiasis (n=3, 12%) -2 withdrawals from treatment due to serious side effects (1 convulsion, 1 alcohol problem); 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); Most common AEs, cannabis group: -nervous system: n=165 (20%) -gastrointestinal: n=109 (13.4%) -respiratory: n=103 (12.6%); 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).

Table 3. Characteristics and Findings^a of RCTs of the Effects of Cannabis Extracts on Pain Outcomes

Trial	Pain Type	N	Intervention Formulation; Dosage; Study Design	Duration	Patients Achieving $\geq 30\%$ Pain Reduction, T vs C, n/N (%)	Mean Difference (T – C) in Change From Baseline		Overall Risk of Bias
						NRS Pain Scale, points ^b	VAS Pain Scale, mm ^c	
Abrams, 2007 ³⁵	Neuropathic sensory, HIV-associated	55	Smoked THC, 4%; 1 cigarette/d (0.9 g)	12 d	13/25 vs 6/25 (52.0 vs 24.0)	–	–	Low
Berman, 2004 ³⁶	Neuropathic brachial plexus avulsion	48	Nabiximols (THC oromucosal spray); ≤ 48 sprays/d; crossover	2 wk (no washout)	–	–	–	Low
Ellis, 2009 ³⁷	Neuropathic sensory, HIV-associated	34	Smoked THC, started at 4% and adjusted as necessary; 4 smoking sessions/d; crossover	5 d (2-wk washout)	–	–	–	Low
Lynch, 2014 ³⁸	Neuropathic chemotherapy-induced	18	Nabiximols; ≤ 12 sprays/d	4 wk (2-wk washout)	–	–	–	Low
Notcutt, 2004 ³³	Mostly neuropathic; 47% MS	34	Sublingual spray delivering 2.5-mg THC, 2.5-mg CBD, or 2.5 mg each; 1 to 8 sprays/d	8 wk	THC: 9/24 vs NR (37.5 vs NR) CBD: 3/24 vs NR (12.5 vs NR) THC+CBD: 9/24 vs NR (37.5 vs NR)	–	–	Low
Nurmikko, 2007 ³⁹	Neuropathic pain with allodynia	125	Nabiximols; ≤ 48 sprays/d	5 wk	16/63 vs 9/62 (25.4 vs 14.5)	–	–8.03 (–13.83 to –2.23)	High
Selvarajah, 2010 ⁴⁰	Neuropathic diabetic peripheral	30	Nabiximols; maximum unclear	12 wk	8/15 vs 9/14 (53.3 vs 64.3)	–	9.50 (–11.30 to 27.80)	Unclear
Serpell, 2014 ⁴¹	Neuropathic peripheral with allodynia	246	Nabiximols; ≤ 24 sprays/d	15 wk	34/123 vs 19/117 (27.6 vs 16.2)	–0.34 (–0.79 to 0.11)	–2.86 (–7.22 to 1.50)	Low

Trial	Pain Type	N	Intervention Formulation; Dosage; Study Design	Duration	Patients Achieving ≥30% Pain Reduction, T vs C, n/N (%)	Mean Difference (T – C) in Change From Baseline		Overall Risk of Bias
						NRS Pain Scale, points ^b	VAS Pain Scale, mm ^c	
Wallace, 2015 ⁴²	Neuropathic diabetic peripheral	16	Vaporized THC, 7%, 4%, or 1%; 4 h observation at each dose; crossover	4 h (2-wk washout)	1% THC: 10/16 vs 10/16 (62.5 vs 62.5) 4% THC: 12/16 vs 10/16 (75.0 vs 62.5) 7% THC: 13/16 vs 10/16 (81.3 vs 62.5)	–	–	Low
Ware, 2010 ⁴³	Neuropathic, postsurgical or posttraumatic	23	Smoked THC, 2.5%, 6%, or 9.4%; crossover	5 d (9-d washout)	–	–	–	Low
Wilsey, 2008 ⁴⁴	Neuropathic	38	Smoked THC, 3.5% or 7%; 9 puffs; crossover	6 h (3- to 21- d washout)	3.5% THC: 4/36 vs 2/33 (11.1 vs 6.1) 7% THC: 0/34 vs 2/33 (0.0 vs 6.1)	–	–	Low
Wilsey, 2013 ⁴⁵	Neuropathic, peripheral	39	Vaporized THC, 1.29% or 3.53%; 4 puffs at 1 h after baseline, 4 to 8 puffs at 3 h; crossover	6 h (3- to 7-d washout)	1.29% THC: 21/37 vs 10/38 (56.8 vs 26.3) 3.53% THC: 22/36 vs 10/38 (61.1 vs 26.3)	–	1.29% THC: –11 3.53% THC: –10	Low
Wilsey, 2016 ⁴⁶	Neuropathic, spinal cord injury	42	Vaporized THC, 2.9% or 6.7%; 400 mg using Foltin Puff Procedure at 8 to 12 puffs over 240 min, adaptable dose design	8 h	2.9% THC: 18/26 vs 8/18 (69.2 vs 44.4) 6.7% THC: 31/35 vs 8/18 (88.6 vs 44.4)	–	–	Low
Collin, 2010 ⁴⁷	MS	337	Nabiximols; ≤ 24 sprays/d	14 wk	–	–	–	Unclear
Corey- Bloom, 2012 ⁴⁸	MS	37	Smoked THC, 4%; one 800-mg cigarette	3 d (11-d washout)	–	–	–	Unclear
Langford, 2013 ⁴⁹	MS	339	Nabiximols; ≤12 sprays/d	14 wk	84/167 vs 77/172 (50.3 vs 44.8)	0.17 (–0.62 to 0.29)	–	Unclear

Trial	Pain Type	N	Intervention Formulation; Dosage; Study Design	Duration	Patients Achieving ≥30% Pain Reduction, T vs C, n/N (%)	Mean Difference (T – C) in Change From Baseline		Overall Risk of Bias
						NRS Pain Scale, points ^b	VAS Pain Scale, mm ^c	
Rog, 2005 ⁵⁰	MS	66	Nabiximols; ≤ 48 sprays/d	5 wk	–	–1.25 (–2.11 to –0.39)	–6.58 (–12.97 to –0.19)	Low
Van Amerongen, 2017 ⁵¹	MS	24	Orally ingested THC, 99% (EPC002A, Namisol); 1.5 or 5 mg 3 times/d	2 wk	–	Week 2: –1.09 (–1.98 to –0.20) (<i>P</i> = 0.018) Week 4: –0.85 (–1.74 to –0.04) (<i>P</i> = 0.061)	–	Unclear
Wade 2003 ³⁰	MS (67%)	24	Pump-action sublingual spray delivering 2.5-mg THC, 2.5-mg CBD, or 2.5 mg each; ≤120 mg/d; crossover	2 wk (no washout)	–	–	Baseline: 30.1 (SD, 17.8) 2 nd week of each group: CBD: 54.8 (SD, 22.6; <i>P</i> < 0.05) THC: 54.6 (SD, 27.4; <i>P</i> < 0.05) THC+CBD: 51.3 (SD, 27.0; <i>P</i> = NS) Placebo: 44.5 (SD, 22.7)	Low
Wade, 2004 ⁵²	MS	160	Nabiximols; ≤ 48 sprays/d	6 wk	–	–	–	Unclear
Zajicek, 2003 ⁵³	MS	657	THC/CBD capsules; ≤ 25 mg/d	15 wk	–	–	–	High
Zajicek, 2012 ⁵⁴	MS	279	THC/CBD capsules; ≤ 25 mg/d	12 wk	–	–	–	Low
Johnson, 2010 ⁵⁵	Cancer	119	Nabiximols; ≤ 8 sprays/d	2 wk	23/53 vs 12/56 (43.4 vs 21.4)	–0.32 (–0.86 to 0.22)	–	Unclear
		117	THC oromucosal spray	2 wk	12/52 vs 12/56 (23.1 vs 21.4)	–0.67 (–1.21 to –0.14)	–	
Noyes, 1975 ⁵⁶	Cancer	10	THC capsules; 5, 10, or 15 mg; crossover	1 d (no washout)	–	–	–	High

Trial	Pain Type	N	Intervention Formulation; Dosage; Study Design	Duration	Patients Achieving ≥30% Pain Reduction, T vs C, n/N (%)	Mean Difference (T – C) in Change From Baseline		Overall Risk of Bias
						NRS Pain Scale, points ^b	VAS Pain Scale, mm ^c	
Portenoy, 2012 ⁵⁷	Cancer	360	Nabiximols; 1 to 4, 6 to 10, or 11 to 16 sprays/d	9 wk	1 to 4 sprays: 30/91 vs 24/91 (33.0 vs 26.4) 6 to 10 sprays: 26/87 vs 24/91 (29.9 vs 26.4) 11 to 16 sprays: 22/90 vs 24/91 (24.4 vs 26.4)	1 to 4 sprays: -0.75 (-1.28 to -0.22) 6 to 10 sprays: -0.36 (-0.89 to 0.18) 11 to 16 sprays: -0.09 (-0.62 to 0.44)	–	Unclear
De Vries, 2016 ⁵⁸	Abdominal pain (includes chronic pancreatitis, postsurgical pain)	65	Orally ingested THC, 99% (EPC002A, Namisol); step-up phase: days 1 to 5, 3 mg 3 times/d; days 6 to 10, 5 mg 3 times/d; stable dose phase: days 11 to 52, 8 mg 3 times/d	7 wk	–	-1.6 (SD, 1.78) vs -1.9 (SD, 2.18) (<i>P</i> = 0.92)	–	High
Blake, 2006 ⁵⁹	Rheumatoid arthritis	58	Nabiximols; ≤48 sprays/d	5 wk	–	–	-3 (-18 to 9)	Unclear

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).⁵³ 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.⁵⁴ 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.²⁷⁻³⁰ Two studies were rated as low risk of bias,^{27,30} one was at high risk of bias,²⁸ and one was unclear.²⁹ In a large multicenter European trial with low risk of

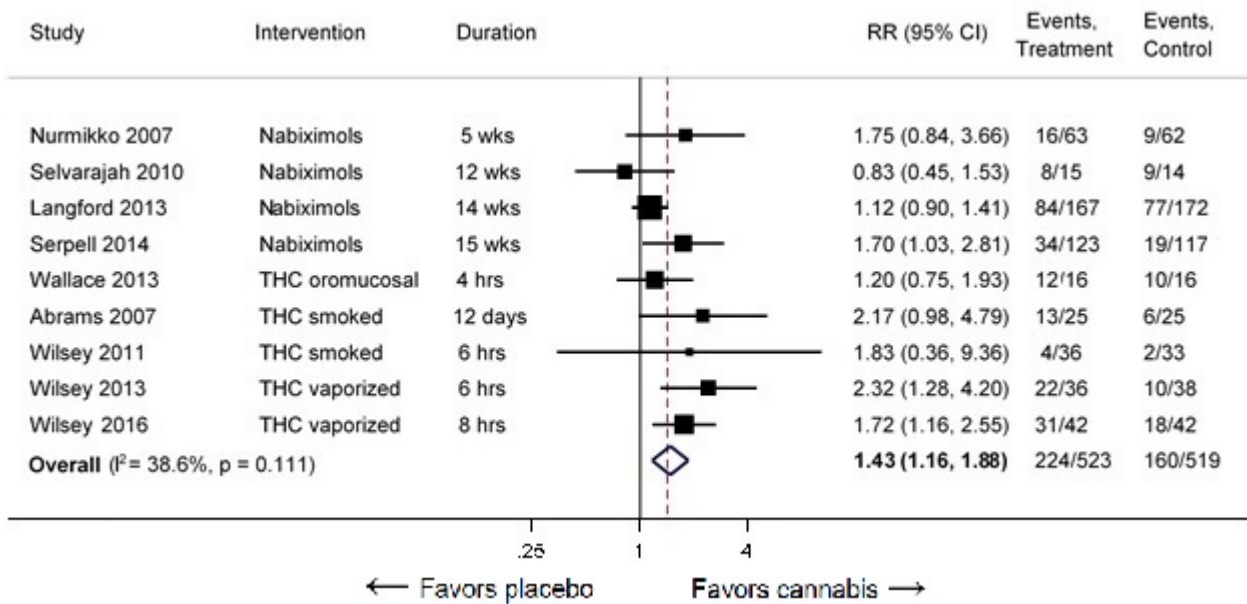
bias (N=241), patients with MS and moderately severe spasticity were randomized to open-label nabiximols or placebo if they initially experienced at least a 20% reduction in spasticity Numeric Rating Scale (NRS) during an open-label nabiximols run-in period. Over half (52.2%) of participants failed to 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.²⁸ 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.³⁰ 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.²⁹ 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

Thirteen trials examined the effects of cannabis-based preparations on neuropathic pain (Table 3). Participants had central or peripheral neuropathic pain related to various health conditions. Of these studies, 11 trials were determined to be at low ROB,^{33,35-38,41-46} 1 as having unclear ROB,⁴⁰ and 1 as having high ROB.³⁹ Overall, we found low-strength evidence that cannabis may improve pain in some patients with neuropathic pain. Studies generally did not find clinically significant differences on continuous pain scales between groups, but a higher proportion of intervention patients experienced clinically significant pain relief at up to several months of follow-up. In a meta-analysis of nine studies that reported $\geq 30\%$ pain reduction, intervention patients were more likely to report improvement in pain (RR 1.43, 95% CI 1.16 to 1.88; $I^2=38.6\%$, $p = 0.111$; Figure 2). Most studies were small, few reported outcomes beyond 2 to 3 weeks, and none reported long-term outcomes.

Figure 2. Odds of achieving $\geq 30\%$ pain reduction with cannabis compared to placebo in trials of patients with neuropathic pain



In the largest RCT, 246 patients with peripheral neuropathic pain self-titrated nabiximols up to a maximum allowable dose of 24 sprays/day or received a placebo.⁴¹ Those who completed the study (79 nabiximols and 94 placebo) and responded positively to the intervention demonstrated a significant decrease in pain (OR 1.97, 95% CI 1.05 to 3.70). However, among all participants, including those who did not have an intervention response, the reduction in the NRS pain scale did not reach clinical or statistical significance. The second-largest low ROB RCT included 55 patients with HIV-associated sensory neuropathy who were randomized to smoke either 3.56% THC cigarettes or placebo 3 times daily for 5 days. Among those who completed the study, 52% (n=13) of the treatment group demonstrated a clinically significant (> than 30%) reduction in pain compared to 24% (n=6) in the placebo group.³⁵

A one-year prospective-cohort study (n=431) among patients with nociceptive and neuropathic chronic non-cancer pain provides information about long-term treatment effects.³¹ Cannabis users experienced a reduction in average pain intensity (VAS) that was stable across 4 time points over a one-year period among cannabis users, but the change was small and not clinically significant (0.92 change, 95% CI 0.62 to 1.23).

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 RCT³³ and one observational study (N=465) (Table 2).³¹

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.³³ 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.³¹ This study assessed the efficacy of a standardized herbal cannabis product (12.5% \pm 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.^{56,57} 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 period⁵⁶ and among the low-dose (1 to 4 sprays per day) and medium-dose (6 to 10 sprays per day) nabiximols groups.⁵⁷ 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.⁵⁷ 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.⁵⁶

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 review¹⁶ and only 2 primary studies^{60,61} meeting our inclusion criteria (Table 4), 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.⁶²⁻⁶⁷ Of the 6 included studies, 3 were on nabilone, a synthetic form of cannabis.⁶²⁻⁶⁴ 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,^{65,66} and the last was a prospective observational study;⁶⁷ 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 47,000.⁶⁰ 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.⁶¹ 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 4. 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 ⁶⁰ VA retrospective cohort study (N=2276) Medium ROB	All Veterans referred for intensive PTSD treatment. Excluded those with prior drug or alcohol use. Mean age 51.7 96.7% male	Self-reported cannabis use during 4-month follow-up period: 850 never users 299 stoppers (use at admission but not at 4 months post-baseline) 296 continuing users (use at admission and 4 months post-baseline) 831 starters (no use at admission but use at 4 months post-baseline) 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: $F=21.47, P<.0001$	Violent behavior: Starters significantly more violence than continuing users, never users, and stoppers. $F=21.28, P<.0001$. Alcohol abuse: Starters significantly more alcohol abuse than continuing users, never users, and stoppers; continuing users significantly more alcohol abuse than stoppers. $F=88.51, P<.0001$. Drug abuse: Continuing users and starters significantly more drug abuse than never users and stoppers. $F=176.26, P<.0001$. Employment status: No significant differences among groups. $F=0.66, P=.58$.
Johnson 2016 ⁶¹ VA matched case-control cross-sectional study (N=700) 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. Mean age 47.1 91.0% male	Self-reported cannabis use within 3 months of the assessment (n=350) Compared to no lifetime cannabis use reported at the time of assessment (n=350) Users were matched to non-users on age and gender.	Users had significantly worse PTSD symptoms than non-users: $t(349) = 0.11, P=.91$	Users vs non-users (%): Employed: 23 vs 40, $\chi^2(1) = 21.38, P<.0001$ Financially stable: 61 vs 71, $\chi^2(1) = 8.15, P<.0001$ Depression symptoms: No significant differences between groups. $t(349) = 1.85, P=.07$ Suicidal ideation: 33 vs 26, $\chi^2(1) = 12.18, P=.04$ 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.³¹ 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.³³ 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 2007,⁶⁸ and 2 more recent prospective cohort studies^{69,70} 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.⁶⁸ 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 5). 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 ($N=5,016$).⁷⁰ 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.⁶⁹ 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.⁷¹ 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 5). 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.⁷² 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.⁷³ 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 5. 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 ⁶⁹ New Zealand Community-based birth cohort (N=1037) Low ROB	Birth cohort of all individuals in Dunedin, New Zealand, enrolled 1972-1973	Cannabis use only: 25% Lifetime cannabis use, joint- years: 16% > 1, 84% ≤ 1 Comparators: Non-users: 23% Tobacco only: 6% Tobacco + cannabis users: 46%	32 years follow-up. FEV1 Change with each joint-year cannabis in non- tobacco smokers: 5.4 mL (95% CI, -7.1 to 18.0). Change with each pack-year tobacco: -3.9 mL (95% CI, -8.7 to 0.9). FVC Change with each joint-year cannabis in non- tobacco smokers: 13.4 mL (95% CI, -0.8 to 27.6). 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 ₂ O, P=.042), and alveolar volume (28.5 mL, P=.021)
Pletcher 2012 ⁷⁰ US, 4 cities Community-based cohort (N=5016) CARDIA Low ROB	Healthy 18-30 year olds enrolled in 1985 Mean age 25 45% male	Cannabis users: 16% Lifetime use, median joint- years: 0.9 2 median episodes in last 30 days Comparators: Non-users: 46% Tobacco only: 17% Tobacco + cannabis users: 21%	20 years follow-up. FEV1 Highest (> 10 joint-years) vs lowest quartile lifetime cannabis exposure: +36 ml (95% CI, -6.5 to 79). Highest (> 20 pack-years) vs lowest quartile tobacco exposure: -101ml (95% CI, -136 to -65) FVC Highest (> 10 joint-years) vs lowest quartile lifetime cannabis exposure: +59 ml (95% CI, 12 to 107). 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 ⁷² US, multicenter Hospital-based cohort (N=2097) Determinants of Myocardial Infarction Onset Study High ROB	Patients interviewed just after MI. Users vs non-users: Mean age: 44 vs 52 % male: 94 vs 77	Cannabis smoking within year prior to MI: 109/2097 (5%) Comparator: No cannabis use within prior year (95%)	12.7 years follow-up. Adjusted HR death, compared to no use: Any use: 1.29 (95% CI, 0.81 to 2.05) < weekly: 1.31 (95% CI, 0.74 to 2.35) ≥ 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 ⁷³ US, multicenter Hospital-based case- crossover (N=3882) Determinants of Myocardial Infarction Onset Study High ROB	Patients interviewed just after MI. Mean age 44 years (cannabis users) 94% male 68% current tobacco smokers	Exposure: cannabis smoking within one hour prior to onset of MI: 9/124 (7%) 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: 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 6). 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).⁷⁴ 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).⁷⁵ 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.⁷⁶ 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).⁷⁷ 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.⁷⁸ 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 6. Observational Studies of Cannabis Use and Cancer Risk

Cancer type Study, setting, design (N patients) Risk of bias (ROB)	Sample description Mean age % male	Description and duration of cannabis use	Primary findings	Comments/other findings
<i>Head and neck cancer</i> Carvalho 2015 ⁷⁴ US, Africa, South America Meta-analysis of 13 case-control studies Hospital-based (6) and cancer-registry (5) studies Medium ROB	Patients with definitive diagnosis of head-neck cancer (in studies of moderate to high methodologic quality). Mean age NR % male NR	<u>% ever cannabis smokers:</u> Cases: range 2.4 to 83; overall 12.6 Controls: range 0.4 to 83; overall 14.3	9 studies contributed data to meta-analysis OR (95% CI) for head neck cancer among cannabis users: 1.02 (0.91 to 1.14); adjusted for age, gender, race, tobacco use	
<i>Lung cancer</i> Zhang 2015 ⁷⁵ International Lung Cancer Consortium North America, New Zealand, Europe Individual-level meta-analysis of 6 case-control studies (2,159 cases, 2,985 controls, combined) Medium ROB	Patients with histologically confirmed lung cancer. Cases vs controls: Median age: 57.3 vs 53.0 % male: 50 vs 53	<u>Cannabis and tobacco use:</u> Cases: ≥ 1 joint-year: 10% ≥ 1 joint-year, non-tobacco users: 3.0% Never smoked tobacco: 17% Controls: ≥ 1 joint-year: 11% ≥ 1 joint-year, non-tobacco users: 4.7% 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)
<i>Lung cancer</i> Callaghan 2013 ⁷⁶ Sweden Community-based cohort study (N=49,231) High ROB	Military conscripts born between 1949-1951 and inducted between 1969 and 1970 100% male	<u>Lifetime cannabis use at time of conscription:</u> Cases: Once (2.5%) 2-4 times (3.0%) 5-10 times (1.7%) 11-50 times (1.5%) > 50 times/"heavy" (1.7%) Controls: Never (82.5%) Tobacco only: 55.2% Tobacco + cannabis: 9.1% Cannabis with no tobacco use: 13.4%	40 years follow-up. 189 incident cases of lung cancer (by ICD-9 codes). HR (95% CI) for lung cancer among self-reported heavy users: 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 Study, setting, design (N patients) Risk of bias (ROB)	Sample description Mean age % male	Description and duration of cannabis use	Primary findings	Comments/other findings
<i>Testicular cancer</i> Gurney 2015 ⁷⁷ US Meta-analysis of 3 case-control studies (719 cases, 1419 controls combined) High ROB	Young adults with histologically confirmed testicular cancer Mean age NR; range 18 to 50 100% male	Overall proportion with ever, never, weekly, and current cannabis use NR	Cancer risk OR (95% CI), compared with never use: 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. ≥ 10 year use: 1.50 (1.08 to 2.09). 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
<i>Transitional cell cancer</i> Chacko 2006 ⁷⁸ US, 2 VA sites Case-control (52 cases, 104 controls) High ROB	Patients under age 60 with transitional cell cancer presenting to urology clinic. Mean age 51 100% male	Cases: Smoked > 40 joint-years: 40.4% Ever smoked cannabis: 88.5% Smoked tobacco and cannabis: 76.9% Smoked tobacco only: 17.3% Smoked cannabis only: 11.5% Controls: Smoked > 40 joint-years: 15.1% Smoked cannabis: 69.2% Smoked tobacco and cannabis: 65.4% Smoked tobacco only: 27.9% Smoked cannabis only: 3.9%	Joint-years cannabis use as continuous variable was significantly associated with transitional cell cancer: <i>P</i> -trend .01 (adjusted for tobacco use, smoked meat use, radiation, agent orange, and dye exposure) Risk of cancer with > 40 joint-years cannabis use compared to none: OR 3.4 (unadjusted, <i>P</i> =.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).⁷⁹ 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.^{80,81} 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.⁷⁹

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.⁸² 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.⁸²

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.⁸³ 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.⁸⁴

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.⁸⁵ 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 review⁸⁴ and 7 studies⁸⁶⁻⁹² 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.^{86-88,92} 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).^{86,87} 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).⁸⁷ 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; $P = .037$).⁸⁶ 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).⁹²

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).⁸⁸

Acute cannabis-induced psychosis

Three studies examined the relationship between cannabis use and acute psychotic symptoms.⁸⁹⁻⁹¹ 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.⁸⁹ 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 ($t=2.28$, $P < .05$).⁹¹ 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.⁹⁰

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.⁹³ 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.⁹³

Schreiner and colleagues' systematic review⁹³ 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)⁹⁴ and the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)⁹⁵ 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 2012.⁹⁶

We did not find any articles comparing rates of CUD in chronic pain or PTSD populations to other populations.

A recent large national prospective cohort study found high prevalence of CUD (36%) among those reporting cannabis use in the past year ($N = 1279$).⁹⁷ Cannabis use was associated with incident cannabis use disorder (adjusted odds ratio, 9.5 [CI, 6.4 to 14.1]) in a large ($N = 34,653$) prospective cohort study. Cannabis use was also associated with increased odds of other substance use disorders (any substance use disorder: odds ratio [OR], 6.2; 95% CI, 4.1-9.4; any alcohol use disorder: OR, 2.7; 95% CI, 1.9-3.8).

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).⁹⁸ 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.⁹⁹ 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.¹⁰⁰ 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.¹⁰¹ Finally, Kevorkian and colleagues (2015) examined data from the National Epidemiologic Survey on Alcohol and Related Conditions ($N=34,396$).¹⁰² 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.¹⁰³ 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.¹⁰⁴⁻¹⁰⁶ 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.¹⁰⁷ 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,^{108 13841} or through the practice of “hotboxing.”¹⁰⁹

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.¹¹⁰⁻¹¹⁶ The largest case series included 98 patients from a single institution.¹¹⁷ 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.¹¹²

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.¹¹⁸ 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.¹¹⁹ 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.¹²⁰ 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.¹²¹ Edible cannabis use has become more common in recent years, especially in states in which cannabis has been legalized for recreational or medical purposes.¹²² A recent case series described 5 patients hospitalized with acute psychosis after ingestion of edible cannabis.¹²³ 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.¹²⁴ 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 7), 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 7. 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) · Crossover RCT · Sponsored by the University of California, San Francisco; National Heart, Lung, and Blood Institute (NHLBI); University of Minnesota - Clinical and Translational Science Institute · 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. 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. 1. Cannabis cigarette: 4.7% THC and 5.1% CBD 2. Placebo cigarette: 0% THC and 0% CBD Participants to receive both treatments in random order for 5 days (2-week washout).	Pain VAS evaluated during the 5-day inpatient exposure. Other outcomes: mood; QOL assessments; inflammation markers and disease progression from blood samples.
Dayan, L (NCT02560545) · Crossover RCT · Sponsored by the Tel-Aviv Sourasky Medical Center · 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. 1. Cannabis oil: 20% THC, 40 mg per 70 kg weight; route of administration not specified 2. Placebo oil	Evaluation of pain using a questionnaire at 1 month. Other outcomes: testing of the pain-modulation system using TSA Neurosensory Analyzer.
GW Pharmaceuticals Ltd. (NCT01262651) · Parallel RCT · 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. 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). 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: 1. Nabiximols (oromucosal spray delivering 2.7 mg THC/2.5 mg CBD) 2. Placebo	mean sleep disruption.
GW Pharmaceuticals Ltd. (NCT01424566) · Crossover RCT · Sponsored by the GW Pharmaceuticals Ltd.; Otsuka Pharmaceutical Development & Commercialization, Inc. · 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. 100 µl oromucosal spray administered twice daily up to a maximum of 10 sprays per day: 1. Nabiximols (oromucosal spray delivering 2.7 mg THC/2.5 mg CBD) 2. Placebo	Mean 11-point NRS average pain score over the last 4 days of treatment period (7 weeks). Other outcomes: percentage improvement in NRS average pain score; mean NRS worst pain score; mean sleep disruption.
Irving, P (NCT01562314) · Parallel RCT · Sponsored by GW Research Ltd · 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. One of the following twice daily for 10 weeks: 1. GWP42003 (oral capsule that contains both CBD and THC) up to 250 mg twice daily 2. Placebo	Percentage of participants achieving remission, quantified as a Mayo score of ≤ 2 (with no sub-score > 1). Other outcomes: NRS pain, Mayo total score, health-related QOL, Subject Global Impression of Change, Global Assessment of Illness Severity.
Martinez, D (NCT02675842) · Parallel RCT · Sponsored by the New York State Psychiatric Institute · 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. 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: 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. 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
Martinez, D (NCT02683018) · Crossover RCT · Sponsored by the New York State Psychiatric Institute · 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.	<p>3.11% THC 2. Placebo: 0.0% CBD and 0.01% THC</p> <p>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.</p> <p>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: 1. High CBD/low THC: 15.76% CBD and 3.11% THC 2. Placebo: 0.0% CBD and 0.01% THC</p>	<p>subjective effects; cognitive status; physiological state; opioid use.</p> <p>Change in pain ratings using the McGill Pain Questionnaire and the 9 item BPI at 4 weeks.</p> <p>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.</p>
Ware, M & Lynch, M (NCT02324777) · Crossover RCT · Sponsored by Prairie Plant Systems Inc., McGill University Health Center, Dalhousie University, Algorithme Pharma Inc., Research Institute of the McGill University Health Center · 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.	<p>40 adults with painful osteoarthritis of the knee (NRS Pain intensity score ≥ 4 out of 10).</p> <p>100 mg of finely ground herbal cannabis drug product formulation administered via the Volcano® Medic Vapourizer (percentages are mass fractions): 1. 21.9% THC and 0.8% CBD 2. 15.0% THC and 5.0% CBD 3. 9.0% THC and 9.5% CBD 4. 3.8% THC and 10.0% CBD 5. 0.6% THC and 13.0% CBD 6. Placebo: < 0.3% THC and < 0.3% CBD Participants to be randomly assigned to</p>	<p>Change in VAS pain intensity at 3 hours post-dose (measured every 15 minutes).</p> <p>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)</p>

PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion	Study Title	Purpose of Study	Participants; Intervention(s)/ Comparator	Outcomes and Timing
Wilsey, BL (NCT02460692) · Parallel RCT · Sponsored by the University of California, San Diego & National Institute on Drug Abuse (NIDA) · 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).	receive all 6 formulations in random order for one day of exposure (6-days washout) 120 adults with chronic low back pain (painDETECT questionnaire score ≥ 19 , and daily NRS Pain intensity ≥ 3 out of 10). One of the following for 8 weeks: 1. Vaporized cannabis: 3.5% THC 2. Dronabinol 3. Placebo	11-point pain intensity NRS. 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) · Crossover RCT · Sponsored by National Institute on Drug Abuse (NIDA) · 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. 1. Vaporized cannabis: 3.5% THC 2. Vaporized cannabis: 7.0% THC 3. Placebo	Pain intensity and pain unpleasantness (timing NR). 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 8). 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 8 provides a summary of ongoing studies related to benefits and harms of cannabis for PTSD.

Table 8. 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) · Double-blind RCT · Funded by VA Clinical Science Research and Development CDA-2 · 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: 1. CBT for insomnia 2. CBT for insomnia + CBT-I coach (mobile app) 3. Placebo control (quasi-desensitization)	Change in cannabis use frequency, point prevalence abstinence, and change in sleep quality post-treatment and 6 months post-treatment.
Bedard-Gilligan, M (NCT02874898) · Single Group Assignment · Funded by the National Institute on Drug Abuse (NIDA) · 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). 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). 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) · Crossover RCT · Funded by The Colorado Department of Public Health and Environment · 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) Smoked cannabis up to 1.8 g/day for 3 weeks: 1. High THC (more THC than CBD) 2. High CBD (more CBD than THC) 3. High THC/High CBD (equal amounts) 4. Placebo cannabis (low levels THC/CBD)	Change in CAPS Global Severity Score at 3 weeks and 8 weeks after randomization. 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 · Observational Study · Unfunded · 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. 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 · Observational Study · Funded by The Colorado Department of Public Health and Environment · 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. Assessment at baseline and 3-, 6-, 9-, and 12-months following baseline. Measures include interview (MINI, CAPS-5, TLFB), self-report, computerized neuropsych 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. 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 · 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
<ul style="list-style-type: none"> · Observational Study · University of Washington Alcohol and Drug Abuse Institute · VA Puget Sound Health Care System Research & Development · 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: <ul style="list-style-type: none"> 1. Anonymous online survey (n=200) 2. Daily symptom and use monitoring (<i>ie</i>, IVR; n=48) 3. In-depth qualitative interviews (n=30) 4. Blood draw for cannabis biomarkers (n=48) 	<ul style="list-style-type: none"> and replicate previous findings related to PTSD symptoms, cannabis use, motives for use, and craving. · Examine (via IVR) day-to-day relations between cannabis use and PTSD symptoms along with a one-time assessment of cannabis use motives. · 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.
<p>Eades, J (NCT02517424)</p> <ul style="list-style-type: none"> · Crossover RCT · Sponsored by Tilray and the University of British Columbia · 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.	<p>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).</p> <p>Cannabis administered via vaporization up to 2.0 g/day as needed:</p> <ol style="list-style-type: none"> 1. High THC/Low CBD cannabis 2. High THC/High CBD cannabis 3. Low THC/Low CBD cannabis 	<p>Change in CAPS Global Severity Score at 3 weeks and 8 weeks after randomization.</p> <p>Other outcomes: anxiety and depression symptoms; psychosocial functioning; preference; sleep quality; problems associated with cannabis use; suicidal thoughts or behaviors.</p>

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 10 summarizes the evidence on the benefits and harms of cannabis use. Overall, we found limited evidence on the potential benefits and harms of cannabis use in chronic pain populations. We found low-strength evidence that cannabis preparations with precisely defined THC-cannabidiol content (most in a 1:1 to 2:1 ratio) may alleviate neuropathic pain but insufficient evidence in populations with other types of pain. The applicability of these findings to current practice may be low, in part because the formulations studied may not be reflective of what most patients are using, and because the consistency and accuracy of labeled content in dispensaries are uncertain.¹²⁵ Furthermore, most studies are small, many have methodological flaws, and the long-term effects are unclear given the brief follow-up of most studies. There is insufficient evidence of effects on quality of life or functional status.

Among neuropathic pain studies, we found a discrepancy between continuous and dichotomous pain outcomes. Possible interpretations are that cannabis is simply not consistently effective or that, although cannabis may not have clinically important effects on average, subgroups of patients may experience large effects. We did not find data to clarify which subgroups of patients are more or less likely to benefit.

We found no trials 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 for most indications, 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.¹²⁶ 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,⁷³ 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,¹²³ and CBD may in fact have antipsychotic effects.^{127,128}

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.^{60,61} 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.¹²⁹ 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).¹³⁰ 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.¹³¹ 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.¹³² 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).¹³² 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,^{9,10,99,133} a greater number of opioid refills,⁹⁹ 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.¹³⁴ 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.¹³⁵

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.¹²⁵

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.¹³⁶ 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 9 lists opportunities for future research in each of the areas we reviewed.

Table 9. Suggestions for Future Research

Area of Inquiry	Research Suggestions
Efficacy of cannabis for treating chronic pain	<ul style="list-style-type: none"> · Populations other than MS or neuropathic pain · Studies with longer follow-up duration · Studies with cannabis-naïve patients · Compare cannabis to other active treatments for pain, including opioids · Use cannabis preparations that are routinely available to consumers in the US, especially given legalization in more states · Examine the effects of different THC:CBD ratio preparations, and more study of CBD preparations · Obtain blood levels of THC and CBD to assess actual level of drug exposure
Efficacy of cannabis for treating PTSD	<ul style="list-style-type: none"> · RCT of treatment · Trials comparing to cognitive behavioral therapy, other standard treatments
CUD	<ul style="list-style-type: none"> · Studies assessing risk of CUD in patients using cannabis
Pulmonary harms	<ul style="list-style-type: none"> · Observational studies in older and multimorbidity populations
Cardiovascular harms	<ul style="list-style-type: none"> · Observational studies with more comprehensive information about exposure history
Cancer	<ul style="list-style-type: none"> · Larger scale observational studies of lung cancer reflecting patterns of use in the US · More studies to investigate the insufficient evidence of a possible link with testicular and transitional cell cancers
Mental health harms	<ul style="list-style-type: none"> · Studies on acute psychosis in chronic pain and PTSD populations · Identification of non-schizophrenic patients at high risk for psychosis · Risk mitigation strategies for cannabis-induced psychosis · Studies on mania and suicidality in PTSD populations · Effects on sleep
Cognitive function	<ul style="list-style-type: none"> · Studies in chronic pain and PTSD populations
Emerging harms	<ul style="list-style-type: none"> · Studies characterizing cannabis hyperemesis syndrome in a larger number of patients · 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. Limited evidence suggests that cannabis may alleviate neuropathic pain, but there is insufficient evidence in other populations. There is insufficient evidence examining the effects of cannabis in PTSD populations. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for potentially serious mental health adverse effects, such as psychosis. Data on its effects on long-term physical health vary; harms in older patients or those with multiple comorbidities have not been studied.

Table 10. 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): - 2 of THC/CBD capsules - 1 of nabiximols - 1 of sublingual spray delivering THC, CBD, or THC/CBD combined	Favorable effect on pain and spasticity: Significant relief from patient-reported muscle stiffness, pain, and spasticity occurred with 12 to 15 weeks of treatment with THC (2.5 mg)/CBD (1.25 mg) capsules in 2 studies. A 12-week study of nabiximols (2.7 mg THC/2.5 mg CBD oromucosal spray) reported significant improvement in spasticity. A sublingual spray delivering 2.5 mg of CBD, THC, or both for sequential 2-week periods reported mixed effects. THC alone significantly improved pain and spasticity, but CBD alone and THC/CBD combined had inconsistent effects.	Low	Few methodologically rigorous studies, but fair number of patients; inconsistent results; little long-term data; restrictive entry criteria in largest study which only included patients with initial response in run-in phase; applicability to formulations available in dispensaries may be low
	3 Unclear ROB studies of nabiximols (combined N=562; 36 to 337 per study)			
	7 High ROB studies (combined N=430; 13 to 160 per study): - 3 of nabiximols - 2 of THC/CBD capsules - 1 of smoked THC - 1 of oral THC			
	4 Low ROB studies (combined N=1017; 24 to 424 per study): - 2 of THC/CBD capsules - 1 of nabiximols - 1 of sublingual spray delivering THC, CBD, or THC/CBD combined	Other outcomes: Small improvements in sleep in 4 studies: Self-reported sleep quality improved in 2 studies of THC/CBD capsules. Nabiximols were significantly superior to placebo for reducing sleep disruption in a 12-week study (N=241). Sleep improved significantly in a small study (N=24) of a sublingual spray containing 2.5 mg each of CBD:THC. Other: Nabiximols were significantly superior to placebo for Barthel Activities of Daily Living ($P=.0067$), Physician Global Impression of Change ($P=.005$), Subject Global Impression of Change ($P=.023$), and Carer Global Impression of Change ($P=.005$) in Function in a 12-week study (N=241).	Low (sleep) Insufficient (other outcomes)	Few methodologically rigorous studies, but fair number of patients; inconsistent results; little long-term data; restrictive entry criteria in largest study which only included patients with initial response in run-in phase; applicability to current practice may be low Only one study of nabiximols – not tested otherwise

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

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

	N studies	Findings	Strength of Evidence^a	Comments
∅ 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 ∅ 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).
∅ 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).
∅ Psychosis	1 systematic review 7 studies including patients without psychotic symptoms at baseline: - 3 Low ROB studies - 3 Medium ROB studies - 1 High ROB study	History of cannabis use was associated with an increase in risk of developing psychotic symptoms.	Low	Consistent evidence from large observational studies and some evidence of increased risk with higher levels of use; consistent with data from small experimental studies suggesting risk of acute psychosis in some patients; magnitude of risk unclear and not specifically studied in chronic pain or PTSD populations

	N studies	Findings	Strength of Evidence^a	Comments
∅ Cognitive effects	1 systematic review of 33 studies	Active long-term cannabis use associated with small negative effects on all aspects of cognition. Mixed, inconsistent findings on long-term effects in past users.	Moderate Insufficient (past use)	Consistent data from large number of studies on effects on active long-term use, but inconsistent findings from smaller number of studies regarding effects in those that were abstinent and no data available specifically in chronic pain or PTSD populations
∅ CUD	One large cohort study (N=34,653; N = 1279 past year cannabis use in last year)	OR incident CUD 9.5 (95% CI 6.4-14.1) Prevalence CUD (among those using in last year) 36% Prevalence past year cannabis dependence 7.7% Prevalence past year cannabis abuse 28%	Low	In cross-sectional studies, the prevalence of CUD in chronic pain populations was about 2%

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

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

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient = Any estimate of effect is very uncertain.

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