Comparative Effectiveness Review
Number 250

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain

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Prepared by:
Pacific Northwest Evidence-based Practice Center
Portland, OR

Investigators:
Marian S. McDonagh, Pharm.D.
Jesse Wagner, M.A.
Azrah Y. Ahmed, B.A.
Rongwei Fu, Ph.D.
Benjamin Morasco, Ph.D.
Devan Kansagara, M.D., M.C.R.
Roger Chou, M.D., FACP

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

David Meyers, M.D.
Acting Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Craig A. Umscheid, M.D., M.S.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.
Task Order Officer
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Technical Expert Panel

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

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to the report follows:

Inna Belfer, M.D., Ph.D.*
Program Officer/Program Director, National Center for Complementary and Integrative Health
National Institutes of Health
Bethesda, MD

Kevin Boehnke, Ph.D.*
Research Investigator, Chronic Pain and Fatigue Research Center, Anesthesiology Department, University of Michigan
Ann Arbor, MI

Wilson M. Compton, M.D., M.P.E.*
Deputy Director, National Institute on Drug Abuse, National Institutes of Health
Bethesda, MD

Emily Deng, M.D., M.P.H., M.S.*
Medical Officer, Controlled Substance Staff
Office of Center Director, Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD

Erin E. Krebs, M.D., M.P.H., FACP*
Chief of General Internal Medicine, Minneapolis Veterans Affairs Health Care System
Professor of Medicine, Department of Medicine, University of Minnesota
Minneapolis, MN

Mallory Loflin, Ph.D.
Principal Investigator/Clinical Scientist, Center of Excellence in Stress and Mental Health, Veterans Affairs, San Diego Healthcare System
Assistant Professor, University of California San Diego School of Medicine, Department of Psychiatry
San Diego, CA

Mark Sullivan, M.D., Ph.D.*
Professor of Psychiatry and Behavioral Sciences, Adjunct Professor of Anesthesiology and Pain Medicine, Adjunct Professor of Bioethics and Humanities
University of Washington
Seattle, WA

C. Michael White, Pharm.D., FCCP, FCP*
Department Head of Pharmacy Practice, University of Connecticut, School of Pharmacy
Co-Director, Health Outcomes, Policy, and Evidence Synthesis Research Group
Hartford, CT

*Provided input on Draft Report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Matthew Bair, M.D., M.S.
Core Investigator, Veterans Affairs Health Services Research and Development Service, Center for Health Information and Communication
Research Scientist, William M. Tierney Center for Health Services Research, Regenstrief Institute
Professor of Medicine, Indiana University School of Medicine, Indiana University
Indianapolis, IN

Tianjing Li, M.D., M.H.S., Ph.D.
Associate Professor, Department of Ophthalmology, University of Colorado Anschutz Medical Campus
Associate Professor, Department of Epidemiology, University of Colorado School of Public Health
Aurora, CO

Kerri Schoedel, Ph.D.
Principal and Director, Altreos Research Partners, Inc.
Toronto, ON, Canada

Heather Tick, M.D., M.A.
Clinical Professor, Department of Family Medicine and Department of Anesthesiology and Pain Medicine, University of Washington
Seattle, WA

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain

Structured Abstract

Objectives. To evaluate the evidence on benefits and harms of cannabinoids and similar plant-based compounds to treat chronic pain.

Data sources. Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases, reference lists of included studies, submissions received after Federal Register request were searched to July 2021.

Review methods. Using dual review, we screened search results for randomized controlled trials (RCTs) and observational studies of patients with chronic pain evaluating cannabis, kratom, and similar compounds with any comparison group and at least 1 month of treatment or followup. Dual review was used to abstract study data, assess study-level risk of bias, and rate the strength of evidence. Prioritized outcomes included pain, overall function, and adverse events. We grouped studies that assessed tetrahydrocannabinol (THC) and/or cannabidiol (CBD) based on their THC to CBD ratio and categorized them as high-THC to CBD ratio, comparable THC to CBD ratio, and low-THC to CBD ratio. We also grouped studies by whether the product was a *whole-plant* product (cannabis), cannabinoids *extracted or purified* from a whole plant, or *synthetic*. We conducted meta-analyses using the profile likelihood random effects model and assessed between-study heterogeneity using Cochran's Q statistic chi square and the I^2 test for inconsistency. Magnitude of benefit was categorized into no effect or small, moderate, and large effects.

Results. From 2,850 abstracts, 20 RCTs (N=1,776) and 7 observational studies (N=13,095) assessing different cannabinoids were included; none of kratom. Studies were primarily short term, and 75 percent enrolled patients with a variety of neuropathic pain. Comparators were primarily placebo or usual care. The strength of evidence (SOE) was low, unless otherwise noted. Compared with placebo, comparable THC to CBD ratio oral spray was associated with a small benefit in change in pain severity (7 RCTs, N=632, 0 to10 scale, mean difference [MD] −0.54, 95% confidence interval [CI] −0.95 to −0.19, I^2=28%; SOE: moderate) and overall function (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI −0.73 to −0.16, I^2=24%). There was no effect on study withdrawals due to adverse events. There was a large increased risk of dizziness and sedation and a moderate increased risk of nausea (dizziness: 6 RCTs, N=866, 30% vs. 8%, relative risk [RR] 3.57, 95% CI 2.42 to 5.60, I^2=0%; sedation: 6 RCTs, N=866, 22% vs. 16%, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%; and nausea: 6 RCTs, N=866, 13% vs. 7.5%, RR 1.79, 95% CI 1.20 to 2.78, I^2=0%). Synthetic products with high-THC to CBD ratios were associated with a moderate improvement in pain severity, a moderate increase in sedation, and a large increase in nausea (pain: 6 RCTs, N=390 to 10 scale, MD −1.15, 95% CI −1.99 to −0.54, I^2=39%; sedation: 3 RCTs, N=335, 19% vs. 10%, RR 1.73, 95% CI 1.03 to 4.63, I^2=0%; nausea: 2 RCTs, N=302, 12% vs. 6%, RR 2.19, 95% CI 0.77 to 5.39; I^2=0%). We found moderate SOE for a large increased risk of dizziness (2 RCTs, 32% vs. 11%, RR 2.74, 95% CI 1.47 to 6.86, I^2=0%). Extracted whole-plant products with high-THC to CBD ratios (oral) were associated

with a large increased risk of study withdrawal due to adverse events (1 RCT, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33) and dizziness (1 RCT, 62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34). We observed a moderate improvement in pain severity when combining all studies of high-THC to CBD ratio (8 RCTs, N=684, MD −1.25, 95% CI −2.09 to −0.71, I^2=50%; SOE: moderate). Evidence on whole-plant cannabis, topical CBD, low-THC to CBD, other cannabinoids, comparisons with active products, and impact on use of opioids was insufficient to draw conclusions. Other important harms (psychosis, cannabis use disorder, and cognitive effects) were not reported.

Conclusions. Low to moderate strength evidence suggests small to moderate improvements in pain (mostly neuropathic), and moderate to large increases in common adverse events (dizziness, sedation, nausea) and study withdrawal due to adverse events with high- and comparable THC to CBD ratio extracted cannabinoids and synthetic products in short-term treatment (1 to 6 months). Evidence for whole-plant cannabis, and other comparisons, outcomes, and PBCs were unavailable or insufficient to draw conclusions. Small sample sizes, lack of evidence for moderate and long-term use and other key outcomes, such as other adverse events and impact on use of opioids during treatment, indicate that more research is needed.

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Evidence Summary

Main Points

In RCTs (mostly placebo controlled) of patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months):

- Studies of cannabis-related products were grouped based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio using the following categories: high-THC to CBD, comparable THC to CBD, and low-THC to CBD.
- Comparable THC to CBD ratio oral spray is probably associated with small improvements in pain severity and overall function. There was no effect on serious adverse events. There may be a large increased risk of dizziness and sedation and a moderate increased risk of nausea.
- Synthetic THC (high-THC to CBD) may be associated with moderate improvement in pain severity, no effect on overall function and increased risk of sedation, and large increased risk of nausea. Synthetic THC is probably associated with a large increased risk of dizziness.
- Extracted whole-plant high-THC to CBD ratio products may be associated with large increases in risk of study withdrawal due to adverse events and dizziness.
- Evidence on whole-plant cannabis (including patient's choice of products), low-THC to CBD ratio products (topical CBD), other cannabinoids (cannabidivarin), and comparisons with other active interventions was insufficient to draw conclusions.
- Other key adverse event outcomes (psychosis, cannabis use disorder, cognitive deficits) and outcomes on the impact on opioid use were not reported.
- No evidence on other plant-based compounds such as kratom met criteria for this review.

Background and Purpose

Chronic pain is defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing[1,2] and affects approximately 100 million people in the United States.[3] Chronic pain adversely affects physical and mental functioning, productivity, and quality of life, and is often refractory to treatment and associated with substantial costs.[4-6] While opioids are often prescribed for chronic pain, they have small to moderate effects on pain and overall function, with frequent adverse effects,[7] and the 2016 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends nonopioid therapy as the preferred treatment of chronic pain.[1,2] However, recent systematic reviews found that several nonopioid drugs,[8] and some nonpharmacologic treatments[9] also have small to moderate effects on chronic pain and overall function. Some nonopioid treatments had frequent overall adverse events and some less frequent yet serious adverse effects, while nonpharmacological treatments typically reported few adverse events.[8]

Cannabinoids are a group of closely related compounds that are active in cannabis, with the two main cannabinoid compounds being THC and CBD. THC has demonstrated analgesic properties,[10,11] although its psychoactive effects and abuse potential may limit its suitability as an analgesic. Based on preclinical studies, CBD and related cannabinoids may also have some analgesic or anti-inflammatory properties and are not thought to be psychoactive or addictive.[12,13] While not derived from plants, two synthetic cannabinoid products, dronabinol

(synthetic THC) and nabilone (a THC analog), have also been studied for treating chronic pain. Other plant-based compounds with effects similar to opioids or cannabis, such as kratom, have been considered to treat chronic pain. These may also have serious harms including dependence, addiction, and physiological withdrawal potential.[14]

The ongoing opioid crisis and the limited efficacy of opioids drive a search for alternative pain treatments, including cannabis and related compounds to better treat chronic pain.[7,15] The purpose of this systematic review was to evaluate the evidence on benefits and harms of cannabinoids and similar plant-based substances (e.g., kratom) to treat chronic pain.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Effective Healthcare Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), and we describe these in the full report. Our searches covered publication dates from database inception to July 2021. Cannabinoid interventions were categorized according to their THC to CBD ratio (comparable, high, low) and according to the source of the compound (whole-plant, extracted from whole-plant, or synthetic). Strength of evidence was assessed as low, moderate, high, or insufficient, and magnitude of effect was assessed according to Table A. Additionally, results that were below the threshold for a small effect were considered to reflect "no effect." Results with a small, medium, or large effect that were not statistically significant were considered to have "potential effects" if the 95 percent confidence interval included meaningful benefit or harm, but were not so wide that they included the potential for both meaningful benefits and harms.[16,17]

Table A. Definitions of effect sizes

Effect Size	Definition
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.

Results

The included randomized controlled trials (RCTs) are described in Table B. Seven observational studies were also included and are described in Table C.

Table B. Characteristics of included randomized controlled trials of cannabinoids

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
THC to CBD Ratio	Comparable	High	High	Low	NA - other cannabinoids
Source	Plant-extracted	Plant-extracted	Synthetic	Plant-extracted	Plant-extracted
N Studies	7	2	9	1	1
Comparator (Study Count)	Placebo (7)	Placebo (2)	Placebo (6); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1)	Placebo (1)	Placebo (1)

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Risk of Bias % High, % Moderate, % Low	29%, 57%, 14%	0%, 50%, 50%	22%, 44%, 33%	100% high	100% moderate
Total Randomized	882	297	534	29	34
Age, Mean Years	53	52	50	68	50
Female, %	66%	89%	61%	38%	3%
% Non-White[a] (Study Count)	1.6% (2)	1% (1)	5.4% (3)	NA	NA
Primary Pain Type (Study Count)	NPP (6); inflammatory arthritis (1)	NPP (1); fibromyalgia (1)	NPP (6); fibromyalgia (1); headache (1); visceral pain (1)	NPP (1)	NPP (1)
Baseline Pain Score, Mean (Range)[b]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.46 (4 to 8.1)[c]	5.38 (4.67 to 6.14)	6.28 (6.12 to 6.44)
Study Duration	4 to 15 weeks	8 to 12 weeks	4 to 47 weeks	4 weeks	4 weeks

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; NA = not applicable; NPP = neuropathic pain; THC = tetrahydrocannabinol.

[a] (Study count) = number of studies reporting this characteristic at baseline.

[b] Scores were standardized to a 0 to 10 scale.

[c] Weighted mean includes median scores for one study (6 vs. 6).

Table C. Characteristics of included observational studies

Characteristic	THC/CBD	THC	Synthetic THC
THC to CBD Ratio	Unclear	High	High
Source	Any cannabis product (patient's choice)	Plant-based	Synthetic (nabilone)
N Studies	5	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (1)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)
ROB % High, % Moderate, % Low	60% high, 40% moderate	100% high	100% moderate
N Total	12,508	431	156
Age, Mean Years	53	49	61
Female, %	55%	57%	59%
% Non-white (study count)	54% (1); NR (4)	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic non-cancer pain	Chronic non-cancer pain	NPP
Baseline Pain Score, Mean (Range)[a]	5.35 (4.56 to 8.00)	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)
Study Duration, Weeks (Range)	12 to 208	52	26

Abbreviations: CBD = cannabidiol; NPP = neuropathic pain; NR = not reported; ROB = risk of bias; THC = tetrahydrocannabinol.

[a] Scores were standardized to a 0 to 10 scale.

Tables D and E summarize the findings of the review. Other prioritized adverse events (cannabis use disorder [CUD], psychosis, cognitive deficits) and the impact on the use of opioids for chronic pain, were not reported in the RCTs.

Table D. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

THC to CBD Ratio	Pain Response Effect Size (N Studies) [SOE][a]	Pain Severity Effect Size (N Studies) [SOE][a]	Overall Function Effect Size (N Studies) [SOE][a]
Comparable THC/CBD Oromucosal Spray	Potential effect (4)[b] [+]	Small effect (7) [++]	Small effect (6) [++]

THC to CBD Ratio	Pain Response Effect Size (N Studies) [SOE][a]	Pain Severity Effect Size (N Studies) [SOE][a]	Overall Function Effect Size (N Studies) [SOE][a]
High-THC – Synthetic, Oral	Insufficient (1)	Moderate effect (5) [+]	No effect (3) [+]
High-THC – Extracted From Whole-plant, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low-THC – Topical CBD	No evidence	Insufficient (1)	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC, Smoked)	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: + = low, ++ = moderate, +++ = high.
[b] Findings with small or larger magnitude of effect, not statistically significant; but with SOE rating of Low or higher (downgraded mainly for imprecision).

Table E. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

THC to CBD Ratio	WAE Effect Size (N Studies) [SOE][a]	SAE Effect Size (N Studies) [SOE][a]	Dizziness Effect Size (N Studies) [SOE][a]	Nausea Effect Size (N Studies) [SOE][a]	Sedation Effect Size (N Studies) [SOE][a]
Comparable THC/CBD Oromucosal Spray	Insufficient (5)	No effect (2) [+]	Large effect (6) [+]	Moderate effect (6) [+]	Large effect (6) [+]
High-THC – Synthetic, Oral	Potential effect[b] (4) [+]	Insufficient (1)	Large effect (2) [++]	Potential effect[b] (2) [+]	Moderate effect (3) [+]
High-THC – Extracted From Whole-plant, Oral	Large effect (1) [+]	Insufficient (1)	Large effect (1) [+]	No evidence	No evidence
Low-THC – Topical CBD	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC, smoked)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.
[a] Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: + = low, ++ = moderate, +++ = high.
[b] Findings with small or larger magnitude of effect, not statistically significant; but with SOE rating of Low or higher (downgraded mainly for imprecision).

Limitations

Key limitations of the evidence base relate to the limited ability to provide strong, reliable, estimates of effect due to: 1) inadequate sample sizes or numbers of studies, 2) narrowness of enrolled populations (see Tables B and C), 3) lack of evidence or adequate evidence on high-THC to CBD products extracted from whole-plant cannabis, whole-plant cannabis products, low-THC to CBD products (e.g., topical CBD), and other plant-based compounds including kratom, and 4) inconsistent reporting of important outcomes such as pain response, overall function or disability, effect on opioid use, and longer-term adverse events, such as CUD, psychosis, and cognitive deficits. These limitations affect both the stability and applicability of the findings.

Implications and Conclusions

The implications of the present findings for clinical practice are mixed. Select individuals with chronic neuropathic pain may experience small to moderate short-term improvements in pain with some cannabis products, but the impact on moderate or long-term outcomes is unknown. The evidence on adverse events with cannabis-related products is much less robust than the evidence on similar outcomes with opioids or nonopioid medications. Comparing the results with recent systematic reviews that used the same methodology, suggests that the risk of sedation and dizziness appear similar between cannabis-related products, opioids, and the anticonvulsants pregabalin and gabapentin, while the risk for nausea appears to be larger with opioids and the antidepressant duloxetine than with cannabis-related products.7,8 These qualitative and indirect comparisons with very limited evidence on cannabis products relative to the other drugs however need confirmation. The comparisons of effects on serious and long-term harms are however not possible, even indirectly. Understanding how the adverse event profiles of cannabis products compare with other available treatments for chronic pain, particularly opioid and non-opioid medications, is essential to determining the benefit to harm ratio. However, the strength of this evidence is mostly low, and more data are needed to confidently recommend this as a treatment for various chronic pain-related conditions or for patients with diverse demographic or clinical characteristics.

In the short term (4 weeks to <6 months), small magnitude improvements in pain severity and overall functioning or disability were found with comparable THC to CBD ratio oral sprays, with large increased risk of dizziness and sedation, and moderate increased risk of nausea compared with placebo. In the short term, moderate improvements in pain severity and no effect on overall function were found with high-THC to CBD synthetic oral products, with moderate increased risk of withdrawal from studies due to adverse events, serious adverse events, and sedation, and a large increased risk of dizziness compared with placebo. In the short-term, moderate improvements in pain severity were found with whole-plant extracted, high-THC to CBD oral products, with large increased risk of study withdrawal due to adverse events and dizziness, and moderate increased risk of serious adverse events. The strength of these findings are low to moderate. Evidence on whole-plant cannabis, topical CBD, and other cannabinoids was insufficient to draw conclusions. There was no evidence on other plant-based compounds such as kratom. Important limitations include small sample sizes, lack of evidence for moderate and long-term use, and few data for key outcomes, such as other serious adverse events (e.g., psychosis, CUD) and impact on use of opioids during treatment. In order to better understand the small to moderate improvements in pain, and the complete adverse event profile of cannabinoids used to treat chronic pain, future studies that resolve these limitations are needed. Specific recommendations for future research are included in the full report.

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Introduction

Background

Chronic pain, defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,[1,2] is a serious public health issue in the United States, affecting approximately 100 million people[3] and resulting in over $560 billion annually in costs.[4] Chronic pain substantially impacts physical and mental functioning, reducing productivity and quality of life. It is the leading cause of disability and is often refractory to treatment.[5,6] Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015.[7] This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[7-9] involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdoses related to prescription opioids in the United States,[1] with an estimated 17,087 prescription opioid overdose deaths in 2016.[7] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[10]

While opioids are often prescribed for chronic pain, they have small to moderate effects on pain and overall function with frequent adverse effects,[11] and the 2016 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends nonopioid therapy as the preferred treatment of chronic pain.[1,2] However, recent systematic reviews found that several nonopioid drugs,[12] and some nonpharmacologic treatments[13] also have small to moderate effects on chronic pain and overall function. Some nonopioid treatments had frequent overall adverse events and some less frequent but serious adverse effects, while nonpharmacological treatments typically reported few adverse events.[12]

The challenges of treating chronic pain in light of the lackluster evidence on commonly prescribed prescription medications and the ongoing opioid crisis drive a search for alternative pain treatments, including cannabis. The goals of current research are to identify alternative treatments with equal or better benefits for pain while avoiding potential unintended consequences that could result in harms. Plants have historically been evaluated for medicinal properties, with some being developed into drug therapies (i.e., the field of pharmacognosy). Some preclinical data suggest that cannabinoids may have analgesic properties, though research in this area is mixed.[14] Tetrahydrocannabinol (THC), one of many cannabinoids in cannabis, has demonstrated analgesic properties,[15,16] though its psychoactive effects and abuse potential increase its risk and suitability as an analgesic. Other cannabinoids (e.g., cannabidiol [CBD], cannabigerol [CBG], and cannabichromene [CBC]) may also have some analgesic or anti-inflammatory properties and are not thought to be psychoactive or addictive,[17,18] but may not be as potent as THC. Observational studies indicate that some patients use cannabis and related compounds as a substitute for opioids.[19-22]

Other plant-based compounds (PBCs) such as kratom, though pharmacologically distinct from cannabis, may be considered as analgesics, in part due to their community-use as substitutes for opioids.[23,24] They may also have serious harms, such as dependence, addiction, and physiological withdrawal potential.[25] Although some PBCs thought to reduce pain are currently classified as Schedule I by the Drug Enforcement Administration, there is disagreement on scheduling others, such as kratom.[26] Recent legalization of cannabis by several states[27] may lead to more, and higher quality research on PBCs with potential for treating chronic pain.[28] Initiatives to develop and study alternative interventions for chronic pain are expected to

contribute to this increase in research on PBCs, specifically for pain. This living review was initiated in response to a request from Congress.[28,29]

The key decisional dilemmas for treating chronic pain with cannabis and other PBCs include the effectiveness in treating chronic pain and the effect of specific formulations, doses or potencies, routes of administration, types of pain, and other patient characteristics on outcomes. Similarly, it is important to identify harms and adverse effects of these interventions which may include risks of frequent or daily use, risk of developing dependence or addiction (e.g., cannabis use disorder), mental health effects, and impacts on harms of co-prescribed opioids. It is also unclear what the impact of using cannabis or other PBCs for pain has on opioid use, and, how their effectiveness compares to other interventions.

Purpose and Scope of the Systematic Review

This is a "living systematic review," which assesses the effectiveness and harms of plant-based treatments for chronic pain conditions. The review is living in the sense that it uses methods to identify and synthesize recently published literature on an ongoing basis. For the purposes of this review, PBCs included are those that are similar to opioids in effect and that have the potential for addiction, misuse, and serious adverse effects; other PBCs, such as herbal treatments are not included. The intended audience includes policy and decision makers, funders and researchers of treatments for chronic pain, and clinicians who treat chronic pain.

Methods

Review Approach

This Systematic Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter "AHRQ Methods Guide").[30] All methods were determined a priori, and a protocol was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol) and on the PROSPERO systematic reviews registry (registration no. CRD42021229579). Below is a summary of the specific methods used in this review. Search strategies appear in Appendix A, and a complete description of methods are presented in Appendix B.

Key Questions

This review will address the following Key Questions (KQs):

1. In adults with chronic pain, what are the benefits of cannabinoids for treatment of chronic pain?
2. In adults with chronic pain, what are the harms of cannabinoids for treatment of chronic pain?
3. In adults with chronic pain, what are the benefits of kratom or other plant-based substances for treatment of chronic pain?
4. In adults with chronic pain, what are the harms of kratom or other plant-based substances for treatment of chronic pain?

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through July 5, 2021. Searches were initially run in September 2020 with ongoing, automated monthly searches to identify newly published studies. Search strategies are available in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and reviewing the two prior AHRQ pain reports[11,12] for studies that met our inclusion criteria. A Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies. Pre-established criteria were used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ Methods Guide, based on the KQs and populations, interventions, comparators, outcomes, timing, and settings (PICOTS; Table 1).[30] See Appendix B for more details on eligibility criteria and methods for study selection, including dual review of studies screened.

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults (including pregnant or breastfeeding women) 18 years and older with chronic pain (>12 weeks or pain persisting past the time for normal tissue healing). See categorization of specifically included pain populations below.	**All KQs:** Children and adolescents <18 years old; adults with acute or subacute pain; patients at end of life or in palliative care (e.g., with late stage cancer-related pain)
Interventions	**KQs 1 and 2:** Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes **KQs 3 and 4 :** Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids **All KQs**: Co-use of other drugs for pain	**All KQs:** Non-plant-based interventions, capsaicin, herbal supplements
Comparators	**All KQs:** Any comparator, or usual care	**All KQs:** No comparison
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, overall function or disability, including pain interference[a]); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder, serious adverse events as defined by study); secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, healthcare utilization)	**All KQs:** Other outcomes
Time of followup	**All KQs:** short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year)	**All KQs:** studies with <1-month (4 weeks) of treatment or followup after treatment
Setting	**All KQs:** Any nonhospital setting or setting of self-directed care	**All KQs**: Hospital care, hospice care, emergency department care
Study design	**All KQs:** RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits	**All KQs:** Other study designs

Abbreviations: KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial.

[a] The degree to which pain directly interferes with patients' ability to participate in their daily activities.

Data Extraction and Risk of Bias Assessment

After studies were selected for inclusion, data were abstracted into evidence tables in categories that included but not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results. Information relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. All study data were verified for accuracy and completeness by a second team member. Quarterly Progress reports describing recently published studies as they were newly identified are available at: https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review

The risk of bias of individual studies was assessed using methods consistent with the AHRQ Methods Guide.[30] Separate criteria were used for randomized controlled trials and observational studies. Two reviewers independently assessed risk of bias, resulting in final ratings of low, moderate, or high, with any disagreements resolved by consensus. For full details about data extraction, risk of bias assessment, and other methods, please see Appendix B.

Data Synthesis and Analysis

To assist with narrative synthesis, we constructed summary tables of the abstracted study characteristics, results, and risk of bias ratings for all included studies. Data were additionally summarized in in-text tables, using ranges and descriptive analysis and interpretation of the results. We assessed the persistence of benefits or harms by evaluating the three periods consistent with prior AHRQ pain reports (1 to 6 months, 6 to 12 months, and ≥12 months).[11-13,31,32]

We organized cannabis interventions into three categories based on their ratios of tetrahydrocannabinol (THC) to cannabidiol (CBD) (Table 2). The first category, high-THC, includes products with a ratio of THC to CBD of at least 2 to 1. This category was further stratified based on whether interventions consisted of synthetic THC or were derived from whole-plant cannabis. We categorized nabilone, which is a synthetic cannabinoid product similar to synthetic THC (such as dronabinol), as a synthetic high-THC product. Whole plant-based products can be either extracted or purified, depending on the process used to isolate higher concentrations of THC or CBD. Extracted products may contain additional cannabinoids and other compounds (e.g., terpenes) present in whole-plant cannabis that may or may not affect the impact of the intervention. Purified products are pharmaceutical grade and considered free of contaminants (i.e., consist of only THC or THC and CBD combinations).

The second category, low-THC, contains a ratio of THC to CBD of less than one (i.e., higher CBD than THC, at least 1 to 2 ratio). These may similarly be extracted or purified products.

The third category, comparable THC to CBD ratios, consists of products with ratios that fall between the other two groups (generally, close to 1 to 1), and these may also be extracted or purified products.

Interventions consisting of whole-plant cannabis products (not extracted, purified, or synthetic) were categorized according to any information provided about the THC to CBD ratio. Interventions using cannabinoids other than THC and CBD were categorized separately.

Table 2. Organizing principle of cannabis-related studies based on ratios of THC to CBD

Intervention Category	Definition	Possible Derivatives	Example Products
High-THC[a]	THC to CBD ratio equals ≥2:1 ratio	Synthetic, extracted or purified from whole-plant, whole-plant	Synthetic: dronabinol/Marinol®, nabilone/Cesamet® Extracted: THC oil (oral)
Low-THC	THC to CBD ratio equals 1:≥2 ratio	Extracted or purified from whole-plant, whole-plant	CBD topical cream or ointment; cannabis flowers, buds, leaves
Comparable THC to CBD	THC to CBD ratio is between threshold for high-THC and low-THC categories	Extracted or purified from whole-plant, whole-plant	Nabiximols (Sativex®)
Whole-Plant Cannabis Products	Potentially unknown THC to CBD ratio; categorized based on information provided	Whole-plant or parts/materials from the plant, not extracted, purified, or synthetic	Cannabis flowers, resins, buds, leaves, hashish
Other Cannabinoids	Interventions testing cannabinoids other than THC and/or CBD	Extracted or purified from whole-plant	Extracted oils (oral)

Abbreviations: CBD = cannabidiol; THC = tetrahydrocannabinol.
[a] Nabilone included in this category.

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were similar enough to provide a meaningful combined estimate.[33] The decision to conduct quantitative synthesis depended on the presence of at least two studies with similar methodology, completeness of reported outcomes, and a lack of statistical heterogeneity among the reported results. Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic.[34] Mean difference was used as the effect measure for change in pain, and pain scales were converted to a standardized 0 to 10 scale. A similar approach was used for other primary continuous outcomes (e.g. overall function). For primary binary outcomes (pain response and adverse events), relative risk was used as the effect measure. See Appendix B for more details.

We used a random effects model based on the profile likelihood method[35] to combine interventions with comparable THC to CBD ratios and high-THC trials. The primary analysis of high-THC trials was stratified by the type of derivative used in the intervention (synthetic vs. whole-plant extracts). Sensitivity analysis was conducted by excluding studies rated as high risk of bias. All meta-analyses were conducted using Stata/SE 16.1 (StataCorp, College Station, TX). Publication bias (small sample size bias) was assessed using both funnel plots and the Egger test when there were eight or more studies included in a meta-analysis.

The magnitude of effects for primary outcomes were classified using the same system used in other recent AHRQ reviews conducted on chronic pain[11-13,31,32] to provide a consistent benchmark for comparing results of pain interventions across reviews. The findings were categorized as small, moderate, and large magnitudes of effect based on the ranges of effect shown in Table 3. Additionally, results that were below the threshold for a small effect were considered to reflect "no effect." Results with a small, medium, or large effect that were not statistically significant were considered to have "potential effects" if the 95 percent confidence interval included meaningful benefit or harm, but were not so wide that they included the potential for both meaningful benefits and harms.

Table 3. Definitions of effect sizes

Effect Size	Definition
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.

Small effects using this system may be below published thresholds for clinically meaningful effects; however, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or overall function using a treatment with low cost or no serious harms may be important.

When data were available, we conducted subgroup analysis based on type of product (synthetic vs. extracted from whole-plant), duration (short-, medium-, long-term followup), and type of pain (e.g. neuropathic, visceral, joint).

Grading the Strength of the Body of Evidence

We assessed the strength of evidence for all primary comparisons and outcomes listed above. Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence for each KQ/body of evidence is initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.[30,36] To ensure consistency and validity of the evaluation, the strength of evidence is reviewed by the entire team of investigators prior to assigning a final grade on the following factors:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting/publication bias (suspected or undetected)

For description of overall grade, please see Appendix B.

In narratively describing the findings on the strength of the evidence, we followed the principles outlined in recent guidance to improve clarity.[37-39] Using these principles, evidence that is low-strength is described as "may" have an effect, moderate strength evidence is described as "probably" has an effect, and high-strength evidence is simply described as having an effect.

Living Systematic Review Methods

This report is a part of a living systematic review, with regular updating of the evidence on a quarterly basis. Methods for the updates are consistent with those described here, and more details can be found in Appendixes A and B. Previous quarterly progress reports, describing new evidence as it became available, can be found at:
https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review
Future updates will be posted at this location.

Results

Description of Included Evidence

The results of this systematic review are organized first by Key Questions (KQs), with evidence on KQs 1 and 2 (benefits and harms of cannabinoids) reported together. The evidence is then organized according to the categories described in the Methods, comparable tetrahydrocannabinol (THC) to cannabidiol (CDB) ratio interventions, high-THC to CBD ratio interventions (stratified into synthetic, extracted from whole-plant, and whole-plant cannabis products), low-THC to CBD ratio interventions (topical CBD), and other cannabinoids. There was no evidence included for KQs 3 and 4.

After screening 2,850 abstracts, 214 full-text publications of studies were dually reviewed, resulting in 20 randomized controlled trials (RCTs) and 7 observational studies being included in this review. All included studies assessed cannabinoid interventions; no studies of kratom or other plant-based compounds met inclusion criteria.

The search results and selection of studies are summarized in the literature flow diagram (Figure 1). Appendix C provides a list of all included studies. In total, seven RCTs evaluated products that contain a combination of THC and CBD (comparable THC to CBD ratio),[40-46] Two RCTs evaluated the effects of high-THC to CBD ratio, whole-plant derived extracts.[47,48] Nine RCTs evaluated synthetic forms of THC (high-THC to CBD ratio).[49-57] One trial assessed the effect of topical CBD (low-THC to CBD ratio),[58] and another evaluated the phytocannabinoid, cannabidivarin (CBDV).[59]

Appendix D contains individual study-level data and additional results for pooled data from studies where data were available. Detailed evidence tables for included studies and risk of bias assessments are available in Appendixes E and F. Appendix G contains details on the strength of evidence, and Appendix H lists excluded studies at the full-text level and their reasons for exclusion.

Figure 1. Literature flow diagram

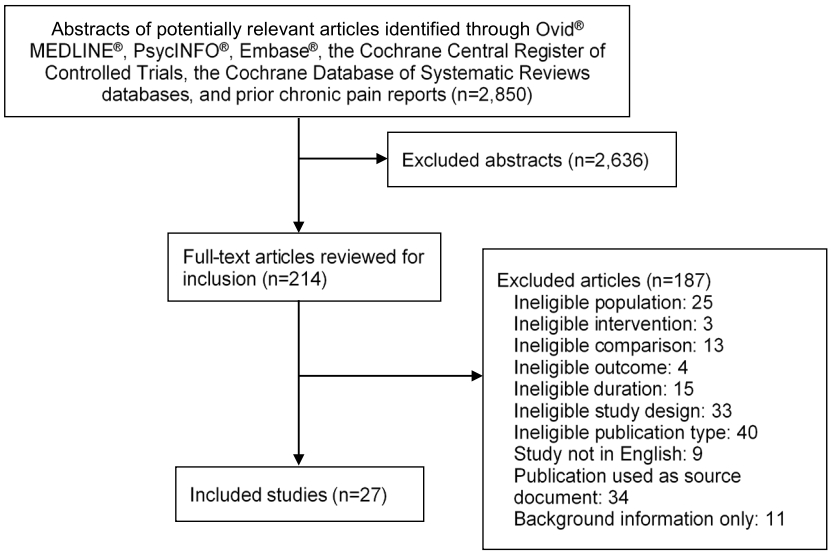


Table 4 summarizes the characteristics of the included trials, and Table 5 provides details on included observational studies.

Table 4. Characteristics of included randomized controlled trials of cannabinoids

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
THC to CBD Ratio	Comparable	High	High	Low	NA - other cannabinoids
Source	Plant-extracted	Plant-extracted	Synthetic	Plant-extracted	Plant-extracted
N Studies	7	2	9	1	1
Comparator (Study Count)	Placebo (7)	Placebo (2)	Placebo (6); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1)	Placebo (1)	Placebo (1)
Risk of Bias % High, % Moderate, % Low	29%, 57%, 14%	0%, 50%, 50%	22%, 44%, 33%	100% high	100% moderate
Total Randomized	882	297	534	29	34
Age, Mean Years	53	52	50	68	50
Female, %	66%	89%	61%	38%	3%
% Non-white[a] (Study Count)	1.6% (2)	1% (1)	5.4% (3)	NA	NA
Primary Pain Type (Study Count)	NPP (6); inflammatory arthritis (1)	NPP (1); fibromyalgia (1)	NPP (6); fibromyalgia (1); headache (1); visceral pain (1)	NPP (1)	NPP (1)
Baseline Pain Score, Mean (Range)[b]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.46 (4 to 8.1)[c]	5.38 (4.67 to 6.14)	6.28 (6.12 to 6.44)
Study Duration	4 to 15 weeks	8 to 12 weeks	4 to 47 weeks	4 weeks	4 weeks

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; NA = not applicable; NPP = neuropathic pain; THC = tetrahydrocannabinol.

[a] (N) = number of studies reporting this characteristic at baseline.

[b] Scores were standardized to a 0 to 10 scale.

[c] Weighted mean includes median scores for one study (6 vs. 6).

Table 5. Characteristics of included observational studies

Characteristic	THC/CBD	THC	Synthetic THC
THC to CBD Ratio	Unclear	High	High
Source	Any cannabis product (patient's choice)	Plant-based	Synthetic (nabilone)
N Studies	5	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (1)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)
ROB % High, % Moderate, % Low	60% high, 40% moderate	100% high	100% moderate
N Total	12,508	431	156
Age, Mean Years	53	49	61
Female, %	55%	57%	59%
% Non-white (study count)	54% (1); NR (4)	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic non-cancer pain	Chronic non-cancer pain	NPP
Baseline Pain Score, Mean (Range)[a]	5.35 (4.56 to 8.00)	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)
Study Duration, Weeks (Range)	12 to 208	52	26

Abbreviations: CBD = cannabidiol; NPP = neuropathic pain; NR = not reported; ROB = risk of bias; THC = tetrahydrocannabinol.

[a] Scores were standardized to a 0 to 10 scale.

KQ 1 and KQ 2. In adults with chronic pain, what are the benefits (KQ 1) and harms (KQ 2) of cannabinoids for treatment of chronic pain?

Key Points for Comparable THC to CBD Ratio

- All results are short-term (4 weeks to <6 months) in duration.
- Comparable THC to CBD ratio products were associated with small improvements in pain severity (7 RCTs, N=702, 0 to 10 scale, mean difference [MD] −0.54, 95% confidence interval [CI], −0.95 to −0.19, I^2=28%) and overall function (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI –0.73 to −0.16) (strength of evidence [SOE]: moderate). While more patients had a response (≥30% improvement from baseline), the difference was small and did not reach statistical significance (4 RCTs, N=733, 38% vs. 31%, relative risk [RR] 1.18, 95% CI 0.93 to 1.71, I^2=0%) (SOE: low).
- Compared with placebo, comparable THC to CBD was associated with a large increase in risk of dizziness (6 RCTs, N=866, 30% vs. 8%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%) and sedation (6 RCTs, N=866, 22% vs. 16%, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%), and a moderate increased risk of nausea (6 RCTs, N=866, 13% vs. 7.5%, RR 1.79, 95% CI 1.20 to 2.78, I^2=0%). There was no effect on study withdrawal due to adverse events (SOE: low).

Summary of Findings for Comparable THC to CBD Ratio

Seven RCTs (N=882, range 18 to 339)[40-46] compared products containing a combination of extracted THC and CBD (THC/CBD; comparable THC to CBD ratio) with placebo in patients experiencing chronic pain. All used nabiximols, extracted from whole-plant cannabis with 2.7 mg of THC and 2.5 mg of CBD per 100 mcl oromucosal spray (specified as the product Sativex® in 6 studies). Six trials enrolled patients with neuropathic pain,[40-44,46] while the other study included patients with rheumatoid arthritis. Studies ranged from 4 to 16 weeks in duration of active treatment; all were short-term followup (1 to <6 months). Across trials, the weighted mean daily dose was 8.4 sprays (21 mg THC/23 mg CBD) for patients assigned to THC/CBD and 12.7 sprays for those assigned to placebo. One study did not specify the product name, strength or dosing in milligrams, but the number of sprays per day (8 vs. 11 for intervention vs. placebo), were similar to other trials.[42] Two trials were high risk of bias: one a small (n=16), 4-week, crossover trial, and the other a small (n=29), 12-week, parallel design trial.[42,45] The rest were parallel design trials, four moderate risk of bias,[40,43,44,46] and one low risk of bias.[41] The mean age of participants was 53 years, and 66 percent were female. Race was poorly reported, with two trials reporting 1.2 percent of participants being non-white, and the others not reporting it at all. Four trials allowed patients using opioids and other analgesics to enroll and to continue using them during the study period.[41-43,46] The proportion of patients taking opioids was low in two studies (11% to 24%)[41,46] and much greater in the third study (63% in the cannabis group vs. 74% in the placebo group).[43] The other three trials did not report opioid use. All of the RCTs of comparable THC to CBD ratio products allowed prior cannabis use, with a range of 5 percent to 64 percent of enrolled patients having used cannabis previously. None of the studies analyzed results according to prior cannabis use.

Study details and results can be found in Appendix E, Tables E-1 to E-5 and risk of bias assessments in Appendix F, Tables F-1 and F-2.

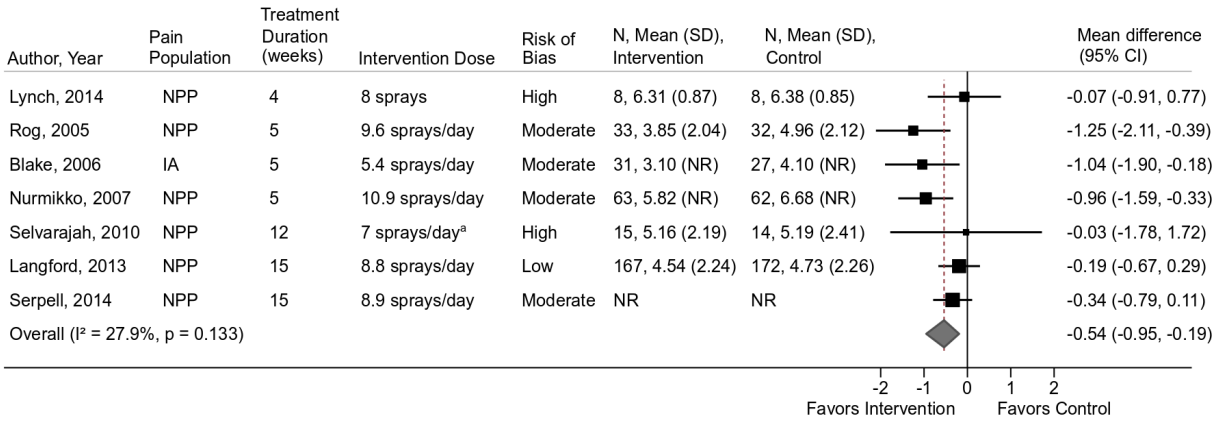
For pain response (≥30% reduction in pain) pooled analysis of four RCTs[41,43,45,46] found a statistically nonsignificant increase with combination THC/CBD treatment (4 RCTs, 38% vs. 31%, RR 1.18, 95% CI 0.93 to 1.71, I^2=0%; Appendix D, Figure D-1). Based on pooled analysis of all seven RCTs, pain severity showed a small, statistically significant improvement with combination THC/CBD treatment (7 RCTs, 0 to 10 scale, MD −0.54, 95% CI −0.95 to −0.19, I^2=28%; Figure 2).[40-46] Figure 2 shows that, except for the small, high risk of bias, crossover study, the size of effect was larger and statistically significant in the shorter studies (4 to 5 weeks) compared with the longer studies (12 to 15 weeks). Subgroup analysis was not conducted because all of the studies are of short duration (1 to <6 months). Sensitivity analysis excluding two high risk of bias studies[42,45] did not alter the findings (0 to 10 scale, MD −0.64, 95% CI −1.15 to −0.24, I^2=43%).[41,46]

Six studies (N=616) with 5 to 15 weeks followup reported on overall function or disability (including measures of pain interference).[40,41,43-46] Pooled analysis showed a small benefit for nabiximols versus placebo (6 RCTs, 0 to 10 scale, MD −0.42, 95% CI –0.73 to −0.16, I^2=24%; Figure 3).

For secondary outcomes, all of the trials reported quality of life. Overall, there were not statistically significant differences in quality of life between groups. Three used the EQ-5D scale (0 to 100), with none finding a significant difference between groups.[41,45,46] One used the Short General Health Questionnaire (GHQ-12; 0 to 36 scale), and found a small, but not statistically significant, difference between groups.[43] Three of the studies reported on the Short Form-36 (SF-36) Physical and Mental scales (0 to 100).[41,42,45] Two did not find statistically significant between-group differences. The third study, a high risk of bias crossover trial (N=16), reported that the SF-36 Physical scale scores improved with placebo, with little change in the THC/CBD group, while the SF-36 Mental scale scores stayed similar in the THC/CBD group and decreased (worsened) in the placebo group.[42] Five studies assessed sleep quality or sleep disturbance using a 0 to 10 scale; four reported statistically significantly better sleep outcomes in the THC/CBD groups versus placebo groups.[40,41,43,44,46] The studies did not report on other secondary outcomes (e.g., depression or anxiety).

The four RCTs that allowed opioid use during the study period did not report on changes in opioid used during the study period.[41,43,46]

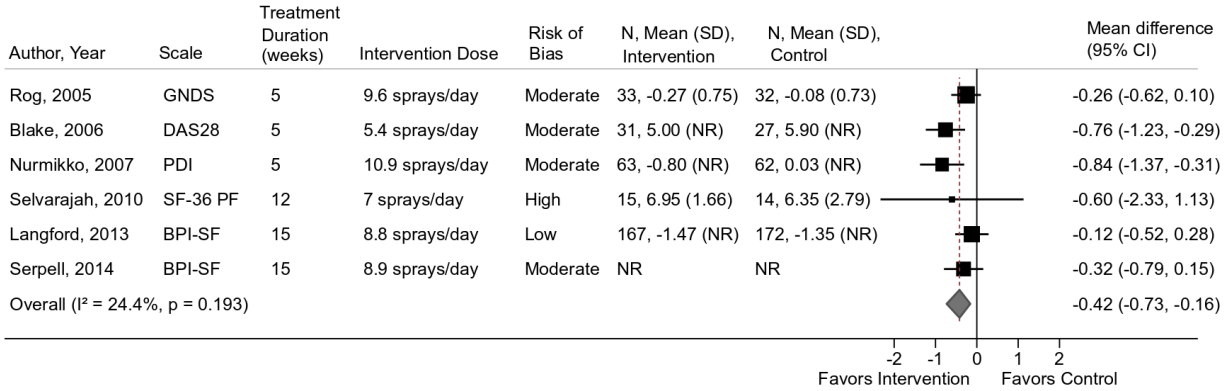
Figure 2. Change in pain severity with comparable THC to CBD ratio versus placebo (short term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; SD = standard deviation; THC = tetrahydrocannabinol.

[a] Calculated by review team.

Figure 3. Overall function: comparable THC to CBD ratio versus placebo (short term, 4 weeks to 6 months followup)



Abbreviations: BPI-SF = Brief Pain Inventory- Short Form; CBD = cannabidiol; CI = confidence interval; DAS28 = 28-Joint Disease Activity Scale; GNDS = Guy's Neurological Disability Scale; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PDI = Pain Disability Index; SD = standard deviation; SF-36 = 36 Item Short Form Survey; SF-36 PF = 36 Item Short Form Survey Physical Functioning; THC = tetrahydrocannabinol.

Adverse events were reported in all the trials. Based on two RCTs, rates of any adverse event were significantly higher in the THC/CBD groups than placebo (2 RCTs, 75% vs. 63%, RR 1.19, 95% CI 1.02 to 1.44, I^2=0%, Appendix D, Figure D-2).[41,44]

Serious adverse events (SAEs) were reported in four studies, with two reporting that none occurred.[42,44] Pooling results from the other two studies found no effect on SAEs with comparable THC/CBD products (2 RCTs, 1.1% vs. 2.2%, RR 0.68, 95% CI 0.04 to 10.85, I^2=38%, Appendix D, Figure D-3).[40,43]

Five RCTs reported on withdrawals from study due to adverse events (WAEs). Pooled analysis of these results found a statistically nonsignificant difference (5 RCTs, 12.5% vs. 10.2%, RR 1.14, 95% CI 0.65 to 3.02, I^2=0%, Appendix D, Figure D-4).[40,41,43,44,46]

Statistically significant differences in specific adverse events of interest occurred more often in the THC/CBD groups than placebo across six RCTs (one did not report specific adverse events).[45] Dizziness occurred significantly more in the THC/CBD groups than placebo groups (6 RCTs, 30% vs. 8%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%, Appendix D, Figure D-5).[40-44,46] Nausea was reported in 13 percent of THC/CBD patients compared with 7.5 percent of placebo patients (6 RCTs, RR 1.79, 95% CI 1.20 to 2.78, I^2=0%, Appendix D, Figure D-6).[40-44,46] Sedation was reported in 8 percent of THC/CBD patients compared with 1.2 percent of placebo patients (6 RCTS, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%, Appendix D, Figure D-7).[40-44,46]

Key Points for High-THC to CBD Ratio

- All RCT results are short-term (4 weeks to <6 months) in duration
- Synthetic high-THC to CBD ratio (100% THC) was associated with a moderate improvement in pain severity (6 RCTs, N=390, 0 to 10 scale, MD −1.15, 95% CI −1.99 to −0.54, I^2=39%) and no effect on overall function or disability (2 RCTs, N=unclear, 0 to 10 scale, MD −0.35, 95% CI −1.9 to 0.94, I^2=40%) (SOE: low).
- Synthetic high-THC to CBD ratio (100% THC) was associated with a moderate increase in risk of sedation (3 RCTs, N=335, 19% vs. 10%, RR 1.73, 95% CI 1.03 to 4.63, I^2=0%) (SOE: low), and dizziness (2 RCTs, N=132, 32% vs. 11%, RR 2.74, 95% CI 1.47 to 6.86, I^2=0%) (SOE: moderate).

- Synthetic high-THC to CBD ratio (100% THC) was associated with a moderate increased risk of study withdrawal due to adverse events (4 RCTs, N=357, 13% vs. 9%, RR 1.72, 95% CI 0.90 to 4.13, I^2=0%) and a large increased risk of nausea (2 RCTs, N=302, 12% vs. 6%, RR 2.19, 95% CI 0.77 to 5.39; I^2=0%), but the differences did not reach statistical significance.
- Plant-based, extracted high-THC to CBD ratio products were associated with a large increased risk of study withdrawal due to adverse events (1 RCT, N=277, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33), and dizziness (1 RCT, N=277, 62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34) (SOE: low). Outcomes of benefit were not reported or insufficient.
- The combined evidence for extracted and synthetic high-THC to CBD ratio products found a moderate improvement in pain severity (8 RCTs, N=684, −1.25, 95% CI −2.09 to −0.71, I^2=50%) (SOE: moderate).

Summary of Findings for High-THC to CBD Ratio

Eleven RCTs studied products with a high-THC to CBD ratio,[47-57] with nine RCTs of synthetic THC (100% THC: 3 dronabinol, 100% THC analog: 6 nabilone),[49-57] and two products extracted from whole-plant cannabis (one with a 48:1 and the other with a 2:1 THC to CBD ratio).[47,48] Six of the synthetic THC RCTs were placebo-controlled,[49,53-57] and three were active-controlled crossover trials.[50-52] Both studies of THC extracted from whole-plant were placebo-controlled. All of the RCTs were short duration (4 weeks to 6 months followup). Additionally, one short duration observational study was included.[60] The evidence for synthetic and plant-derived products are presented below separately. Where meta-analyses could be conducted for placebo-controlled trials, the data for both types of products are presented on one plot, stratified by type, with subgroup analyses conducted when possible.

Synthetic THC

Nine RCTs (N=467; 3 dronabinol, and 6 nabilone)[49-57] studied synthetic THC for treating chronic pain. Six of the trials enrolled patients with neuropathic pain (3 multiple sclerosis [MS], 1 each painful diabetic neuropathy, spinal cord injury, and mixed neuropathic pain conditions),[50,52,53,55-57] and one each in patients with chronic abdominal pain,[49] medication overuse headache,[51] and fibromyalgia.[54] All studies were of short-duration followup, ranging from 4 to 14 weeks of active treatment. Both medications were titrated upward, with a maximum dose of 15 to 20 mg per day of dronabinol and 0.5 to 2 mg per day of nabilone (mean dose received at endpoint was inconsistently reported).

One trial of nabilone used an enriched enrollment randomized withdrawal design, with a 4-week, single-blind, flexible dose run-in period prior to randomization.[55] Only patients who achieved a 30 percent improvement in pain severity, completed 75 percent of diary entries, and did not withdraw from the study due to adverse events were randomized to treatment or placebo. Thirty percent of patients (11/37) were withdrawn from the study during the run-in period.

Six trials were parallel design placebo-controlled, with one adding nabilone or placebo to gabapentin treatment in patients who had not achieved pain relief (visual analog scale [VAS] score for pain >50).[56] The other three RCTs were crossover trials with an active control arm; one using diphenhydramine as an active control (47 weeks),[52] another using ibuprofen (8 weeks),[51] and the third using dihydrocodeine (6 weeks).[50] Risk of bias was high in two trials,[52,57] moderate in four,[49,50,54,56] and low in three.[51,53,55] The mean age of participants was 50 years, and 61

percent were female. Race was poorly reported, with only three trials reporting 5.4 percent of participants being non-White. Three studies allowed patients to continue taking their current medication for pain, not specifically excluding opioids or requiring their discontinuation,[49,53,54] with one specifically allowing tramadol as rescue medication for acute pain during the trial.[53] The other studies required patients to discontinue opioid use before the study[50,52] or did not report baseline opioid use or use during the study period.[51,55-57] Five parallel design placebo-controlled trials (2 dronabinol, 3 nabilone) excluded patients with prior cannabis use.[49,53-56] One crossover designed trial (nabilone vs. dihydrocodeine) excluded patients with prior cannabis use.[50]

A small (n=156), moderate risk of bias cohort study evaluated nabilone and gabapentin in patients with neuropathic pain of various types for six months.[60] Patients were prospectively allowed to initiate nabilone or gabapentin, or to add one of them to pre-existing treatment with the other. The mean dose at 6 months was 3 mg per day for nabilone and 2,296 mg per day for gabapentin.

Study details and results can be found in Appendix E, Tables E-1 to E-5, and risk of bias assessments can be found in Appendix F, Tables F-1 and F-2.

Placebo-Controlled Trials of Synthetic THC

Based on pooled analysis of six RCTs, synthetic high-THC to CBD ratio products were associated with moderate improvements in pain severity (6 RCTs, 0 to 10 scale, MD −1.15, 95% CI −1.99 to −0.54, I^2=39%; Figure 4).[49,53-57] Stratified analysis showed that the pooled effect estimate for nabilone (MD −1.59, 95% CI −2.49 to −0.82, I^2=0%) was somewhat larger than with dronabinol (MD −0.52, 95% CI −1.43 to 0.07, I^2=0%; Appendix D, Figure D-8, Table D-6), but the difference was not statistically significant (p=0.077).[49,53-57] A single, low risk of bias RCT (n=26) of patients with diabetic neuropathy reported on pain response (≥30% improvement from baseline), finding a large effect with nabilone (85% vs. 38%, RR 2.20, 95% CI 1.06 to 4.55).[55]

Three RCTs reported on overall function (including pain interference) or disability.[55-57] Pooled analysis of two RCTs (N=41) did not find a statistically significant difference between synthetic high-THC and placebo (0 to 10 scale, MD −0.35, 95% CI −1.9 to 0.94, I^2=40%; Appendix D, Figure D-9). The third RCT (n=13) reported that neither group had a change in disability, measured with the Bartell Index (no data reported).[57]

Few synthetic THC studies reported on secondary outcomes. A small (n=26), low risk of bias RCT of patients with diabetic neuropathy reported no difference in depression using the Hospital Anxiety and Depression-D [HADS-D] scale (0 to 10, MD −0.4, 95% CI −1.26 to 1.46), but statistically significantly improved anxiety (HADS-A, 0 to 10 scale, MD −2.9, 95% CI −3.80 to −2.0) with nabilone after five weeks.[55] Quality of life findings were mixed, with a statistically nonsignificant difference between groups using the EQ-5D Utility scores (endpoint scores 72.6 vs. 61.4) and a statistically significant difference using the EQ-5D Index scores (endpoint scores 0.74 vs. 0.60, p<0.05 using analysis of covariance [ANCOVA]). A small, moderate risk of bias study (n=40) of patients with fibromyalgia evaluated secondary outcomes using the Fibromyalgia Impact Questionnaire (FIQ). The overall FIQ score improved more at four weeks with nabilone than with placebo (MD −12.07, p<0.02). Using the anxiety questions on the FIQ, anxiety was significantly improved in the nabilone group after 4 weeks (FIQ anxiety questions, 0 to 10 scale, MD −2.2, p<0.01).[54] Depression was not significantly improved using the FIQ. The

three RCTs that allowed opioid use during the study period did not report on the effect of the study medications on opioid use.[50,53,54]

Adverse events were poorly reported. The most commonly reported was WAEs. Pooled analysis of WAEs in four trials showed a statistically nonsignificant increase with synthetic THC (13% vs. 9%, RR 1.72, 95% CI 0.90 to 4.13, I^2=0%, Appendix D, Figure D-10). Of these four studies, two were of nabilone and two of dronabinol; there was no apparent difference in the direction or magnitude of effect between the drugs, with no heterogeneity found in the meta-analysis (I^2=0%). Pooled analysis of two RCTs reporting any adverse event (1 nabilone, 1 dronabinol) found a nonsignificant increase with synthetic THC (2 RCTs, 86% vs. 71%, RR 1.20, 95% CI 0.96 to 1.48, I^2=0%, Appendix D, Figure D-11).[53,55] A single study reported SAEs and found a non-statistically significant increased risk with dronabinol (n=240, 10% vs. 6%, RR 1.60, 95% CI 0.65 to 3.93).[53]

Specific adverse events of interest were reported more often in the synthetic THC groups, reaching statistically significant differences with dizziness (2 dronabinol RCTs, 32% vs. 11%, RR 2.74, 95% CI 1.47 to 6.86, I^2=0%, Appendix D, Figure D-12)[49,53] and sedation (3 RCTs, 1 nabilone, 2 dronabinol, 19% vs. 10%, RR 1.73, 95% CI 1.03 to 4.63, I^2=0%, Appendix D, Figure D-13).[49,53,54] There were too few studies to conduct subgroup analyses, but the study of nabilone (n=33) had a greater magnitude of effect (RR 8.40, 95% CI, 1.16 to 60.84) than either dronabinol study (n=240, RR 1.87, 95% CI 0.66 to 5.31; n=62, RR 1.45, 95% CI, 0.80 to 2.64). Nausea was also reported more often with synthetic THC (dronabinol), but the difference was not statistically significant (2 RCTs, 12% vs. 6%, RR 2.19, 95% CI 0.77 to 5.39, I^2=0%, Appendix D, Figure D-14).[49,53]

Active-Control Studies of Synthetic THC

Three crossover design trials[50-52] and one observational study,[61] compared a synthetic cannabinoid with active-controls. One high risk of bias trial used diphenhydramine as the control (47 weeks),[52] another low risk of bias trial used ibuprofen (8 weeks),[51] and the third moderate risk of bias trial used dihydrocodeine (6 weeks).[50] None of the crossover trials reported pain response (≥30% reduction in pain from baseline). In a 6-week RCT of patients with neuropathic pain (n=96 randomized, 73 analyzed) comparing nabilone versus dihydrocodeine (30 to 240 mg per day), dihydrocodeine resulted in greater reduction in pain severity (VAS 0 to 100 scale; MD −5.7, 95% CI −10.9 to −0.5, p=0.03).[50] There were no statistically significant differences in secondary outcome measures (depression, anxiety, quality of life, or sleep). While the study indicated patients could continue to use other drugs for pain, it was not clear what those were or if new drugs (including other opioids) were started outside of the protocol.

A low risk of bias RCT of nabilone and ibuprofen (400 mg per day) in patients with medication overuse headache (n=60) found that after 8 weeks of treatment, there was not a significant difference in pain severity between treatments.[51] There were no statistically significant differences in secondary outcomes measured (depression, anxiety, and quality of life). There were no differences in rates of any adverse events or WAEs (SAEs were not reported). Analgesic intake and dependence for headache control were measured at baseline and 2 weeks after the end of study, but the specific medications were not reported, except that the most common form of analgesic consisted of "combination medications." At two weeks post-study, treatment with nabilone resulted in lower daily analgesic intake than after ibuprofen (0.89/d vs. 1.34/d; p=0.03).[51] Although overall rates were low, dizziness (7.7% vs. 0%) and cognitive

deficits (3.8% vs. 0%) occurred more frequently when taking nabilone, while nausea (3.8% vs. 7.7%) and sedation (0% vs. 3.8%) occurred more frequently with ibuprofen.

In the very small (n=7), high risk of bias RCT comparing dronabinol with diphenhydramine in patients with spinal cord injury, pain intensity did not differ between treatments.[52] No other outcomes were reported for efficacy. More patients withdrew from the study when assigned to nabilone (2 of 7 patients), and dry mouth, constipation, fatigue, and drowsiness were reported in similar numbers of patients for both groups.

A moderate risk of bias, prospective observational study of nabilone and gabapentin (or the combination, not reported here) among patients with mixed neuropathic pain found no difference in pain severity between groups at 3 months. At 6 months nabilone was associated with a greater reduction in pain intensity (0 to 100 VAS, MD −5.8, 95% CI −10.18 to −1.42), and better sleep scores on the Medical Outcomes Study Sleep Scale (scale 0 to 60, MD −3.1, 95% CI −7.57 to 1.37 vs. gabapentin) than gabapentin.[60] There were no differences in pain interference, quality of life, depression, or anxiety at 6 months. Overall adverse events were lower in the nabilone group (47% vs. 35%), and no SAEs were reported. WAEs were also lower in the nabilone group (10% vs. 23%). More patients in the gabapentin group reported sedation (60%) than in the nabilone group (35%). Dizziness was reported in similar proportions of patients in the groups (33% vs. 39%).

Plant-Based Extracted THC

Two placebo-controlled RCTs (N=294) studied THC extracted from whole-plant cannabis, with different ratios of THC to CBD.[47,48] A 12-week, moderate risk of bias RCT of 277 patients with pain due to MS studied a product described as an extract from *Cannabis sativa* L. using an extraction medium of ethanol 96 percent. The product contained 2.5 mg of THC and CBD in the range of 0.8 to 1.8 mg per soft gelatine capsule.[48] Dosing was THC 2.5 mg twice daily titrated to a maximum daily dose of 25 mg/day or placebo (mean not reported). More than half of patients enrolled were using an analgesic at baseline, but the type or whether they could continue use during the trial was not reported; patients using cannabis within 30 days of study enrollment were excluded.[48] An 8-week, low risk of bias RCT of 17 patients with fibromyalgia studied low-dose, sublingual THC oil.[47] The product contained 24.44 mg/mL of THC and 0.51 mg/mL of CBD; a 48 to 1 THC to CBD ratio, and small quantities of other cannabinoids, but the extraction process was not described. Dosing was described as starting with THC 1.2mg/CBD 0.02 mg oil per dropper-full (a 60 to 1 ratio) given as a single daily dose. The mean daily dose was 4.4 mg THC/0.08 mg CBD in the active treatment group. The dose of CBD in this preparation was described as so low as to not contribute meaningfully to outcomes. Twenty five percent of patients had used an opioid prior to the study, but did not report on opioid use during the trial.

In pooled analysis, pain severity was improved with the extracted THC products, but the difference was not statistically significant (2 RCTs, 0 to 10 scale, MD −1.97, 95% CI −5.91 to 1.21, I^2=66%; Figure 4). There was a high degree of heterogeneity in this combined estimate, likely due to multiple differences between the studies, including sample size, dose, duration, and specific pain condition (fibromyalgia vs. multiple sclerosis), resulting in a large difference in the magnitude of effect across the two studies. Individually, each study found a statistically significant reduction in pain severity. The 8-week, low-dose THC oil study of 17 women with fibromyalgia reported a larger effect (MD −3.92, 95% CI −5.98 to −1.86)[47,48] on pain than the larger (n=277) 12-week study of a much higher dose of extracted cannabis (MD −0.90, 95% CI −1.49 to −0.31).[47,48] Pain response was not reported.

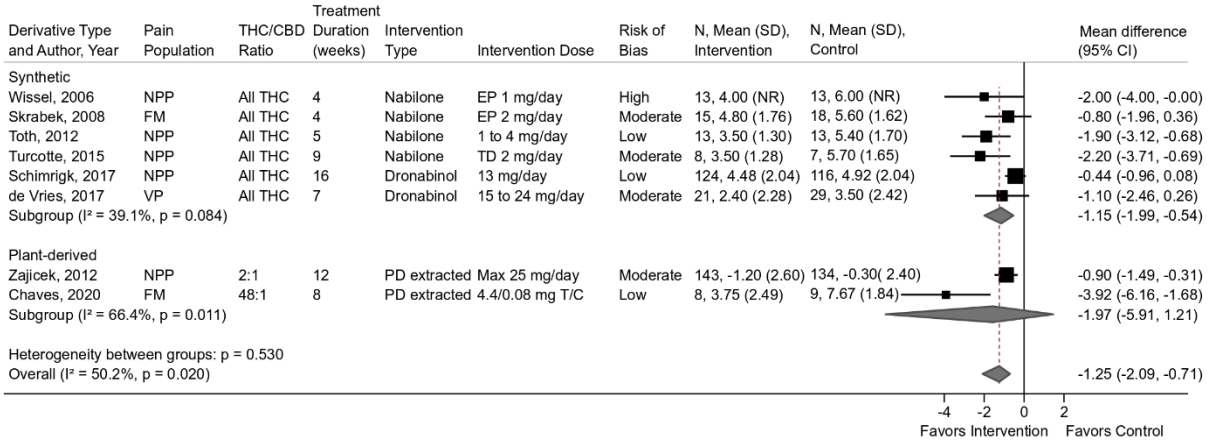
In patients with fibromyalgia, physical functioning was not improved (1 RCT, FIQ subscale 0 to 10, MD 1.75, 95% CI −0.46 to 3.98) compared with placebo.[47] Quality of life was improved with extracted THC (1 RCT, FIQ scale 0 to 100 scale, MD 36.0, p=0.005).[47] These analyses did not adjust for potentially important differences in baseline scores between groups. Differences in depression and anxiety were not found between groups.

In patients with MS there was a higher risk of WAEs, (1 RCT, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33), and dizziness (1 RCT, 62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34) with extracted THC compared with placebo.[48] An increased risk of SAEs was also found, but the difference did not reach statistical significance (1 RCT, 4.9% vs. 2.2%, RR 2.19, 95% CI 0.58 to 8.28). In patients with fibromyalgia, there was a large increased risk of somnolence with extracted THC (1 RCT, 88% vs 11%, RR 7.9, 95% CI 1.2 to 50.9).[47] No other adverse events of interest were reported by either study.

Combined Analysis of Synthetic THC and Plant-Based Extracted THC Products

To evaluate whether there was an effect for any form of high-THC product (synthetic or extracted), we combined results from all studies of high-THC to CBD ratio interventions (Figure 4). The overall combined mean difference is −1.25 (95% CI −2.09 to −0.71, I^2=50%). Although there is substantial statistical heterogeneity in the overall pooled estimate, subgroup analysis of synthetic versus plant-extracted forms of high-THC (Appendix D, Table D-7) did not find statistically significant differences in estimates of effect (p=0.42). This analysis allowed evaluation of publication (small-study size) bias (≥8 studies). Both the funnel plot and the Egger test indicated potential bias, with smaller studies with small effect sizes missing (Appendix I, Figure I-1).

Figure 4. Change in pain severity with high-THC ratio versus placebo (short term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; FM = fibromyalgia; NPP = neuropathic pain; SD = standard deviation; THC = tetrahydrocannabinol; VP = visceral pain; WP = whole plant.

Key Points for Low-THC to CBD Ratio and Other Cannabinoids

- In the *short-term*, low-THC to CBD ratio (CBD topical cream) had insufficient evidence to draw conclusions (1 RCT, N=29)

- In the *short-term*, evidence on cannabinoids other than THC and CBD was insufficient to draw conclusions (1 RCT, N=31)

Summary of Findings for Low-THC to CBD Ratio

A single, small (n=29), high risk of bias RCT of topical CBD oil in patients with neuropathic pain (mean age 68 years, 38% female) was included.[58] Patients were randomized to four weeks of CBD cream (250 mg/3 oz) applied to symptomatic areas up to 4 times daily or placebo; the total daily dose received was not reported.

Improvement in pain intensity was statistically significantly greater in the CBD group versus the placebo group (−1.34 vs. −0.59, p=0.009 by ANCOVA). It was not clear if the analysis also included a crossover extension phase wherein patients initially randomized to placebo were given CBD. A planned analysis taking baseline score into account was not reported. This study did not report pain response, pain interference, overall function/disability, or secondary outcomes. No adverse events were reported.

Other Cannabinoids

A small (n=31), moderate risk of bias trial of oral CBDV (described as "a novel phytocannabinoid derived from the *Cannabis sativa* L. plant") was included.[59] Patients with HIV-related chronic pain (mean age 50 years, 3% female) were randomized to oral CBDV oil (50 mg/ml) dosed at 8 ml daily (400 mg CBDV) or placebo oil for 4 weeks, then crossed over after a 21-day washout.

Using the numerical rating scale (NRS)

pain scale (10-point scale), statistically significantly fewer patients achieved response (≥30% pain reduction) with CBDV compared with placebo (38% vs. 81%, RR 0.46, 95% CI 0.24 to 0.91). There was no difference between CBDV and placebo in the change in pain severity from baseline (MD 0.62, 95% CI −0.05 to 1.32). Secondary outcomes of anxiety, depression, and insomnia also did not differ statistically between the groups. Although more patients reported any adverse event while using CBDV than placebo (91% vs. 79%), the difference was not statistically significant (p=0.28). Other adverse event outcomes occurred slightly more often in the CBDV groups than placebo (WAEs, 1 vs. 0; SAEs, 1 vs. 0; diarrhea, 3 vs. 0; dry mouth, 3 vs. 0).

Key Points for Whole-Plant Cannabis and Mixed (Patient-Choice) Cannabis Products

- There was insufficient evidence to draw conclusions about the effectiveness and harms of whole-plant cannabis products or patient-choice cannabis products in treating chronic pain.

Summary of Findings for Whole-Plant Cannabis and Mixed (Patient-Choice) Cannabis Products

Six observational studies (N=12,939) reported on the effects of cannabis, with five (3 high, 2 moderate risk of bias) studies evaluating medical cannabis programs,[62-64] or self-reported use of cannabis,[65,66] and one moderate risk of bias study evaluating a specific whole-plant cannabis product.[61] Patient characteristics are summarized across studies in Table 5. The type of pain was

not well reported. Mean age was 53 years, and 55 percent were female. Baseline pain was 5.35 (95% CI 4.56 to 8.00) on a 0 to 10 scale. One study evaluated outcomes at 3 months (short duration),[64] and the other five were long duration (1 to 4 years observation).[61-63,65,66] The three studies of medical cannabis programs allowed patients to self-select the cannabis products they used and compared them with patients who chose not to enroll in the programs (assumed to be no cannabis use).[61-63] Two of the studies are retrospective analyses of larger prospective cohort studies of patients with chronic pain taking opioids,[65,66] based on patient self-report of cannabis use, but specific products used were not reported. In the study of a whole-plant cannabis product, the cannabis group received herbal cannabis containing 12.5 percent (+/- 1.5%) THC.[61] Total daily doses received were reported in two studies with one reporting 93 mg of THC per week (mean) in a medical cannabis program,[64] and the other reporting 2.5 grams per day of a whole-pant cannabis product (dose confirmed with study authors).[61]

Two studies reported on primary pain or function outcomes. A high risk of bias study assessing a medical cannabis program study (n=46) found nonstatistically significant differences between groups on measures of pain severity, pain-related disability, quality of life, depression, anxiety, and sleep.[64] A moderate risk of bias study of opioid users also reported no statistically significant differences on pain or pain interference outcomes between frequent cannabis users (daily or near-daily)[65] and non-users over 4 years of followup. Because the number of patients enrolled changed from year to year along with their cannabis use status, these analyses were conducted based on use in the prior 12 months.

A high risk of bias cohort study (n=431) of a whole-plant cannabis product with 12.5 percent THC (amount of CBD not reported) with 52 weeks of followup reported on adverse events.[61] Patients for whom standard treatments were not effective were enrolled, with patients already using cannabis for pain preferentially enrolled in the treatment group. The median dose was 2.5 gm of herbal cannabis per day (confirmed with study authors as amount dispensed). While the overall percentage of patients reporting any adverse event or serious adverse events was greater than in other studies, differences were not statistically different between groups. Dizziness was also not reported more often in the cannabis group. Both nausea (16.7% vs. 9.7%, RR 1.72, 95% CI 1.04 to 2.85) and sedation (13.5% vs. 4.6%, RR 2.91, 95% CI 1.46 to 5.83) were reported significantly more frequently in the cannabis group. Study withdrawal due to adverse events was poorly reported for the usual care group and occurred in 4.7 percent of those using cannabis.

Four observational studies reported on the association between cannabis use and opioid use for chronic pain.[62,63,65,66] The studies used different methods and reported outcomes differently, with no consistent direction of effect across the studies. A large, moderate risk of bias, retrospective cohort study (n=10,746) with propensity matching found a nonstatistically significant decrease in weekly oral morphine equivalent (OME) doses in the cannabis group (−183.2 OME, 95% CI −449.8 to 83.3). Preplanned subgroup analyses found that patients taking lower initial doses of opioids (<50 OME/week) increased opioid use after medical cannabis authorization, while those using higher doses at baseline (>100 OME/week) had a decrease (−435.5, 95% CI −596.8 to −274.2). Discontinuation of prescription opioids was found to be less likely in the cannabis group versus the control group (49.3% vs. 72.3%, adjusted odds ratio [OR] 0.38, 95% CI 0.34 to 0.41).

In a moderate risk of bias study (n=1,514 at baseline, 1,217 at year 4) of opioid users with chronic pain, a statistically nonsignificant difference in OME use at one year was found between patients reporting daily or near daily cannabis use (type and dose reported) and those reporting no use.[65] The analysis used a lagged mixed-effects linear regression model, identifying cannabis

use in the prior year and opioid use in the current year across four possible years of study enrollment. The adjusted mean daily OMEs were 97.1 in frequent cannabis users and 85.5 in non-users (difference 32.76 mg/day, 95% CI, −25.04 to 90.57).

A high risk of bias, 52-week, prospective cohort study of patients with HIV-related chronic pain (n=433) evaluated the effect of cannabis use.[66] At baseline 47 percent were using an opioid for chronic pain. Among daily or near daily cannabis users also using opioids, the adjusted OR for discontinuing opioids was 1.67 (95% CI 0.52 to 5.37). Among daily or near daily cannabis users not using opioids at baseline, the adjusted OR for initiating an opioid was 2.29 (95% CI 0.86 to 6.16). Impact on morphine equivalents were not reported.

In a small (n=66), high risk of bias, retrospective cohort of patients in a medical cannabis program for low back pain, compared with a group who declined to participate, those in the cannabis program were more likely to reduce their daily opioid dose than the control group (83.8% vs. 44.8%, OR 5.12, 95% CI 1.56 to 16.88).[63] The reduction in dose was small, but statistically significant (MD −0.64 mg intravenous morphine equivalent, 95% CI −1.10 to −0.18 from starting mean doses in the two groups of 24.4 mg vs. 16.2 mg).

KQ 3 and KQ 4. In adults with chronic pain, what are the benefits (KQ 3) and harms (KQ 4) of kratom or other plant-based substances for treatment of chronic pain?

Key Points

- No studies of kratom or other plant-based substances with properties similar to cannabis were found.

Summary of Findings

No evidence was found for kratom or other plant-based substances.

Discussion

Findings in Relation to the Decisional Dilemma(s)

The key decisional dilemmas for treating chronic pain with plant-based compounds include their effectiveness and safety in treating chronic pain and the effect of route of administration, formulation, dose or potency of products, types of pain, and other patient characteristics on outcomes, including harms. Important harms include typical adverse effects such as dizziness, sedation and nausea, but may also include more serious risks, such as cannabis use disorder (CUD), psychosis, and cognitive impairment. Potential benefits and harms must be considered in the context of frequent, possibly daily, long-term use.

The findings are applicable to the *short-term* treatment (1 to <6 months), in patients with chronic pain (mainly neuropathic pain) compared with placebo. Change in pain severity was reported across all studies, but other pain-related and overall functional outcomes (including pain interference) were reported sporadically.

Comparable tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio oromucosal spray is probably associated with small improvements in pain severity (strength of evidence [SOE]: moderate) and overall functioning (SOE: low) in the short-term. Combined THC/CBD may also be associated with a moderate to large increased risk of dizziness, sedation and nausea, with no effect on serious adverse events. There was a small increase in the proportion of patients with at least 30 percent improvement in pain (pain response); while the SOE was low, the finding was not statistically significant due to inadequate sample size (imprecision). For secondary outcomes, sleep quality was improved in the treatment groups, and quality of life was not different between groups.

Synthetic oral THC (which had high-THC to CBD ratios) may be associated with moderate improvement in pain severity and no effect on overall function (SOE: low). They are probably associated with a large increase in risk of dizziness (SOE: moderate) and may be associated with large increased risk of nausea and moderate increased risk of sedation (SOE: low). There was a moderate increase in the proportion of patients that withdrew from studies due to adverse events; the SOE was low, but the finding was not statistically significant due to inadequate sample size (imprecision). For secondary outcomes, evidence was very limited with no clear effect on quality of life or depression, and inconsistent results for anxiety and global disease improvement for patients with fibromyalgia treated with synthetic high-THC to CBD ratio products.

Extracted whole-plant high-THC to CBD ratio products may be associated with large increases in risk of study withdrawal due to adverse events and dizziness (SOE: low). For secondary outcomes, a single study found no difference between groups in depression or anxiety. Combining the evidence for all high-THC to CBD ratio products resulted in a moderate improvement in pain severity, with a low SOE.

Evidence on whole-plant cannabis, mixed forms of cannabis (patient-choice), low-THC to CBD ratio products (topical CBD), other cannabinoids (cannabidivarin [CBDV]), and comparisons with other active interventions were insufficient to draw conclusions. Similarly, evidence for other outcomes reported for comparable THC to CBD and high-THC to CBD ratio products was insufficient. See Appendix G for details.

Other adverse events (psychosis, CUD, cognitive deficits) and secondary outcomes were not reported for any product.

While there are no applicable clinical practice guidelines with which to compare these results, there have been multiple systematic reviews conducted on the use of cannabinoids to

treat chronic pain, including a 2015 publication in the Journal of the American Medical Association, a 2018 Cochrane review, and a 2017 Veteran's Affairs Evidence Synthesis Program review.[16,67-69] These high-quality reviews found generally similar results as this review indicating some benefit in pain outcomes, primarily for short-term treatment in patients with neuropathic pain. These prior reviews combined all forms of cannabinoids in meta-analyses, hence our review has more stratified results based on the THC to CBD ratio, leading to a higher strength of evidence rating in some cases.[16] Although these were high-quality reviews, they are not current and may be missing newer evidence. An additional four unrelated systematic reviews examining utility of cannabis for chronic pain were published in 2020; overall, these findings are also consistent with the present systematic review results.[70-73] One of the reviews conducted meta-regression, finding that the impact on pain was similar between neuropathic and non-neuropathic pain populations[72] and that pain reduction was of a small magnitude and similar across formulations (inhaled, oral, oromucosal spray).

Our review did not identify eligible evidence on kratom to treat chronic pain. Two recent reviews of kratom provided limited information, and are based on noncomparative data or pharmacological data. One evaluated surveys, cross-sectional studies, and poison-control center studies on the use of kratom; the other is a nonsystematic review covering pharmacology, pharmacokinetics, prevalence and type of usage, and harms evidence.[23,24] Both found that patients report using kratom as a substitute for opioids apparently as a treatment for self-diagnosed opioid addiction or dependence in Thailand and Malaysia. They reported growing use in the United States for chronic pain and for recreational purposes. They also suggested that kratom may have addictive properties itself with symptoms of physiological withdrawal being common. Nonserious adverse effects include hyperpigmentation of the skin, constipation, weight loss, insomnia, xerostomia, and loss of libido. Poison control center data indicated an increase in calls involving kratom over the past five years with multi-substance exposures involving kratom associated with a statistically significant increase in a serious medical event. In cases where kratom was the only substance involved (N=1,174), symptoms included agitation or irritability (23%), tachycardia (21%), nausea (15%), drowsiness/lethargy (14%), vomiting (13.2%), confusion (11%), hypertension (10%), and seizures (10%).[24]

Tables 6 and 7 provide a summary of the evidence for primary outcomes and harms related to cannabis interventions. Additional details on the SOE for these outcomes are located in Appendix G.

Table 6. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

THC to CBD Ratio	Pain Response Effect Size (N Studies) [SOE][a]	Pain Severity Effect Size (N Studies) [SOE][a]	Overall Function Effect Size (N Studies) [SOE][a]
Comparable THC/CBD Oromucosal Spray	Potential effect (4)[b] [+]	Small effect (7) [++]	Small effect (6) [++]
High-THC – Synthetic, Oral	Insufficient (1)	Moderate effect (5) [+]	No effect (3) [+]
High-THC – Extracted From Whole-plant, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low-THC – Topical CBD	No evidence	Insufficient (1)	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence

THC to CBD Ratio	Pain Response Effect Size (N Studies) [SOE][a]	Pain Severity Effect Size (N Studies) [SOE][a]	Overall Function Effect Size (N Studies) [SOE][a]
Whole Plant Cannabis (12% THC)	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: [+] = low, [++] = moderate, [+++] = high.
[b] Findings with small or larger magnitude of effect, not statistically significant; but with SOE rating of Low or higher (downgraded mainly for imprecision).

Table 7. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

THC to CBD Ratio	WAE Effect Size (N Studies) [SOE][a]	SAE Effect Size (N Studies) [SOE][a]	Dizziness Effect Size (N Studies) [SOE][a]	Nausea Effect Size (N Studies) [SOE][a]	Sedation Effect Size (N Studies) [SOE][a]
Comparable THC/CBD Oromucosal Spray	Insufficient (5)	No effect (2) [+]	Large effect (6) [+]	Moderate effect (6) [+]	Large effect (6) [+]
High-THC – Synthetic, Oral	Potential effect[b](4) [+]	Insufficient (1)	Large effect (2) [++]	Potential effect[b] (2) [+]	Moderate effect (3) [+]
High-THC – Extracted From Whole-plant, Oral	Large effect (1) [+]	Insufficient (1)	Large effect (1) [+]	No evidence	No evidence
Low-THC – Topical CBD	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole Plant Cannabis (12% THC)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.
[a] Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: [+] = low, [++] = moderate, [+++] = high.
[b] Findings with small or larger magnitude of effect, not statistically significant; but with SOE rating of Low or higher (downgraded mainly for imprecision).

Strengths and Limitations

The evidence base on cannabis and other plant-based treatments for chronic pain has multiple important limitations. Eighty percent of trials enrolled patients with chronic pain due to a neuropathic cause (7 in patients with multiple sclerosis, 4 with a mix of conditions or not specified, 2 with diabetic neuropathy, and 1 each with chemotherapy, HIV, or spinal cord injury). There is little or no evidence on other types of chronic pain, including low back pain, osteoarthritis, fibromyalgia, and inflammatory arthritis. In terms of age, there is limited evidence on younger and older populations, with most patients being middle-aged (mean age 52 years). Studies generally excluded patients with a history of psychiatric disorders other than prior history of depression or anxiety. Importantly, there was either no evidence or inadequate evidence to evaluate important patient populations based on sex/gender, race/ethnicity, age, or pregnancy/lactating status.

Another limitation is the lack of consistent nomenclature detailing the interventions and products studied. For example, products are described as extracted in some studies, but without a

consistent way of describing the process or the resulting purity of the products. Other studies used words such as "standardized" to describe the amount of THC in a whole-plant cannabis product, again with lack of description of how this was defined or determined. Studies did not consistently report the ratio of THC to CBD in the products, particularly outside of the products that are close to a 1 to 1 ratio (oromucosal spray, Sativex). Other limitations include the complete lack of evidence on other plant-based compounds like kratom, no randomized controlled trial (RCT) evidence on whole-plant cannabis products, and only a single, small study each for topical CBD or cannabinoids other than THC or CBD.

Change in pain severity was the most commonly reported outcome. Other important outcomes were mainly not reported or inconsistently reported or defined. Pain response, defined as a 30 percent or greater improvement in pain, was reported in 5 of 23 studies (22%); 6 of 23 studies (26%) reported specifically on pain interference, and 8 of 23 (35%) reported measures of physical function or disability. The studies poorly reported baseline use of opioids for pain, and only one high risk of bias observational study reported the impact of cannabis interventions on changes to prescription opioid use. While almost all studies reported the number of patients who withdrew from studies due to adverse events, 30 percent did not report serious adverse events, and 65 percent did not report the overall adverse events, particularly by group. When serious adverse events were reported, studies either used a unique definition, or did not provide one. In reporting on specific adverse events, not all studies were clear about whether the events were the number of individuals with at least one event, or if a single patient could contribute to an event more than once. Other adverse events that have been reported in noncomparative observational studies and were prioritized for this review (development or exacerbation of psychosis, CUD, and cognitive deficits) were not reported.

Trials were limited by study design and small sample sizes (range 9 to 339; mean 89), particularly for assessing harms. The SOE of the findings was very commonly downgraded due to imprecise estimates as a result of too few patients enrolled (see Appendix G). There were also differences in some key baseline characteristics, including baseline pain scores, which were frequently not adjusted for in study analyses. Another methodologic concern is that many conclusions in the included studies were drawn from post-hoc analyses. Study durations were short-term and included less than 6 months followup; 37 percent of studies were 4 to 6 weeks long. This is a key limitation, as pain severity in patients with chronic pain may vary substantially in the short-term and may be influenced temporarily by an intervention or treatment; it is most useful to understand the enduring impact of a treatment on pain severity. Similarly, adverse events such as CUD, cognitive deficits, and serious adverse events may take time to develop and longer studies are required to capture such events. Well-designed head to head studies comparing a plant-based product with a standard of care treatment for chronic pain are lacking. The current evidence consists only of small, poorly designed, crossover or observational studies.

Despite limitations in the evidence base, our review has several strengths. First the living systematic review approach allows us to add new studies soon after they are published, thereby providing an opportunity to update conclusions in a rapid fashion. This may be important as cannabis and other plant-based treatments become more readily available to patients, providers and researchers. Also, using an organizational framework that categorizes cannabis-related products by both their THC and CBD ratios and their origin (plant-based versus synthetic) allows a way to conceptualize the evidence on these two prominent cannabinoids that is consistent with how they are available to consumers. A final strength that separates this review from others is the

exclusion of very short-term studies (e.g., a small number of dosing sessions), improving the applicability of the findings to chronic pain.

There are also some limitations to our review process. We excluded non-English language publications and study results published only as abstracts. We categorized nabilone as a synthetic high-THC product though it is more accurately described as a synthetic cannabinoid – a chemical analog to THC, and could have differing effects to THC. To address this possibility, we performed stratified analyses among outcomes that were pooled for synthetic high-THC interventions. The effect size for change in pain severity was larger with nabilone than with dronabinol, but the difference between the effect sizes was not statistically significant. Our inclusion criteria required that the study population have chronic pain, or have subgroup analyses for this group, which may be why we did not find evidence related to kratom. We were unable to assess publication bias (small sample size bias) for most outcomes, as most meta-analyses included fewer than eight studies. The exception was the analysis of change in pain severity with high-THC interventions, where we were unable to rule out important publication bias. Additional studies are needed to clarify the effect size estimates and our confidence in the findings. Since this is a living systematic review, new evidence will be incorporated into the review and findings updated on a regular basis. As in other recent systematic reviews of interventions to treat chronic pain, we grouped the magnitude of effects into small, moderate and large effects, rather than according to published minimal clinically important difference (MCID) thresholds. Defining clinical significance in chronic pain is difficult because it is subjective and difficult to correlate with real-life experiences of patients. For example, the MCID for improvement in pain is 15 points on a 0 to 100 scale. However, interventions commonly used for chronic pain, including opioids and nonsteroidal anti-inflammatory drugs do not achieve this level of reduction.[11,12] The typical reduction with opioids, nonopioid medications, nonpharmacological interventions, and cannabinoids is small, 5 to 10 points and may be considered a clinically important effect by patients and clinicians.

Applicability

A number of factors could impact the applicability of our findings. The evidence currently is most applicable to patients with neuropathic pain with mostly moderate to severe pain (mean baseline score was 6.6 on a 0 to 10 scale, with a range of 4 to 7.9). There is also considerable variability within the included studies among the types of neuropathic pain patients experience, and treatment effects might be different depending on the specific neuropathic pain condition.

The evidence base is generally applicable to women with around 71 percent of enrolled participants being female. While the age range across studies was broad, 18 to 84 years, the evidence is mainly applicable to middle-aged patients (mean age 50 years). Currently, the evidence is poorly applicable to patients of non-White race. It is also unclear how the evidence applies to patients currently taking prescription opioids to treat chronic pain or patients with serious mental illness or other comorbidities who are often excluded from trials. In terms of interventions, this evidence is applicable to comparable THC to CBD ratio oromucosal spray and to high-THC synthetic medications. The evidence for comparable THC to CBD oral spray is applicable to mean dosing of 8.4 sprays per day (21 mg THC/23 mg CBD). The evidence for high-THC to CBD ratio synthetic drugs applies to dosing that was titrated upward, with a maximum dose of 15 to 20 mg per day of dronabinol and 0.5 to 2 mg per day of nabilone (mean doses not reported). For high-THC to CBD products extracted from whole-plants, the evidence

was too heterogeneous and limited (2 RCTs) to describe an applicable dose. Applicability to other products including whole plant cannabis is very low or non-existent.

This evidence applies to short-term treatment and mainly informs the impact on mean changes in pain severity and common adverse events. The outcomes after longer term treatment may be different and could influence other outcomes not considered in short-term studies included here (e.g. psychosis, CUD, cognitive deficits). None of the studies reported other information relevant for assessing applicability, such as the description of the source of potential study participants or the number of women randomized relative to the number of women enrolled.

Although 60 percent of studies were conducted in the United States, we were unable to assess the impact of country of study or other geographic location characteristics (e.g., rural, metropolitan) on the applicability of specific results.

A number of evidence gaps or limitations in the evidence potentially impacted the applicability of our findings including lack of evidence on extracted whole-plant or purified interventions, whole-plant cannabis, and kratom.

Implications for Clinical Practice, Education, Research, or Health Policy

The implications of the present findings for clinical practice are mixed. These results suggest that select individuals with chronic neuropathic pain may experience moderate short-term improvements in pain when using cannabis products (synthetic or extracted from whole-plant) that have a high-THC to CBD ratio. The impact of this intervention on moderate or long-term outcomes is unknown. Cannabis products with a comparable THC to CBD ratio may also result in small improvements in pain severity. Those who take products containing comparable or high ratios of THC are also at increased risk for adverse events, including dizziness, sedation and nausea. The expected benefit of this treatment is comparable to prescription opioids, several nonopioid medications, and nonpharmacological interventions.[11-13] The evidence on adverse events with cannabis-related products is much less robust than the evidence on similar outcomes with opioids or nonopioid medications. The risk of sedation and dizziness appears similar with cannabis-related products, opioids, and the anticonvulsants pregabalin and gabapentin, while the risk for nausea appears to be larger with opioids and the antidepressant duloxetine than with cannabis-related products. These are only indirect comparisons, with very limited evidence on cannabis products relative to the other drugs, and comparisons of effects on serious and long-term harms are not possible even indirectly. Understanding how cannabis products' adverse event profiles compare with other available treatments for chronic pain, particularly opioid and non-opioid medications, is essential to determining the benefit to harm ratio. However, the strength of this evidence is mostly low, and more data are needed to confidently recommend this as a treatment for various chronic pain-related conditions or for patients with diverse demographic or clinical characteristics.

As noted in the limitations above, baseline use of opioids for pain and the impact of cannabinoids on the use of opioids for pain were very poorly reported. In an effort to address the opioid epidemic, a prominent goal of current research is to identify alternative treatments with equal or better benefits for pain while avoiding potential unintended consequences that could result in harms. Unfortunately, much of the findings to date are low SOE or insufficient evidence, and more high-quality studies are needed.

Our synthesis of the evidence leads to several important additional questions that could be addressed most effectively in a clinical practice guideline. Examples of questions that could be best addressed through a guideline process include: At what point in the treatment decision tree should cannabis-based medicines be considered? How should patient preferences be taken into account? What are pragmatic dosing guidelines? And finally, what are the comparative effects on costs of care?

Implications for Future Research

The gaps in the research evidence that are outlined above lead to specific recommendations for conducting future studies that will improve the strength of the conclusions that can be drawn, and provide better guidance for policymakers, clinicians and patients alike. These are summarized in Table 8.

Table 8. Future research needs for cannabis and other plant-based treatments for chronic pain

PICOTS Element	Gap in Evidence	Suggested Future Research
Populations	• Non-White populations, older adults, women • Pain conditions other than neuropathic pain	• Studies to assess possible differential effects in different races or ethnicities • Stratified analyses according to sex, including effects in pregnant and lactating persons • Studies to assess effects based on age differences • Pain populations expanded to include persons with non-neuropathic chronic pain, specifically back pain, other musculoskeletal pain, and fibromyalgia
Interventions	• High THC to CBD ratio from plant origin (not synthetic) • Comparable THC to CBD ratio formulations other than oromucosal spray • Low THC to CBD ratios, whole-plant cannabis, and other cannabinoids • Kratom	• Studies of high THC to CBD ratio products derived from whole-plant cannabis, with clear description of extraction or purification process and consistent nomenclature regarding the final product • Studies to compare different routes of administration (e.g., oromucosal spray, oral oil, oral capsule, smoked, etc.) • Studies should include and compare standardized treatment plans • Exploration of effects of different cannabinoids • Studies to asses kratom and/or other plant-based treatments
Comparators	• Head-to-head comparisons	• Studies comparing plant-based interventions with other plant-based treatments, opioids, non-opioid medications, or nonpharmacological interventions to evaluate active-control comparisons to provide direct evidence on comparative effectiveness

PICOTS Element	Gap in Evidence	Suggested Future Research
Outcomes	• Pain response (>30% improvement in pain severity) • Overall function, quality of life • Depression, anxiety, sleep, opioid use • Adverse event outcomes	• Outcomes should be consistently defined and reported across studies; ideally a core set of outcomes should be developed for future studies of treatments for chronic pain. • Future studies should include pain response, measures of overall function, and adverse events (overall, serious, and withdrawals due to adverse events at a minimum), in addition to changes in pain severity. • Patient-centered and patient-reported outcomes (e.g., QOL, depression, anxiety, and sleep) should be measured using validated tools for diagnosis and measurement of change. • In addition to reporting on opioid use prior to study enrollment, future studies should report on use of opioids, and other pain medications, during the trial. In particular, there is a need for more information on possible opioid sparing effects of plant-based treatments. • Studies need to assess serious harms such as development of cannabis use disorder, psychosis, and cognitive deficits. Other adverse events (e.g. sexual dysfunction) may need to be studied as new data emerge.
Timing	• Limited evidence on studies >6 weeks in duration	• Considering the chronic nature of the conditions, studies should provide followup assessments at longer timepoints, e.g., ≥3, 6 or 12 months

Study Design	• RCTs and cohort studies with adequate sample sizes to evaluate all important outcomes
	• Cohort studies with adequate control for confounding, ascertainment of exposures and outcomes
	• RCT and cohort studies with low risk of bias
		• All Designs:
		  ○ Studies with larger sample sizes to adequately power statistical analyses for key outcomes are needed across all interventions except the synthetic medications
		  ○ Should be designed and powered *a priori* to conduct subgroup analyses on important factors such as race, age, sex, and type of product or dose where these are variable
		• Cohort studies:
		  ○ Should be conducted prospectively where possible, and conduct and report on ascertainment and validation of exposure and outcomes following best-practice guidance[74]
		  ○ Should use appropriate methods to control for confounding on prognostic factors (e.g., baseline pain, prior and continued use of other interventions for pain, psychiatric illnesses)
		• RCTs:
		  ○ Should not use run-in periods, or enriched enrollment randomized withdrawal designs that may overestimate effects and limit the generalizability of the findings[75]
		  ○ Should be conducted using the parallel design (not crossover)
		• Systematic Reviews
		  ○ As more evidence emerges, analyses should stratify and conduct subgroup analyses based on product specifics, pain conditions, and population characteristics.

Abbreviations: CBD = cannabidiol; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial; THC = tetrahydrocannabinol.

Conclusions

Only short-term evidence is available for cannabis-related interventions containing THC and/or CBD to treat primarily neuropathic chronic pain. Improvement in pain was small to moderate with high and comparable THC to CBD ratio products. Compared with placebo, these interventions resulted in greater risk of common adverse events (dizziness, nausea, sedation) and study withdrawal due to adverse events. Evidence for other interventions, including kratom, was insufficient or not found. Additional studies are needed to improve confidence in these findings

and to provide evidence on longer-term followup, other outcomes, and other interventions including whole plant cannabis.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ANCOVA	analysis of covariance
BPI-SF	Brief Pain Inventory – Short Form
CBC	cannabichromene
CBD	cannabidiol
CBDV	cannabidivarin
CBG	cannabigerol
CI	confidence interval
CUD	cannabis use disorder
DAS28	28-Joiny Disease Activity Scale
EPC	Evidence-based Practice Center
FIQ	Fibromyalgia Impact Questionnaire
FM	fibromyalgia
GHQ-12	Short General Health Questionnaire
GNDS	Guy's Neurological Disability Scale
HADS-D	Hospital Anxiety and Depression Scale
IA	inflammatory arthritis
KQ	Key Question
MCID	minimal clinically important difference
MCP	New Mexico Medical Cannabis Program
MD	mean difference
MS	multiple sclerosis
NA	not applicable
NPP	neuropathic pain
NR	not reported
NRS	numerical rating scale
ODI	Oswestry Disability Index
OME	oral morphine equivalent
OR	odds ratio
PBC	plant-based compound
PDI	Pain Disability Index
PICOTS	populations, interventions, comparators, outcomes, timing, and settings
QOL	quality of life
RA	rheumatoid arthritis
RCT	randomized controlled trial
RDQ	Roland-Morris Disability Questionnaire

ROB	risk of bias
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SEADS	Supplemental Evidence and Data for Systematic review
SF-36	Short Form-36
SMD	standardized mean difference
SOE	strength of evidence
SRDR+	Systematic Review Data Repository Plus
THC	tetrahydrocannabinol
TOO	Task Order Officer
VAS	visual analogue scale
VP	visceral pain
WAE	withdrawal due to adverse events
WP	whole plant

Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) ALL 1946 to July 16, 2021

1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab,kw.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8 1 or 2 or 5 or 6 or 7
9 Cannabis/
10 exp Cannabinoids/
11 Medical Marijuana/
12 Mitragyna/
13 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,kf.
14 or/9-13
15 8 and 14
16 limit 15 to english language
17 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
18 ((animal or animals or avian or bird or birds or bovine or canine or cow* or dog or dogs or cat or cats or feline or hamster* or horse* or lamb or lamb* or mouse or mice or monkey or monkeys or murine or pig or piglet* or pigs or porcine or primate* or rabbit* or rat or rats or rodent* or songbird* or veterinar*) not (human* or patient*)).ti,kf,jw.
19 or/17-18
20 16 not 19

Database: EBM Reviews - Cochrane Central Register of Controlled Trials March 2021

1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab,hw.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,hw.
8 1 or 2 or 5 or 6 or 7
9 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,hw.
10 8 and 9

11 conference abstract.pt.
12 "journal: conference abstract".pt.
13 "journal: conference review".pt.
14 "http://.www.who.int/trialsearch*".so.
15 "https://clinicaltrials.gov*".so.
16 11 or 12 or 13 or 14 or 15
17 10 not 16

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 16, 2021
1 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab.
2 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
3 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab.
4 (1 or 2) and 3

Database: APA PsycInfo 1806 to July 16, 2021
1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
8 1 or 2 or 5 or 6 or 7
9 Cannabis/
10 exp Cannabinoids/
11 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab.
12 or/9-11
13 8 and 12
14 limit 13 to english language

Database: Elsevier Embase to July 5, 2021
('cannabis'/exp OR cannabis OR cannabinoid* OR 'cannabinol'/exp OR cannabinol OR 'marijuana'/exp OR marijuana OR 'cannabidiol'/exp OR cannabidiol OR phytocannabinoid* OR 'tetrahydrocannabinol'/exp OR tetrahydrocannabinol OR 'dronabinol'/exp OR dronabinol OR 'nabilone'/exp OR nabilone OR 'sativex'/exp OR sativex OR 'cbd' OR 'thc' OR 'kratom'/exp OR kratom OR 'khat'/exp OR khat OR 'qat'/exp OR qat OR 'psilocybin'/exp OR psilocybin OR 'hemp'/exp OR hemp OR hydroxymitragynine) AND ('chronic pain'/exp OR arthralgia OR 'back pain' OR headache OR 'musculoskeletal pain' OR 'neck pain' OR neuralgia OR 'nociceptive pain'

OR 'intractable pain' OR fibromyalgia OR myalgia OR arthritis OR osteoarthrtis) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Database: Elsevier Scopus to July 12, 2021
(TITLE (cannabis OR cannabinoid* OR cannabinol OR marijuana OR cannabidiol OR phytocannabinoid* OR tetrahydrocannabinol OR dronabinol OR nabilone OR sativex OR "CBD" OR "THC" OR kratom OR khat OR qat OR psilocybin OR hemp OR hydroxymitragynine)) AND (TITLE ("chronic pain" OR arthralgia OR "back pain" OR headache OR "musculoskeletal pain" OR "neck pain" OR neuralgia OR "nociceptive pain" OR "intractable pain" OR fibromyalgia OR myalgia OR arthritis OR osteoarthritis OR "neuropathic pain"))

Appendix B. Methods

Inclusion and Exclusion Criteria

Table B-1 outlines the inclusion and exclusion criteria related to populations, interventions, comparators, outcomes, timing, and settings (PICOTS), and study designs of interest for each Key Question (KQ):

KQ1. In adults with chronic pain, what are the benefits of cannabinoids for treatment of chronic pain?

KQ2. In adults with chronic pain, what are the harms of cannabinoids for treatment of chronic pain?

KQ3. In adults with chronic pain, what are the benefits of kratom or other plant-based substances for treatment of chronic pain?

KQ4. In adults with chronic pain, what are the harms of kratom or other plant-based substances for treatment of chronic pain?

Table B-1. PICOTS

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults (including pregnant or breastfeeding women) 18 years and older with chronic pain (>12 weeks or pain persisting past the time for normal tissue healing). See categorization of specifically included pain populations below.	**All KQs:** Children and adolescents <18 years old; adults with acute or subacute pain; patients at end of life or in palliative care (e.g., with late stage cancer-related pain)
Interventions	**KQs 1 and 2:** Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes **KQs 3 and 4:** Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids **All KQs**: Co-use of other drugs for pain	**All KQs:** Non-plant-based interventions, capsaicin, herbal supplements
Comparators	**All KQs:** Any comparator or usual care	**All KQs:** No comparison
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, function, disability, pain interference); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder); secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, health care utilization)	**All KQs:** Other outcomes
Time of followup	**All KQs:** short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year)	**All KQs:** studies with <1-month (4 weeks) of treatment or followup after treatment
Setting	**All KQs:** Any nonhospital setting or setting of self-directed care	**All KQs**: Hospital care, hospice care, emergency department care
Study design	**All KQs:** RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits	**All KQs:** Other study designs

Abbreviations: KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial.

Important subgroups to consider in evaluating this evidence are:

- Specific types of pain: neuropathic pain (including nociceptive and centralized; patients with multiple sclerosis and painful skin disorders are included in this category), musculoskeletal pain (including low-back pain), visceral pain, fibromyalgia, inflammatory arthritis, headache disorders, sickle cell disease, and cancer pain (non-end of life)
- Degree of nociplasticity/central sensitization
- Patient demographics (e.g., age, race, ethnicity, sex, socioeconomic status)
- Comorbidities, including past or current substance use disorders, mental health disorders, medical comorbidities, and high risk for opioid use disorder)
- Plant-based compound characteristics: route of administration, frequency of administration, potency of product, dose or estimated dose, specific compounds (e.g. tetrahydrocannabinol, cannabidiol, terpenes, flavonoids), and specific formulations used
- Co-use of other interventions for pain: opioids, nonopioids (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentin, pregabalin)

Below are additional details on the scope of this project:

Study Design: For all Key Questions, we included randomized controlled trials (RCTs) of at least 4 weeks duration. Initially, in the base-year of this living systematic review, we included observational studies for both benefits (to address gaps in evidence where RCTs are not available) and harms. Eligible observational studies must have assessed a mean duration of treatment of at least 4 weeks, and have concurrent controls (e.g., cohort and case-control studies). Those controlling for potential confounders were prioritized. As the evidence grows, and more RCTs become available throughout the project, we will reassess the need to include observational studies, specifically to address benefits. A decision to discontinue including them will be made based on the strength of the RCT evidence. When the RCT evidence on a given Key Question and outcome is insufficient, we will include observational studies that meet inclusion criteria. When the strength of evidence is low, moderate, or high based on RCTs, we will update our protocol to exclude observational studies. We do not anticipate excluding observational studies assessing harms. For all Key Questions, we excluded uncontrolled observational studies, case series, and case reports. Systematic reviews were used to supplement searches and identify primary studies.

Non-English Language Studies: We restricted to English-language articles, but reviewed English-language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria in order to help assess for the likelihood of language bias.

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through July 5, 2021. Searches were initially run in September 2020 with ongoing, automated monthly searches to identify newly published studies. Search strategies are available in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and reviewing the two prior AHRQ pain reports[1,2] for studies that met our inclusion criteria. A Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies. As part of living systematic review methods, the

electronic searches were automated to be run on a biweekly basis, with results emailed directly to the EPC librarian and the research team for processing. Citations were uploaded into DistillerSR® software for study selection management.

The pre-established criteria listed above were used to determine eligibility for inclusion and exclusion of abstracts. Using Distiller® SR, the review team conducted manual online assessment of study citations. All citations deemed potentially relevant by at least one of the reviewers were retrieved for full-text review. To ensure accuracy, any citation deemed not relevant for full-text review were reviewed by a second researcher. We initially planned to explore using the Distiller® AI feature to automate exclusion of abstracts that are clearly not relevant. Briefly, Distiller®SR AI is training in the background, learning from the human decisions on abstract eligibility. When the Distiller® AI decisions reach a level of 95 percent accuracy, we will deploy the system to assist with dual review (this typically takes 2000 citations, but varies by topic).[3] To date, the biweekly citation counts have been low, and the AI feature has not been utilized.

Data Extraction

After studies were selected for inclusion, data were abstracted into categories that included but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results relevant to each Key Question as outlined in the previous inclusion and exclusion criteria section. Information that was abstracted that was relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. All study data were verified for accuracy and completeness by a second team member. On a quarterly basis, any newly identified studies were abstracted and evidence tables updated. Quarterly reports were published to the Agency for Healthcare Research and Quality (AHRQ) website, and evidence tables will be updated in AHRQ's Systematic Review Data Repository Plus (SRDR+).

Risk of Bias Assessment of Individual Studies

Predefined criteria were used to assess the risk of bias of individual controlled trials, systematic reviews, and observational studies. RCTs were evaluated using criteria and methods developed by the Cochrane Back Review Group,[4] and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force.[5] These criteria and methods were used in accordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews developed by AHRQ.[6] Studies were given an overall rating of "low," "medium," or "high" risk of bias. We used DistillerSR® software to conduct these assessments, using dual review by two independent reviewers. Disagreements identified by DistillerSR® were resolved through consensus. Assessments and final ratings were converted to evidence tables, and will be uploaded on a quarterly basis to SRDR+.

Data Synthesis and Analysis

We constructed evidence tables showing study characteristics (as discussed above), results, and risk of bias ratings for all included studies, and summary tables to highlight the main

findings. Data were qualitatively summarized in tables, using ranges and descriptive analysis and interpretation of the results. Studies identified in prior AHRQ chronic pain reports[1,2] that meet inclusion criteria are included in this review. We evaluated the persistence of benefits or harms by evaluating the three periods identified in prior AHRQ pain reports (3 to 6 months, 6 to 12 months, and ≥12 months).[1,2,7-9]

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were homogeneous enough to provide a meaningful combined estimate.[10] The decision to conduct quantitative synthesis depends on presence of at least two studies, completeness of reported outcomes and a lack of heterogeneity among the reported results. To determine whether meta-analyses were indicated, we considered the risk of bias of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Meta-analyses were conducted using a random effects model, and statistical heterogeneity was assessed using the I^2 method. Publication bias (small sample size bias) is assessed using funnel plots when there are eight or more studies in meta-analyses. To evaluate subgroup effects, we summarized within-study analyses of subgroup differences and performed study-level analyses on key demographic and clinical factors. Sensitivity analyses were conducted on study risk of bias.

The magnitude of effects for pain and function is classified using the same system used in other recent AHRQ Evidence-based Practice Center (EPC) reviews conducted on chronic pain[1,2,7-9] to provide a consistent benchmark for comparing results of pain interventions across reviews. Table B-2 provides thresholds for determining the magnitude of effect. A small effect is defined for pain as a mean between-group difference following treatment of 5 to 10 points on a 0- to 100-point visual analog scale (VAS), 0.5 to 1.0 points on a 0- to 10-point numeric rating scale, or equivalent; for function as a mean difference of 5 to 10 points on the 0- to 100-point Oswestry Disability Index (ODI) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A moderate effect is defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large effects are defined as greater than moderate. We apply similar thresholds to other outcomes measures. Small effects using this system may be below published thresholds for clinically meaningful effects; however, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or function using a treatment with low cost or no serious harms may be important.

Table B-2. Definitions of effect sizes

Effect Size	Definition
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.

Findings that were not statistically significant were interpreted as follows:

- In determining the strength of evidence (SOE), the precision of evidence was downgraded two levels if inadequate sample size (optimal information size) ***and*** the 95% confidence interval includes both potentially meaningful benefit and harm (e.g. for a relative effect, the lower bound is ≤ 0.75 ***and*** the upper bound is ≥ 1.25)[11]
- If the magnitude of effect is below the threshold for a small effect, the finding is considered to have "No effect"[1]
- If the magnitude of effect is small or greater, and SOE is at least Low, the finding is considered to have a "Potential effect, not statistically significant"
- If the magnitude of effect is small or greater, and SOE is insufficient, the finding is considered to have "failed to demonstrate or exclude a beneficial/detrimental effect."[12]

Grading the Strength of the Body of Evidence

We assessed the SOE for all primary comparisons and outcomes listed in Table B-1. Regardless of whether evidence is synthesized quantitatively or qualitatively, the strength of evidence for each Key Question/body of evidence is initially assessed by one researcher for each clinical outcome by using the approach described in the AHRQ Methods Guide.[6] To ensure consistency and validity of the evaluation, the strength of evidence is reviewed by the entire team of investigators prior to assigning a final grade on the following factors:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting/publication bias (suspected or undetected)

The SOE was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- High—We are 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. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have 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). We believe that 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—We have no evidence, we are unable to estimate an effect, or we have 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.

Plain-language statements are used in the Main Points, the Evidence Summary and the Discussion to convey the SOE. High SOE is described as "is associated with" or simply

"reduces/increases;" moderate SOE is described as "probably;" and low SOE is described as "may be."[13]

Peer Review and Public Commentary

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Assessing Applicability

Applicability is assessed in accordance with the AHRQ Methods Guide,[14] which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies. For example, exclusion of chronic pain patients with psychiatric comorbidities reduces applicability to clinical practice since many patients with chronic pain have such comorbidities and may respond more poorly to treatment. Similarly, trials that use active run-in periods evaluate highly selected populations who tolerated and responded well to the study intervention, rather than the general population of chronic pain patients being considered for the intervention. Factors that may affect applicability which we have identified a priori include eligibility criteria and patient factors (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical and psychiatric comorbidities, event rates and symptom severity in treatment and control groups), intervention factors (e.g., dose and duration of therapy, intensity and frequency of monitoring, level of adherence, use of co-interventions), comparisons (e.g., type and dosing of comparison), outcomes (e.g., use of unvalidated or nonstandardized outcomes, measurement of short-term or surrogate outcomes), settings (e.g., primary care vs. specialty setting, country), and study design features (e.g., use of run-in periods) relevant to applicability. We use this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

Appendix B References

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Appendix C. Included Studies List

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Appendix D. Results

Appendix D-1. Individual Study Summary Tables

Tables D-1 through D-5 present details and results for primary outcomes, serious adverse events and withdrawals due to adverse events for each included study. Tables D-1 through D-3 provide information for randomized controlled trials and are organized by their respective ratio of tetrahydrocannabinol to cannabidiol. Table D-4 includes details for studies of other cannabinoids, and Table D-5 presents details of observational studies.

Table D-1. Comparable THC to CBD ratio study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Blake, 2006 Moderate RCT Inflammatory arthritis-rheumatoid arthritis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 5.4 sprays/day (31) B: Placebo (27) 5 weeks Whole plant extracted	Pain severity (mean [SD NR] 0 to 10 NRS scale): 3.1 vs. 4.1, MD −1.04[b] (95% CI −1.9 to −0.18)	Function (mean [SD NR] 0 to 10 28−Joint Disease Activity Score scale): 5 vs. 5.9, MD −0.76[c] (95% CI −1.23 to −0.28)	SAE: 0/31 (0%) vs. 2/27 (7.41%) WAE: 0/31 (0%) vs. 3/27 (11.11%)
Langford, 2013 Low RCT Neuropathic pain-multiple sclerosis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.8 sprays/day (167) B: Placebo (172) 15 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 83/167 (49.75%) vs. 77/172 (44.77%), RR 1.11 (95% CI 0.89 to 1.39) Pain severity (mean [SD] 0 to 10 NRS scale): 4.54 (2.24) vs. 4.73 (2.26), MD −0.19 (SE 0.24) (95% CI −0.67 to 0.29)	Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.12, p=0.56 Function (0 to 100 SF−36 Physical Functioning scale): Treatment difference −0.45, p=0.785	WAE: 14/167 (8.38%) vs. 9/172 (5.23%)
Lynch, 2014 High RCT (crossover) Neuropathic pain-chemotherapy induced	A: THC/CBD oromucosal spray (dose NR), mean dose 8 sprays/day (8) B: Placebo (8) 4 weeks Whole plant extracted	Pain severity (mean, 0 to 10 NRS−PI scale): 6 (95% CI 6.98 to 5.02) vs. 6.38 (95% CI5.67 to 7.09)	Function (mean [SD] 0 to 100 SF−36 Physical Functioning scale): 35.5 (9.19) vs. 46.5 (8.5), MD −11 (4.43) (95% CI −20.49 to −1.51)	SAE: 0/8 (0%) vs. 0/8 (0%) WAE: 0/8 (0%) vs. 0/8 (0%)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Nurmikko, 2007 Moderate RCT Neuropathic pain-mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 10.9 sprays/day (63) B: Placebo (62) 5 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 16/73 (25.4%) vs. 9/62 (14.52%), RR 1.75 (95% CI 0.84 to 3.66) Pain severity (mean [SD NR] 0 to 10 NRS scale): 5.82 vs. 6.68, treatment difference −0.96 (95% CI −1.59 to −0.32)	Function (0 to 70 Pain Disability Index scale): MD −5.85 (95% CI −9.62 to −2.09)	SAE: 1/63 (1.6%) vs. 0/62 (0%) WAE: 11/63 (17.46%) vs. 2/62 (3.23%)
Rog, 2005 Moderate RCT Neuropathic pain-multiple sclerosis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 9.6 sprays/day (34) B: Placebo (32) 5 weeks Whole plant extracted	Pain severity (mean [95% CI] 0 to 10 NRS scale): 3.85 (3.13 to 4.58) vs. 4.96 (4.19 to 5.72), treatment difference −1.25 (95% CI −2.11 to −0.39)	NR	SAE: 0/34 (0%) vs. 0/32 (0%) WAE: 2/34 (5.88%) vs. 0/32 (0%)
Selvarajah, 2010 High RCT Neuropathic pain-diabetic neuropathy	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 7 sprays/day[d] (15) B: Placebo (14) 12 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 100 NPS scale): 51.6 (21.9) vs. 51.9 (24.1), MD −0.3 (SE 8.54) (95% CI −17.83 to 17.23)	Function (mean [SD] 0 to 100 SF−36 Physical Functioning scale): 30.5 (16.6) vs. 36.5 (27.9), MD 6 (SE 8.5) (95% CI −11.35 to 23.35)	NR
Serpell, 2014 Moderate RCT Neuropathic pain-mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.9 sprays/day (128) B: Placebo (118) 15 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 34/123 (27.64%) vs. 19/117 (16.24%), RR 1.7 (95% CI 1.03 to 2.91) Pain severity (mean [SE NR] 0 to 10 NRS scale): Mean reduction −0.34 (0.23) (95% CI −0.79 to 0.11)	Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.32 (SE 0.241) (95% CI −0.8 to 0.15)	SAE: 10/128 (7.81%) vs. 6% WAE: 25/128 (19.53%) vs. 25/118 (21.19%)

Abbreviations: BPI−SF = brief pain inventory−short form; CBD = cannabidiol; CI = confidence interval; MD = mean difference; NPS = neuropathic pain scale; NR = not reported; NRS = numeric rating scale; NRS−PI = numeric rating scale for pain intensity; SAE = serious adverse events; SD = standard deviation; SE = standard error; SF−36= short form−36; THC = tetrahydrocannabinol; RCT = randomized controlled trial; RR = relative risk; WAE = withdrawal due to due adverse events

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

[b] Difference in median differences.

[c] Difference in mean differences.

[d] Mean sprays calculated by systematic review team.

Table D-2. High-THC to CBD ratio study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Chaves, 2020 Low RCT Fibromyalgia	A: 1.2 mg THC/0.02 mg CBD sublingual drops, mean 3.6 drops/day (8) B: Placebo (9) 8 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 FIQ scale): 3.75 (2.49) vs. 7.67 (1.84), MD −3.92 (1.05) (95% CI −6.17 to −1.68)	Function (mean [SD] 0 to 10 FIQ scale): 5.83 (2.02) vs. 4.07 (2.25), MD 1.76 (1.04) (95% CI −0.46 to 3.98)	WAE: 0/8 (0%) vs. 0/9 (0%)
de Vries, 2017 Moderate RCT Visceral pain- chronic pancreatitis and postsurgical abdominal pain	A: THC oral tablet (Dronabinol), range 15 to 24 mg/day (30) B: Placebo (32) 7 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 2.4 (2.28) vs. 3.5 (2.42), MD −1.1 (SE 0.68) (95% CI −2.46 to 0.26)	NR	WAE: 7/30 (23.33%) vs. 2/32 (6.25%)
Frank, 2008 Moderate RCT (crossover) Neuropathic pain	A: THC oral capsule (Nabilone), max dose 2 mg/day (48) B: Dihydrocodeine 30 mg, max dose 240 mg/day (48) 6 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): Treatment effect 5.7 (95% CI 0.5 to 10.9)	Function (mean [SD NR] 0 to 100 SF−36 Physical Functioning scale): Treatment effect 10.8 (95% CI 2.3 to 19.2)	SAE: 0/48 (0%) vs. 0/48 (0%) WAE: 2/48 (4%) vs. 6/48 (12.5%)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Pini, 2012 Low RCT (crossover) Headache- medication overuse headache	A: THC 0.5 mg oral capsule (Nabilone) daily (26) B: Ibuprofen 400 mg/day (26) 8 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 5.55 (2.5) vs. 6.75 (2.4), MD −1.2 (0.68) (95% CI −2.57 to 0.17)	NR	WAE: 1/30 (3.33%) vs. 1/30 (3.33%)
Rintala, 2010 High RCT (crossover) Neuropathic pain- spinal cord injury	A: THC 5 mg oral capsule (Dronabinol), max dose 20 mg/day (7) B: Diphenhydramine 25 mg, max dose 75 mg/day (5) 47 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 BPI scale): 5.8 vs. 5.8	NR	SAE: 1/7 (14.29%) vs. 1/5 (20%) WAE: 1/7 (14.29%) vs. 0/5 (0%)
Schimrigk, 2017 Low RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg oral capsule (Dronabinol), mean dose 13 mg/day (124) B: Placebo (116) 16 weeks Synthetic	Pain severity (mean [SD] 0 to 10 NRS scale): 4.48 (2.04) vs. 4.92 (2.04), MD NR, p=0.676	NR	SAE: 12/124 (9.68%) vs. 7/116 (6.03%) WAE: 19/124 (15.32%) vs. 12/116 (10.34%)
Skrabek, 2008 Moderate RCT Fibromyalgia	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 2 mg/day (15) B: Placebo (18) 4 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 VAS scale): 4.8 vs. 5.6, MD −1.43, p<0.05	NR	SAE: 0/15 (0%) vs. 0/18 (0%) WAE: 1/20 (5%) vs. 1/20 (5%)
Toth, 2012 Low RCT Neuropathic pain- diabetic neuropathy	A: THC 0.5 mg oral capsule (Nabilone), max dose 4 mg/day (13) B: Placebo (13) 5 weeks Synthetic	Pain response ≥30% (NRS scale): 11/13 (84.62%) vs. 5/13 (38.46%), RR 2.2 (95% CI 1.06 to 4.55) Pain severity (mean [SD] 0 to 10 NRS scale): 3.5 (1.3) vs. 5.4 (1.7), MD −1.9 (0.59) (95% CI −3.13 to −0.68)	Pain interference (mean [SD] 0 to 10 MBPI scale): 2.5 (1.6) vs. 3.6 (0.9), MD −1.1 (0.51) (95% CI −2.15 to −0.05)	NR

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Turcotte, 2015 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), max dose 2 mg/day (8) B: Placebo (7) 9 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): 35 vs. 57[b]	Pain interference (mean [SD NR] 0 to 100 VAS impact scale): 41 vs. 40[b]	SAE: 0/8 (0%) vs. 0/7 (0%) WAE: 1/8 (12.5%) vs. 0/7 (0%)
Wissel, 2006 High RCT (crossover) Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 1 mg/day (13) B: Placebo (13) 4 weeks Synthetic	Pain severity (median [SD NR] 11 Point Box Test): 4 vs. 6, p<0.05	NR	WAE: 2/13 (15.38%) vs. 0/13 (0%)
Zajicek, 2012 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg capsule, max dose 25 mg/day (143) B: Placebo (134) 12 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 CRS scale): 4.1 (2.9) vs. 4.7 (3.0), MD −0.6 (95% CI −1.3 to 0.1)	NR	SAE: 7/143 (4.9%) vs. 3/134 (2.24%) WAE: 30/143 (20.98%) vs. 9/134 (6.72%)

Abbreviations: BPI = brief pain inventory; CBD = cannabidiol; CI = confidence interval; CRS = category rating scale; FIQ = fibromyalgia impact questionnaire; MBPI = modified brief pain inventory; MD = mean difference; NR = not reported; NRS = numeric rating scale; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; SE = standard error; THC = tetrahydrocannabinol; RR = relative risk; VAS = visual analog scale; WAE = withdrawal due to due adverse events.

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

[b] Estimated from graph.

Table D-3. Low-THC to CBD ratio study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Xu, 2020 High RCT (crossover) Neuropathic pain-mixed	A: CBD cream (250 mg/3 oz) up to 4 times daily (15) B: Placebo (14) 4 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 NPS scale): 3.33 (2.02) vs. 5.55 (2.81), MD −2.22 (95% CI −4.07 to −0.37)	NR	SAE: 0/15 (0%) vs. 0/14 (0%)

Abbreviations: CBD = cannabidiol; MD = mean difference; NPS = neuropathic pain scale; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; THC = tetrahydrocannabinol.

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

Table D-4. Other cannabinoids study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Eibach, 2020 Moderate RCT (crossover) Neuropathic pain- HIV associated	A: CBDV oral solution (50 mg/mL) 400 mg/day (16) B: Placebo (16) 4 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 6/16 (37.5%) vs. 13/16 (81.25%), RR NR Pain severity (mean [SD] 0 to 10 NRS scale): 2.74 (1.47) vs. 3.67 (2.62), MD −0.62 (95% CI −0.27 to 1.51)	Pain interference (0 to 10 BPI−SF scale): MD −0.35 (95% CI −1.36 to 0.43)	SAE: 1/16 (6.25%) vs. 0/16 (0%) WAE: 1/16 (6.25%) vs. 0/16 (0%)

Abbreviations: CBDV = cannabidivarin; HIV = human immunodeficiency virus; MD = mean difference; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SD = standard deviation.

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

Table D-5. Observational study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Bestard, 2011 Moderate Prospective cohort Neuropathic pain-mixed	A: THC oral capsule (Nabilone), mean dose 3.05 mg/day (49) B: Gabapentin, mean dose 2,295.5 mg/day (52) C: Gabapentin + THC capsule, mean dose NR + 3.02 mg/day (55) 6 months Synthetic	Pain intensity (mean [SD] 0 to 100 VAS scale): 28.0 (10.5) vs. 33.8 (11.6) vs. 33.1 (20.2), MD −5.8 (95% CI −10.18 to −1.42) for A vs. B, −5.1 (95% CI −11.48 to 1.28) for A vs. C	Pain interference (mean [SD] 0 to 10 BPI scale): 4.5 (2.3) vs. 4.6 (2.2) vs. 4.5 (2.2), MD −0.1 (95% CI −0.99 to 0.79) for A vs. B, 0.00 (95% CI −0.88 to 0.88) for A vs. C Function (mean [SD] 0 to 100 SF-36 scale): 48.3 (27.2) vs. 46.5 (25.1) vs. 43.7 (26.4), MD 1.80 (95% CI −8.53 to 12.13) for A vs. B, 4.60 (95% CI −5.83 to 15.03) for A vs. C	SAE: 0/49 (0%) vs. 0/52 (0%) vs. 0/55 (0%) WAE: 5/49 (10%) vs. 12/52 (23%) vs. 5/55 (9%)
Campbell, 2018 Moderate	A: Self-reported frequent cannabis use of ≥20 days/mo B: No cannabis use Overall N Baseline: 1,514 4-year followup: 1,217 Groups unclear 4 years Unclear THC concentration; patient-driven choice	A vs. B (reference) Pain intensity (Adjusted mean [SE]; BPI, 0-10 scale): 5.2 (0.14) vs. 4.9 (0.03); Beta: 0.37 (95% CI, −0.23 to 1.10), p=0.20	A vs. B Pain Interference (Adjusted mean [SE]; BPI pain interference, 0-10 scale): 5.2 (0.19) vs. 5.4 (0.04); Beta: −0.63 (95% CI, −1.46 to 0.19), p=0.13	NR
Gruber, 2021 High Prospective cohort Mixed (primarily musculoskeletal)	A: THC/CBD: Medicinal cannabis program, mean dose THC 13.3 mg/day, CBD 28.9 mg/day (37) B: Usual care, dose NA (9) 12 weeks Mixed cannabis products	Pain intensity (mean [SD] 0 to 100 VAS scale): 34.07 (22.36) vs. 48.78 (30.42); MD −14.71 (95% CI, −32.71 to 3.29)	A vs. B Function (mean [SD], 0 to 10 PDI scale): 18.13 (12.26) vs. 19.22 (12.73); MD −1.09 (95% CI −10.33 to 8.16) SF-36 Function (mean [SD], 0 to 100 scale[a]): 70.00 (22.87) vs. 69.44 (26.98); MD 0.56 (95% CI −17.17 to 18.29)	NR

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Lee, 2021[b] Moderate Matched cohort NR	A: Chronic opioid users authorized to use medical cannabis in Canada (5,373) B: Controls who did not receive authorization for medical cannabis in Canada (5,373) 20 months Unknown THC concentration; patient-driven choice	NR	NR	NR
Merlin, 2019[b] High Prospective cohort Chronic non-cancer pain (HIV)	A: Daily or weekly use of marijuana (55) B: Monthly or 1-2 times a month use of marijuana (65) C: No use (313) 52 weeks Unknown THC concentration; patient-driven choice	NR	NR	NR
Vigil, 2017[b] High Preliminary historical cohort Mixed musculoskeletal pain	A: THC/CBD: Participation in New Mexico Medical Cannabis Program (37) B: Not participating in medical marijuana program and not using cannabis (29) 21 months Unknown THC concentration	NR	NR	NR

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Ware, 2015 High Prospective cohort Chronic non-cancer pain	A: THC 12.5 +/- 1.5% herbal cannabis, median dose 2.5 g/day (215) B: Usual care (216) 13 months Whole plant non-extracted	NR	NR	SAE: 28/215 (13%) vs. 42/216 (19.4%) WAE: 10/215 (4.65%) vs. NR (assumed 0)

Abbreviations: BPI = brief pain inventory; CI = confidence interval; MD = mean difference; NR = not reported; SAE = serious adverse events; SD = standard deviation; SF−36= short form−36; THC = tetrahydrocannabinol; VAS = visual analog scale; WAE = withdrawal due to due adverse events.

[a] Higher scores indicate better outcomes.

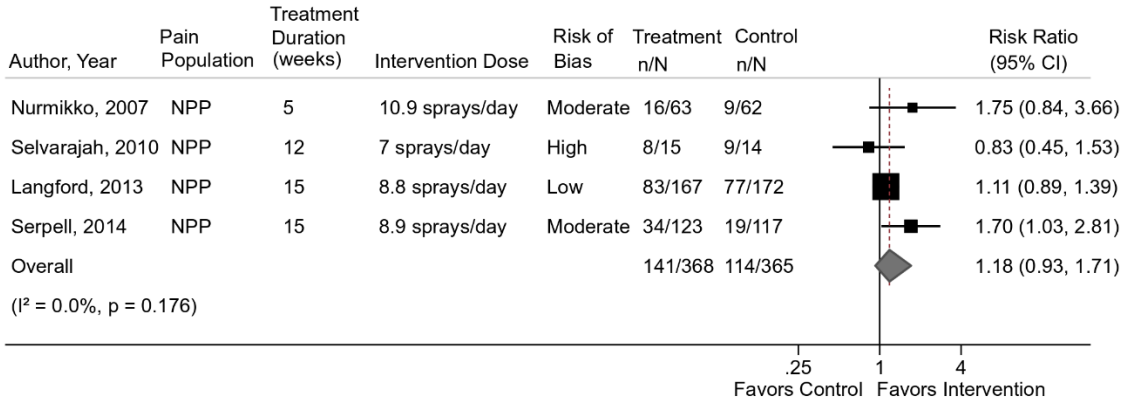
[b] Only included outcome reported was opioid-use.

Appendix D-2. Meta-Analyses

Comparable THC to CBD Ratio Studies

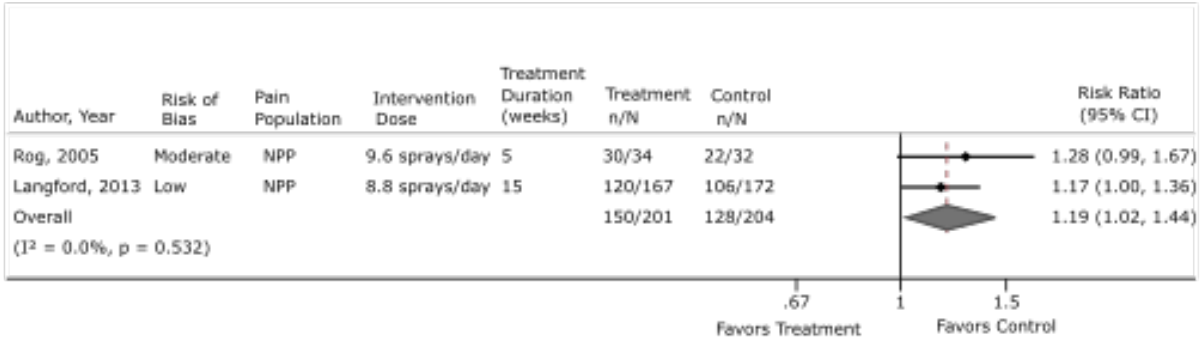
Pooled results and the forest plot for the sensitivity analysis conducted for improvement in pain severity are available upon request by emailing wagnerje@ohsu.edu.

Figure D-1. Proportion of patients with pain response (≥30% improvement) with comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



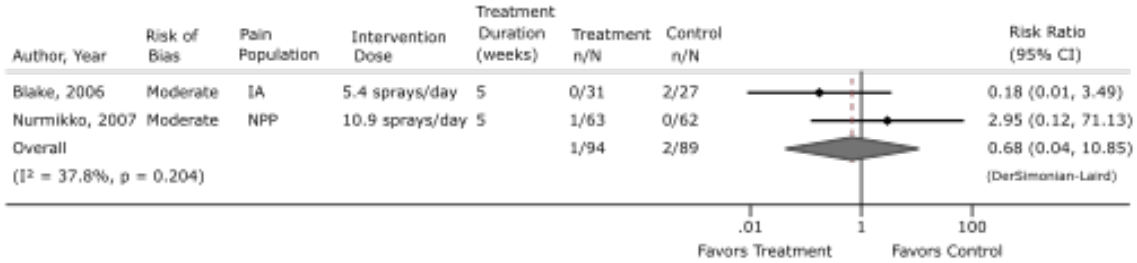
Abbreviations: CI = confidence interval; NPP = neuropathic pain
[a] Calculated by review team

Figure D-2. Adverse events for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



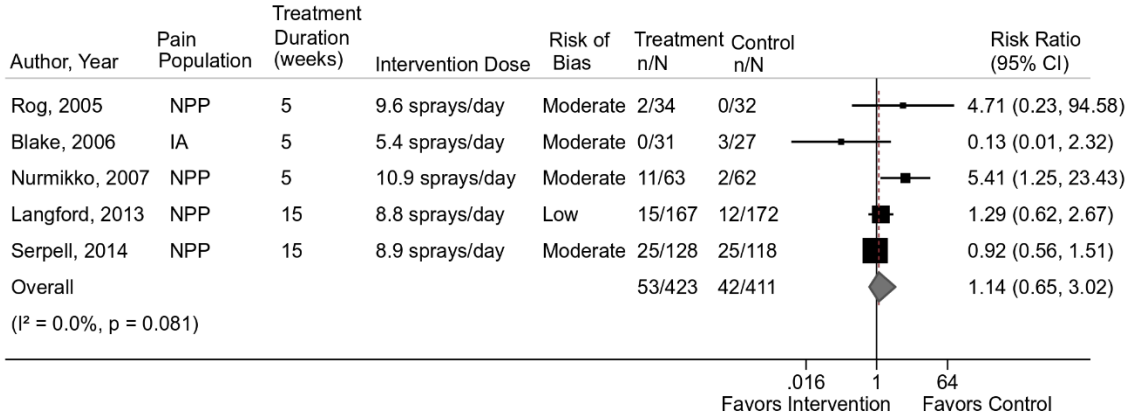
Abbreviations: CI = confidence interval; NPP = neuropathic pain

Figure D-3. Serious adverse events for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



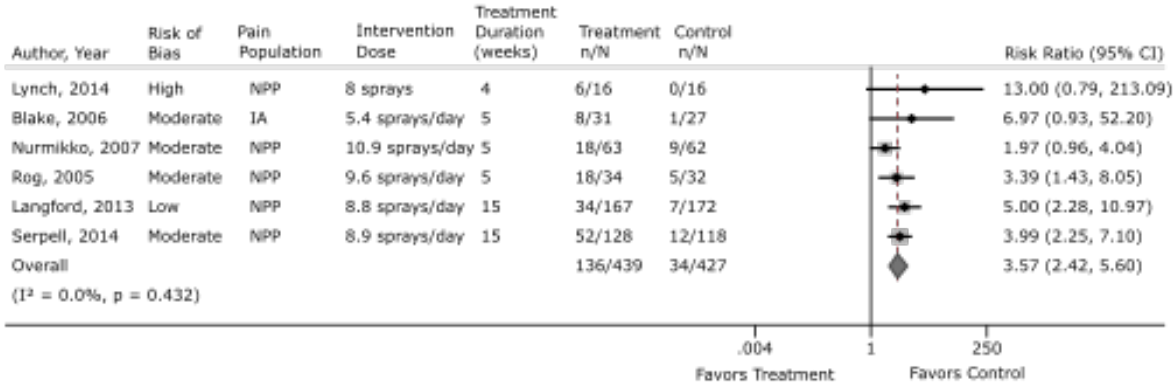
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

Figure D-4. Withdrawal due to adverse events for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



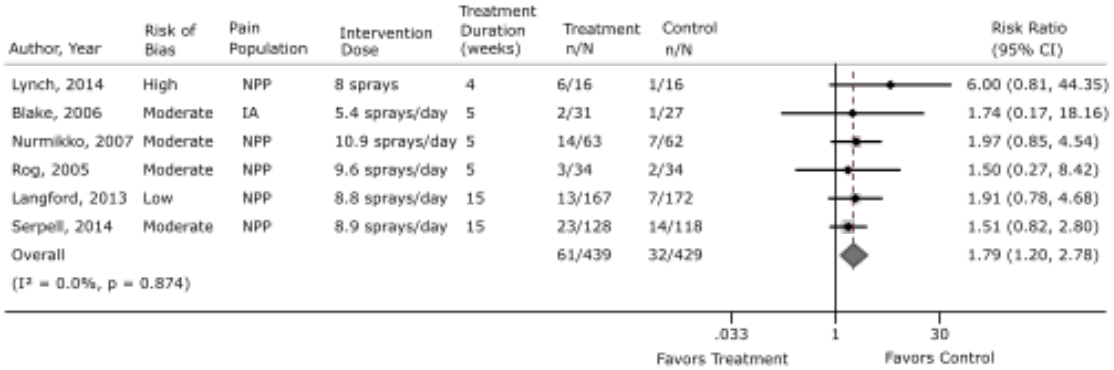
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

Figure D-5. Dizziness for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



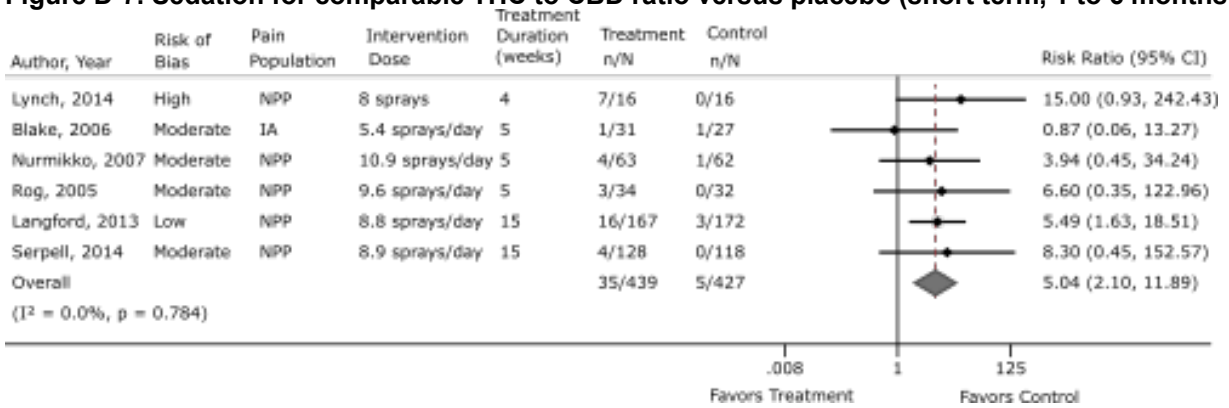
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

Figure D-6. Nausea for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

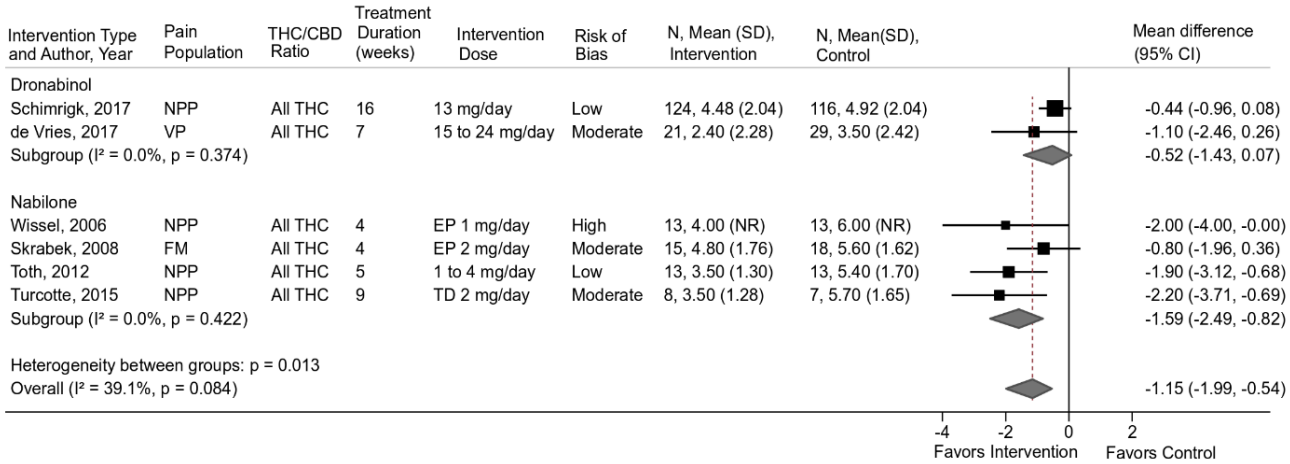
Figure D-7. Sedation for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

High-THC to CBD Ratio Studies

Figure D-8. Stratified results on pain severity of RCTs using dronabinol and nabilone (short term, 1 to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain

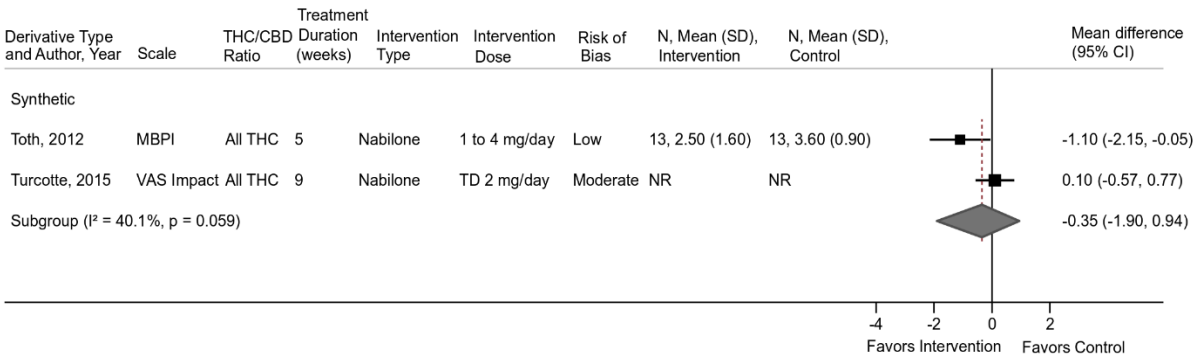
Table D-6. Interaction effect of RCTs assessing synthetic cannabinoids: nabilone versus dronabinol

Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−1.06	0.445	−2.37	0.077	−2.29 to 0.18

Table D-7. Interaction effect of RCTs: synthetic versus plant-based interventions

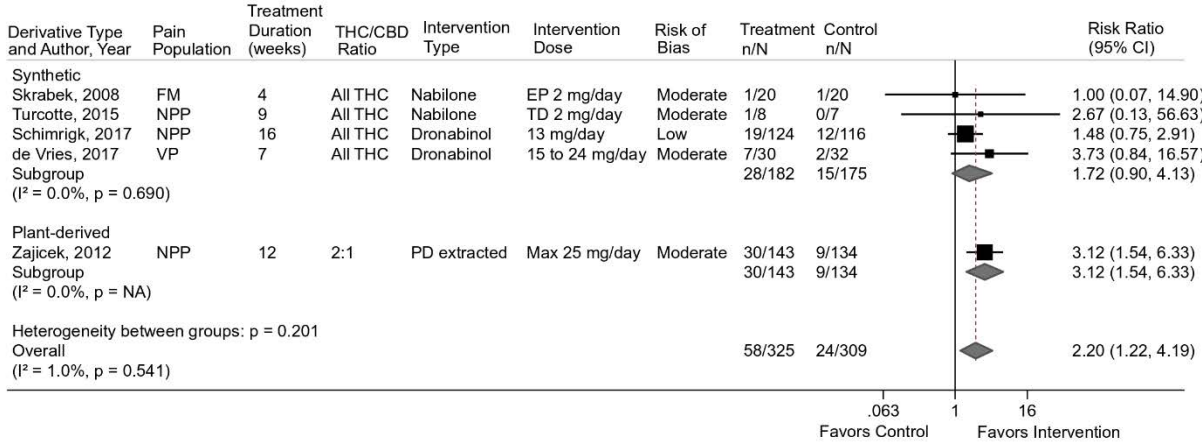
Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−0.682	0.81	−0.84	0.423	−2.55 to 1.18

Figure D-9. Overall function for high-THC versus placebo (short term, 1-6 months followup)



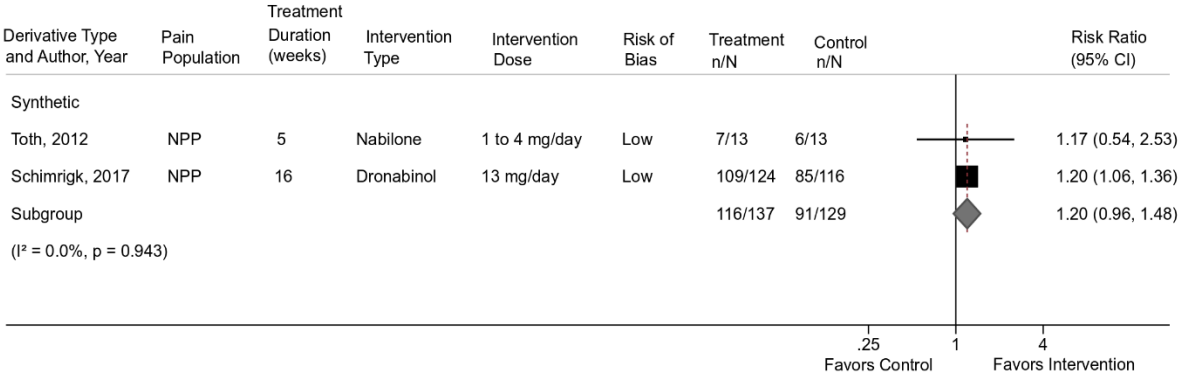
Abbreviations: CBD = cannabidiol; CI = confidence interval; MBPI = Modified Brief Pain Inventory; NPP = neuropathic pain; NR = not reported; SD = standard deviation; THC = tetrahydrocannabinol; VAS = Visual Analogue Scale

Figure D-10. Withdrawal due to adverse events for high-THC versus placebo (short term, 1 to 6 months followup)



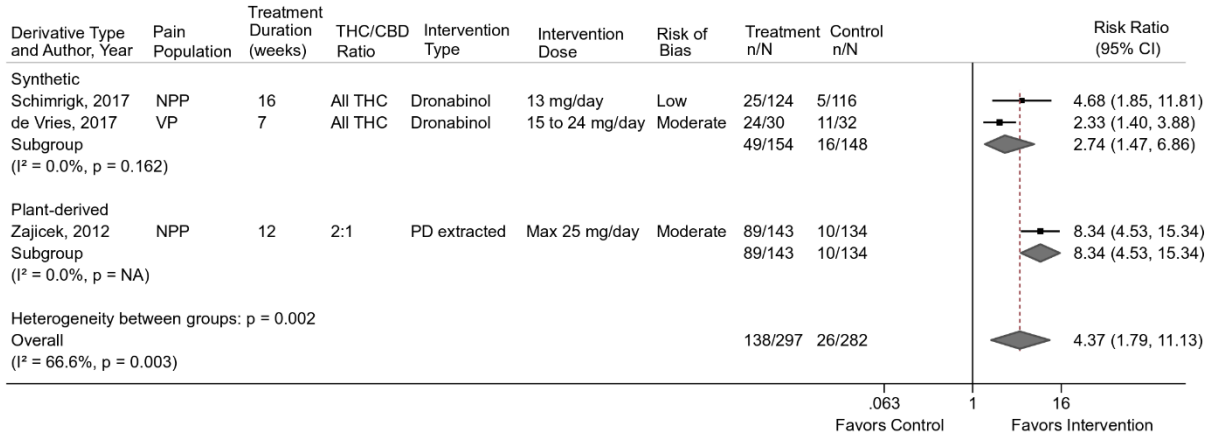
Abbreviations: CI = confidence interval; FM = fibromyalgia; NPP = neuropathic pain; THC = tetrahydrocannabinol; WP = whole plant

Figure D-11. Any adverse event for high-THC versus placebo (short term, 1 to 6 months followup)



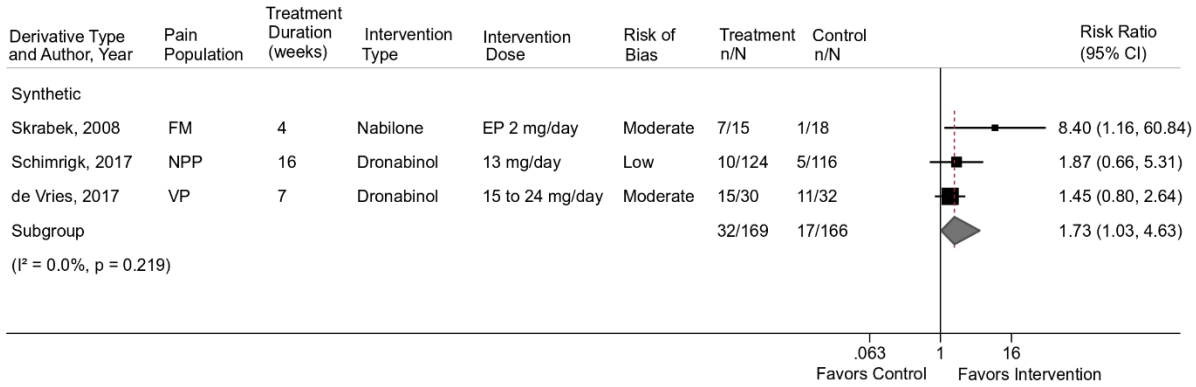
Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol

Figure D-12. Dizziness for high-THC versus placebo (short term, 1 to 6 months followup)



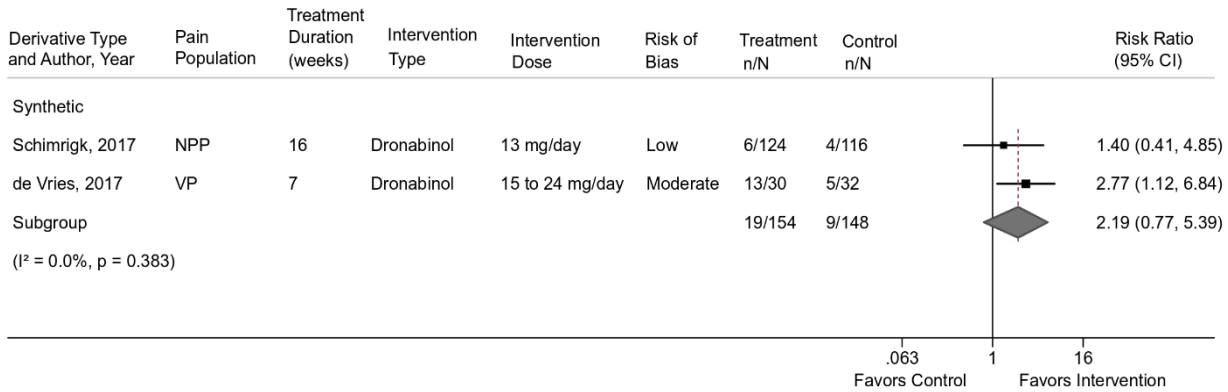
Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol; VP = visceral pain; WP = whole plant

Figure D-13. Sedation for high-THC versus placebo (short term, 1 to 6 months followup)



Abbreviations: CI = confidence interval; FM = fibromyalgia; NPP = neuropathic pain; VP = visceral pain

Figure D-14. Nausea for high-THC versus placebo (short term, 1 to 6 months followup)



Abbreviations: CI = confidence interval; NPP = neuropathic pain; VP = visceral pain

Appendix E. Evidence Tables

Shown in associated Excel files.

Appendix F. Risk of Bias Assessment

Shown in associated Excel files.

Appendix G. Details on Strength of Evidence

Table G-1. KQ1 and 2: Cannabinoids to treat chronic pain – comparable THC to CBD ratio

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Pain response (≥30% improvement from baseline)	4 RCTs (N=733)[1-4]	Moderate	Direct	Consistent	Imprecise	Unknown	Potential small effect, not statistically significant, with THC:CBD 38% versus 31%, RR 1.18 (0.93 to 1.71); I2=0%	Low
Comparable THC to CBD Ratio vs. Placebo	Pain severity (change)	7 RCTs (N=878)[1-7]	Moderate	Direct	Consistent	Precise	Unknown	Small benefit with THC:CBD 0 to 10 scale, MD −0.54 (−0.95 to −0.19; I^2=30%) Subgroup analysis removing high risk of bias studies: Moderate benefit MD -0.64 (-1.15 to -0.24)	Moderate
Comparable THC to CBD Ratio vs. Placebo	Function or Disability	6 RCTs (N=616)[1-5,7]	Moderate	Direct	Consistent	Precise	Unknown	Small benefit with THC:CBD, MD −0.42, 95% CI –0.73 to −0.16, I^2=24% (scale 0 to 10)	Moderate
Comparable THC to CBD Ratio vs. Placebo	WAEs	5 RCTs (N=834)[1,2,4,5,7]	Moderate	Direct	Consistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 13% vs. 10%, RR 1.14 (0.65 to 3.02); I^2=0%	Low
Comparable THC to CBD Ratio vs. Placebo	SAEs	2 RCTs (N= 183)[2,5]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 1.1% vs. 2.2%, RR 0.68 (0.04 to 10.85; I^2=38%)	Low

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Dizziness	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Large effect with THC:CBD 30% vs. 8%, RR 3.57 (2.42 to 5.60; I^2=0%)	Low
Comparable THC to CBD ratio vs. Placebo	Nausea	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with THC:CBD 14% vs. 7.5% RR 1.79 (1.20 to 2.78; I^2=0%)	Low
Comparable THC to CBD Ratio vs. Placebo	Sedation	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Large effect with THC:CBD RR 5.04 (2.10 to 11.89; I^2=0%)	Low

Abbreviations: BPI-SF = Brief Pain Inventory (Short Form); CBD = cannabidiol; CI = confidence interval; KQ = Key Question; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-2. KQ1 and 2: Cannabinoids to treat chronic pain – high-THC to CBD ratio, synthetic THC

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Synthetic THC vs. Placebo	Pain response (≥30% improvement from baseline)	1 RCT (N=26)[8]	Low	Direct	Unknown	Imprecise	Unknown	Large effect with nabilone 85% vs. 38%, RR 2.20 (CI 1.06 to 4.55)	Insufficient
	Pain severity	5 RCTs (N=364)[8-12]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with synthetic THC 0 to 10 scale, MD −1.08 (−1.96 to −0.43; I^2=42%)	Low
	Function/disability	2 RCTs (N=41)[8,12] 1 RCT (N=13) not Included in meta-analysis[13]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect (scale 0 to 10) MD : -0.35, 95% CI -1.9 to 0.94, 0 to 10 scale, I^2=40%;	Low
	WAEs	4 RCTs (N=357)[9-12]6	Moderate	Direct	Consistent	Imprecise	Unknown	Potential Moderate effect, not statistically significant 13% vs. 9%, RR 1.72 (0.90 to 4.13; I^2=0%)	Low
	SAEs	1 RCT (N=240)[10]	Low	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 10% vs. 6%, RR 1.60 (0.65 to 3.93)	Insufficient
	Dizziness	2 RCTs (N=302)[9,10]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 32% vs. 11%, RR 2.74 (1.47 to 6.86; I^2=0%)	Moderate
	Nausea	2 RCTs (N=302)[9,10]	Low	Direct	Consistent	Imprecise	Unknown	Potential large effect with dronabinol, not statistically significant	Low

								12% vs. 6%, RR 2.19 (0.77 to 5.39; I^2=0%)	
	Sedation	3 RCTs (N=335)[9-11]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with dronabinol 19% vs. 10%, RR 1.73 (1.03 to 4.63; I^2=0%)	Low

Abbreviations: CBD = cannabidiol; CI = confidence interval; KQ = Key Question; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-3. KQ1 and 2: Cannabinoids to treat chronic pain – high-THC to CBD ratio, extracted from whole plant

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Extracted THC vs. Placebo	Pain severity	2 RCTs (N=297)[14,15]	Moderate	Direct	Inconsistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD −2.05 (−5.94 to 1.26; I^2=72%)	Insufficient
	Function/disability	1 RCT (N=18)[15]	High	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 1.75 (−0.46 to 3.98)	Insufficient
	WAEs	1 RCT (N=277)[14]	Moderate	Direct	Unknown	Imprecise	Unknown	Large increased risk 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Low
	SAEs	1 RCT (N=277)[14]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 4.9% vs. 2.2%, RR 2.19 (0.58 to 8.28)	Insufficient
	Dizziness	1 RCT (N=277)[14]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect 62.2% vs. 7.5%, RR 8.34 (4.53 to 15.34)	Low

Abbreviations: CBD = cannabidiol; CI = confidence interval; KQ = Key Question; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event .

Table G-4. KQ1 and 2: Cannabinoids to treat chronic pain – high-THC to CBD ratio, combined synthetic and whole-plant extracted studies

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Combined High THC Ratio Studies (Synthetic and Whole-plant extracted)	Pain severity improvement	7 RCTs (N=658)[8-12,14,15]	Moderate	Direct	Consistent	Precise	Unknown	Moderate effect MD −1.26 (−2.17 to −0.65; I^2=59%)	Moderate

Abbreviations: CBD = cannabidiol; CI = confidence interval; KQ = Key Question; MD = mean difference; RCT = randomized controlled trial; SOE = strength of evidence; THC = tetrahydrocannabinol.

Table G-5. KQ1 and 2: Cannabinoids to treat chronic pain – whole plant cannabis

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Whole-plant Cannabis (Standardized to 12% THC) vs. Placebo	Pain Severity change	1 (N=431, 302 contribute to pain outcome)[16]	High	Direct	Unknown	Imprecise	Unknown	Moderate effect 0 to 10 scale, Adjusted MD at 12 months: −1.10 (−1.56 to −0.72)	Insufficient
	WAE	1 (N=431)[16]	High	Direct	Unknown	Imprecise	Unknown	Large effect with cannabis 4.7% vs. 0%, RR 21.10 (1.24 to 357.80)	Insufficient
	SAE	1 (N=431)[16]	High	Direct	Unknown	Imprecise	Unknown	No effect 13% vs. 19%, OR 0.64 (0.38 to 1.04)	Insufficient
	Dizziness	1 (N=431)[16]	High	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 12.6% vs. 9.7%, RR 1.29 (0.75 to 2.21)	Insufficient
	Nausea	1 (N=431)[16]	High	Direct	Unknown	Imprecise	Unknown	Moderate effect 16.7% vs. 9.7%, RR 1.72 (1.04 to 2.85)	Insufficient
	Sedation	1 (N=431)[16]	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.5% vs. 4.63%, RR 2.91 (1.46 to 5.83)	Insufficient
	Cognitive Disorder	1 (N=431)[16]	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Insufficient

Abbreviations: CI = confidence interval; KQ = Key Question; MD = mean difference; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-6. KQ1: Cannabinoids to treat chronic pain – low-THC to CBD ratio

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Topical CBD vs. Placebo	Pain severity (change)	1 RCT (N=29)[17]	High	Direct	Unknown	Imprecise	Unknown	Small effect with CBD cream MD −0.75, P=0.009 by ANCOVA (0 to 10 scale)	Insufficient

Abbreviations: ANCOVA = analysis of covariance; CBD = cannabidiol; CI = confidence interval; KQ = Key Question; MD = mean difference; RCT = randomized controlled trial; SOE = strength of evidence; THC = tetrahydrocannabinol.

Table G-7. KQ1 and 2: Cannabinoids to treat chronic pain – low-THC to CBD ratio

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
CBDV vs. Placebo	Pain Response (≥30% improvement from baseline)	1 RCT (N=31)[18]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect, favors placebo 38% vs. 81%, RR 0.46 (95% CI 0.24 to 0.91)	Insufficient
CBDV vs. Placebo	Pain severity (change)	1 RCT (N=31)[18]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 0.62 (−0.05 to 1.32)	Insufficient

Abbreviations: CBDV = cannabidivarin; CI = confidence interval; KQ = Key Question; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence.

Appendix G References

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Appendix H. Excluded Studies List

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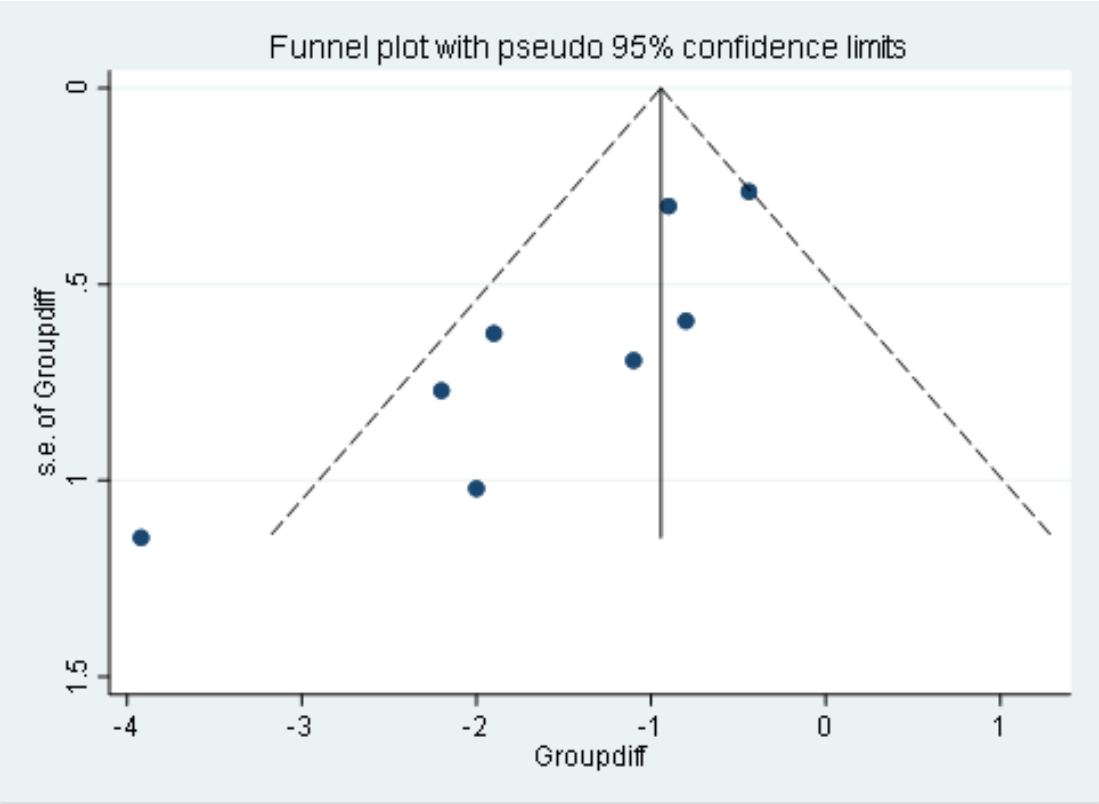
Appendix I. Funnel Plot of High-THC Ratio Studies Included in Meta-Analysis for Pain Severity

Figure I-1. Funnel plot of eight trials of pain severity for high-THC ratio products versus placebo



Abbreviations: Groupdiff = group difference; SE = standard error.