Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: Surveillance Report 2

Literature Update Period: August 2021 through October 2021

Overview

This is the second surveillance report for a living systematic review on cannabis and other plant-based treatments for chronic pain.

The systematic review synthesizes evidence on the benefits and harms of plant-based compounds (PBCs), such as cannabinoids and kratom, used to treat chronic pain, addressing concerns about severe adverse effects, abuse, misuse, dependence, and addiction.

The purpose of this surveillance report is to describe new studies identified since the last search (mid-August 2021) and provide a synthesis of the accumulated evidence. Surveillance reports are planned on a quarterly basis, and the systematic review will be updated annually. Table 1 provides a summary of the version history.

Table 1. Version history

Search End Date	Report (Publication Date)
July 2021	Systematic Review (Oct. 27, 2021)
August 2021	Surveillance Report 1 (Oct. 27, 2021)
October 2021	Surveillance Report 2 (Jan. 28, 2022)

Main Points

One new study[1] on oral synthetic cannabidiol (CBD) was identified during this surveillance period.

Overall, in 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 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 function. 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 and increased risk of sedation, and potential 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 withdrawal due to adverse events and dizziness.

- Evidence on whole-plant cannabis, low THC to CBD ratio products (topical or oral 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.

Table 2 presents the conclusions from the systematic review, findings from ongoing literature surveillance, and an assessment of new studies on conclusions.

Table 2. Assessment of systematic review conclusions

Key Question[a]	Conclusions From Systematic Review	Findings From Surveillance	Assessment
KQ1 and KQ2. Comparable THC to CBD Ratio Benefits and Harms	Benefits: small improvements in pain severity and in function (SOE: moderate; 7 RCTs) Harms: no effect on serious adverse events (SOE: low; 2 RCTs); large increased risk of dizziness and sedation; moderate increased risk of nausea (SOE: low; 6 RCTs)	No new studies	No change in conclusions
KQ1 and KQ2. Synthetic High THC to CBD Ratio Benefits and Harms	Benefits: moderate improvements in pain severity (SOE: low; 5 RCTs); no effect on overall function/disability (SOE: low; 2 RCTs) Harms: moderate increased risk of sedation (SOE: low; 3 RCTs); potential large increased risk of nausea (SOE: low; 2 RCTs); and large increased risk of dizziness (SOE: moderate; 2 RCTs)	No new studies	No change in conclusions
KQ1 and KQ2. Extracted Whole-Plant High THC to CBD Ratio Benefits and Harms	Benefits: insufficient evidence (2 RCTs) Harms: large increase in risk of dizziness and in study withdrawal due to adverse events (SOE: low; 1 RCT)	No new studies	No change in conclusions
KQ1 and KQ2. Low THC to CBD Benefits and Harms	Insufficient evidence (1 RCT)	1 new moderate risk of bias RCT of oral synthetic CBD (n=129)	No change in conclusions
KQ1 and KQ2. Whole-Plant Cannabis and Other Cannabinoids Benefits and Harms	Insufficient evidence (2 RCTs)	No new studies	No change in conclusions

Key Question[a]	Conclusions From Systematic Review	Findings From Surveillance	Assessment
KQ3 and KQ4. Kratom or Other Plant-Based Substances Benefits and Harms	Insufficient evidence (0 RCTs)	No new studies	No change in conclusions

[a] For Key Question wording, see the Background section below.
Abbreviations: CBD = cannabidiol; KQ = Key Question; RCT = randomized controlled trial; SOE = strength of evidence; THC = tetrahydrocannabinol.

Summary of Findings Tables

The Key Questions (KQs) for this review focus on the benefits (KQ1) and harms (KQ2) of cannabinoids for treating chronic pain, as well as the benefits (KQ3) and harms (KQ4) of other PBCs, such as kratom, for treating chronic pain. Tables 3 and 4 summarize benefits and harms of cannabinoids. No evidence was available for other PBCs.

Table 3. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

Product, THC to CBD Ratio	Pain Response Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD Oromucosal Spray	Potential effect (4)[a] [+]	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
Low THC – Oral CBD	No evidence	Insufficient (1)	Insufficient (1)
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[b]	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[b] Comparison was "usual care."
Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased benefit; SOE: [+] = low, [++] = moderate, [+++] = high.

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

Product, THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
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[a] (4) [+]	Insufficient (1)	Large effect (2) [++]	Potential effect[a] (2) [+]	Moderate effect (3) [+]
High THC – Extracted From Whole Plant, Oral	Large effect (1) [+]	Insufficient (1)	Large effect (1) [+]	No evidence	No evidence

Product, THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Low THC – Topical CBD	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Oral CBD	Insufficient (1)	Insufficient (1)	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)[b]	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] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[b] Comparison was "usual care."
Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: [+] = low, [++] = moderate, [+++] = high.

Background

Chronic pain is defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,[2,3] and it affects approximately 100 million people in the United States.[4] Chronic pain adversely affects physical and mental functioning, productivity, and quality of life, and is often refractory to treatment and associated with substantial costs.[5-7]

While opioids are often prescribed for chronic pain, a recent series of systematic reviews found that opioids,[8] several nonopioid drugs,[9] and some nonpharmacologic treatments[10] have small to moderate effects on pain and function, with some frequent adverse effects and some less frequent but serious ones. The 2016 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends that nonopioid therapy is preferred for treatment of chronic pain.[2,3] The limited efficacy of opioids and the ongoing opioid crisis drive a search for alternative pain treatments, including PBCs such as cannabis and related compounds, as some data suggest they may have analgesic properties.[11]

The term *cannabinoid* refers to 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,[12,13] although its psychoactive effects and abuse potential may limit its suitability as an analgesic. CBD and other cannabinoids may also have some analgesic or anti-inflammatory properties and are not thought to be psychoactive or addictive.[14,15] 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 PBCs 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.[16]

Four Key Questions (KQs) guide the review:

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?

The protocol for the systematic review can be found on the Agency for Healthcare Research and Quality (AHRQ) website (https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol) and on the PROSPERO systematic reviews registry (registration number CRD42021229579).

Methods

In brief, we searched Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases monthly through October 2021 for studies of patients with chronic pain for at least 4 weeks of treatment or followup. We selected studies of cannabis, kratom, and similar PBCs compared with a placebo, no treatment, each other, or another treatment. Pain is the primary outcome for this review; details on the search strategies are in Appendix A. The full inclusion and exclusion criteria for all primary and secondary outcomes for this report are in Appendix B.

We followed the methods guidance in the AHRQ Methods Guide,[17] and abstracted key information and conducted risk-of-bias assessments for each included study. Our methods include categorizing the duration of studies as short-, intermediate-, and long-term. Studies that assessed the cannabinoids, THC and/or CBD, were grouped based on their THC to CBD ratios and categorized as high THC to CBD ratio, comparable THC to CBD ratio, and low THC to CBD ratio (Table 5). 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. (See Appendix B, Table B-2.)

Table 5. Organizing principle of cannabis-related studies based on ratios of THC to CBD

Intervention Category	Definition	Possible Derivatives
High THC	THC to CBD ratio equals ≥2:1 ratio	Synthetic, extracted or purified from whole plant, whole-plant
Low THC	THC to CBD ratio equals 1:≥2 ratio	Extracted or purified from whole plant, whole-plant
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
Whole-Plant Cannabis Products	Potentially unknown THC to CBD ratio; categorized based on information provided	Whole-plant, not extracted, purified, or synthetic
Other Cannabinoids	Interventions testing cannabinoids other than THC and/or CBD	Extracted or purified from whole plant

Abbreviations: CBD = cannabidiol; THC = tetrahydrocannabinol.

A more detailed discussion of methods can be found in the protocol and in Appendix B.

Results to Date

Results Overview

Across the monthly literature searches, 2,984 citations were screened, from which we included 28 studies,[1,18-44] one of which is new to this progress report.[1] Appendix C contains a list of included studies, and a literature flow diagram can be found in Appendix D. Appendix E contains summary tables of individual study data for all included studies and the results of synthesis (i.e., forest plots). Appendix F contains detailed evidence tables of included studies, and Appendix G contains risk-of-bias assessments. Appendix H contains details on strength-of-evidence ratings. A list of studies excluded after reviewing the full manuscripts can be found in Appendix I along with reasons for their exclusion. Appendix J provides a funnel plot of high-THC ratio studies included in the meta-analysis for pain severity.

In total, seven randomized controlled trials (RCTs) evaluated products that contain a combination of THC and CBD (comparable THC to CBD ratio).[19,24-26,29,31,32] Two RCTs evaluated the effects of high THC to CBD ratio, whole-plant derived extracts.[20,40] Nine RCTs evaluated synthetic forms of THC (high THC to CBD ratio).[21,23,27,28,30,33-35,38] One trial assessed the effect of topical CBD (low THC to CBD ratio),[39] one new trial evaluated oral CBD (low THC to CBD ratio),[1] and another evaluated the phytocannabinoid cannabidivarin (CBDV). The findings are applicable to *short-term* treatment (4 weeks 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 functional outcomes were reported sporadically.

Seven observational studies were included, five allowing use of any medicinal cannabis product,[36,41-44] one assessing a whole-plant cannabis product with a known content of 12.5 percent THC (CBD content not reported),[37] and one assessing the synthetic THC product nabilone.[18] The characteristics of the RCTs are listed in Table 6; observational study characteristics are in Table 7.

Table 6. Characteristics of included randomized controlled trials

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	2	1
Risk of Bias % High, % Moderate, % Low	29%, 57%, 14%	0%, 50%, 50%	22%, 44%, 33%	50%, 50%, 0%	0%, 100%, 0%
Total Randomized	882	297	534	165	34
Age, Mean Years	53	52	50	65	50
Female, %	66%	89%	61%	41%	3%
% Non-White[a]	1.6% (2)	1% (1)	5.4% (3)	NR	NR
Primary Pain Type (n studies)	NPP (6)	NPP (1)	NPP (6)	NPP (1); OA (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 and 12 weeks	4 weeks

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; NA = not applicable; NPP = neuropathic pain; OA = osteoarthritis; 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 1 study (6 vs. 6).

Table 7. Characteristics of included observational studies

Characteristic	THC/CBD[a]	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	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)[b]	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] Patients could choose any medicinal product they preferred in these studies.

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

KQs 1 and 2: Benefits and Harms of Cannabis

The findings for intervention effects and the strength of the evidence (SOE) are summarized in Tables 3 and 4. Comparable THC to CBD ratio oromucosal spray is probably associated with small improvements in pain severity (SOE: moderate) and may be associated with small improvements in functioning (SOE: moderate). Combined THC/CBD may also be associated with a moderate to large increased risk of dizziness, sedation, and nausea (SOE: low). Low SOE of no effect was found for pain interference (the degree to which pain directly interferes with patients' ability to participate in their daily activities) and 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 (high THC to CBD ratio) may be associated with moderate improvement in pain severity (SOE: low). Synthetic THC treatments are probably associated with a large increase in risk of dizziness (SOE: moderate), and may be associated with a large increased risk of nausea and moderate increased risk of sedation (SOE: low). There was a moderate increase in the proportion of patients who withdrew 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 for treatment with synthetic high THC to CBD ratio products was very limited, with no clear effect on quality of life or depression, inconsistent results for anxiety, and global disease improvement for patients with fibromyalgia.

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 similarly low SOE.

Evidence on whole-plant cannabis (solely from observational studies), low THC to CBD ratio products (topical CBD), other cannabinoids (CBDV), and comparisons with other active interventions were insufficient to draw conclusions. The new moderate risk-of-bias RCT of synthetic oral CBD added in this surveillance report did not alter the findings[1] from the systematic review. There were no statistically significant differences in the proportion with at least a 30-percent improvement in pain (pain response), change in pain severity, or general functioning in those with hand osteoarthritis or psoriatic arthritis. Reporting on adverse events was sparse. Similarly, evidence for other outcomes reported for comparable THC to CBD and high THC to CBD ratio products was insufficient. See Appendix H for details.

Other key adverse event outcomes (psychosis, cannabis use disorder, cognitive deficits) and outcomes on the impact on prescription opioid use were not reported.

KQs 3 and 4: Kratom and Other Plant-Based Compounds

No evidence was identified.

Discussion

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 6 and 7); (3) lack of evidence or inadequate evidence on high THC to CBD products extracted from whole-plant cannabis, whole-plant cannabis products, low THC to CBD products, and other plant-based compounds, including kratom; and (4) inconsistent reporting of important outcomes such as pain response, function, or disability; effect on opioid use; and longer term adverse events, such as cannabis use disorder, psychosis, and cognitive deficits. These limitations affect both the stability and applicability of the findings.

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 THC/CBD oral spray, synthetic oral THC, and products extracted from whole cannabis plants with a high THC to CBD ratio. Compared with placebo, these interventions resulted in greater risk of common adverse events (dizziness, nausea, sedation) and withdrawals from studies 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.

Conclusion

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.

Next Reports

The next quarterly surveillance report is scheduled to be available in March 2022.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: research associate and librarian Tracy Dana, M.L.S., from Oregon Health & Science University, and Task Order Officer Suchitra Iyer, Ph.D., at the Agency for Healthcare Research and Quality.

Disclaimers

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00006). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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 health care 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.

AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work is the second update report of a living systematic evidence report, Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

Suggested citation: McDonagh MS, Wagner J, Ahmed AY, Morasco B, Kansagara D, Chou R. Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: Surveillance Report 2. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 22-EHC011. Rockville, MD: Agency for Healthcare Research and Quality; February 2022.
DOI: 10.23970/AHRQEPCCANNABISSURVEILLANCE2. Posted final reports are located on the Effective Health Care Program search page.

Afterword

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.

This and future quarterly progress reports will provide up-to-date information about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. 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 report, 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. They will be considered in the next version of the report.

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Appendix Contents

Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) ALL 1946 to October 29, 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 October, 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: APA PsycInfo 1806 to September Week 4, 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 October 24, 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 October 18, 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.

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 surveillance 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,[1] and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force.[2] 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.[3] 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 are 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[4,5] 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).[4-8]

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.[9] The decision to conduct quantitative synthesis depends on the 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[4-8] 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).[10]
- If the magnitude of effect is below the threshold for a small effect, the finding is considered to have "No effect."[4]
- 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."[11]

Grading the Strength of the Body of Evidence

We assessed the strength of evidence 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.[3] 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 strength of evidence 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 and the Results to Date sections 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."[12]

Peer Review and Public Commentary

Peer reviewers are invited to provide written comments on the annual draft report/systematic reviews 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,[13] 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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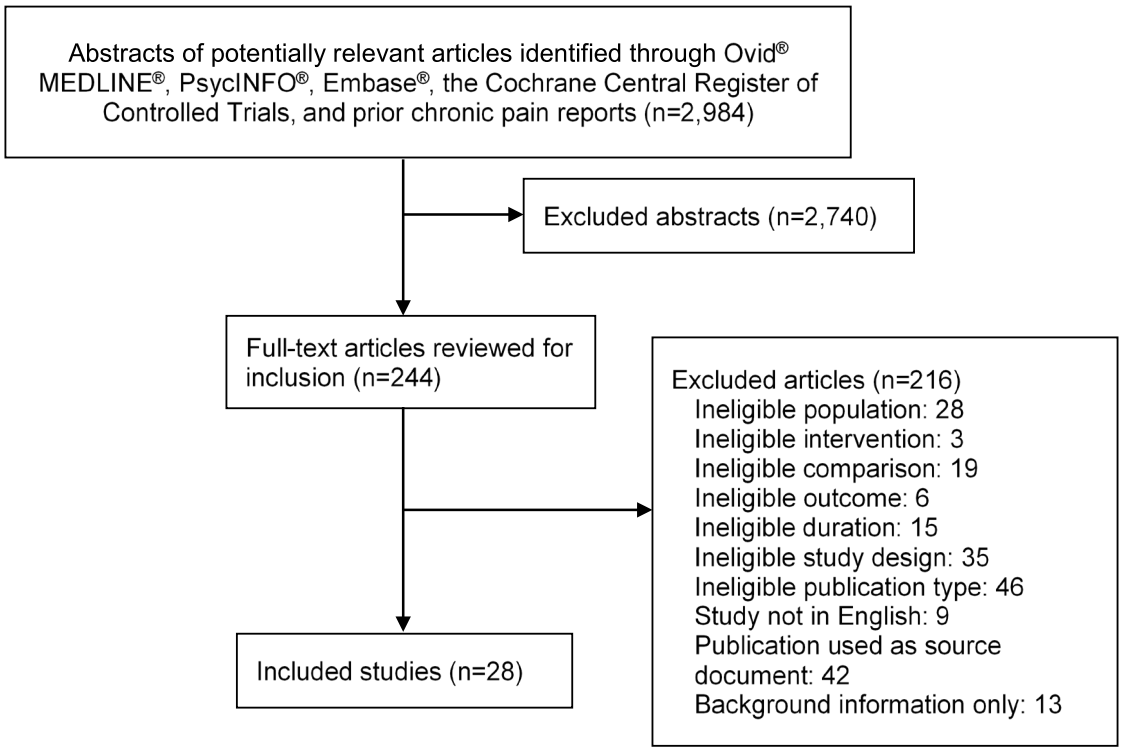
Appendix D. Literature Flow Diagram

Figure D-1. Literature flow diagram



Appendix E. Results

Individual Study Summary Tables

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

Table E-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)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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)	SAE: 0/31 (0%) vs. 2/27 (7.41%) WAE: 0/31 (0%) vs. 3/27 (11.11%)	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)
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)	WAE: 14/167 (8.38%) vs. 9/172 (5.23%)	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
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)	SAE: 0/8 (0%) vs. 0/8 (0%) WAE: 0/8 (0%) vs. 0/8 (0%)	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)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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)	SAE: 1/63 (1.6%) vs. 0/62 (0%) WAE: 11/63 (17.46%) vs. 2/62 (3.23%)	Function (0 to 70 Pain Disability Index scale): MD −5.85 (95% CI −9.62 to −2.09)
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)	SAE: 0/34 (0%) vs. 0/32 (0%) WAE: 2/34 (5.88%) vs. 0/32 (0%)	NR
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)	NR	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)
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)	SAE: 10/128 (7.81%) vs. 6% WAE: 25/128 (19.53%) vs. 25/118 (21.19%)	Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.32 (SE 0.241) (95% CI −0.8 to 0.15)

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 E-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)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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)	WAE: 0/8 (0%) vs. 0/9 (0%)	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)
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)	WAE: 7/30 (23.33%) vs. 2/32 (6.25%)	NR
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)	SAE: 0/48 (0%) vs. 0/48 (0%) WAE: 2/48 (4%) vs. 6/48 (12.5%)	Function (mean [SD NR] 0 to 100 SF−36 Physical Functioning scale): Treatment effect 10.8 (95% CI 2.3 to 19.2)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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)	WAE: 1/30 (3.33%) vs. 1/30 (3.33%)	NR
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	SAE: 1/7 (14.29%) vs. 1/5 (20%) WAE: 1/7 (14.29%) vs. 0/5 (0%)	NR
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	SAE: 12/124 (9.68%) vs. 7/116 (6.03%) WAE: 19/124 (15.32%) vs. 12/116 (10.34%)	NR
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	SAE: 0/15 (0%) vs. 0/18 (0%) WAE: 1/20 (5%) vs. 1/20 (5%)	NR
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)	NR	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)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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]	SAE: 0/8 (0%) vs. 0/7 (0%) WAE: 1/8 (12.5%) vs. 0/7 (0%)	Pain interference (mean [SD NR] 0 to 100 VAS impact scale): 41 vs. 40[b]
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	WAE: 2/13 (15.38%) vs. 0/13 (0%)	NR
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)	SAE: 7/143 (4.9%) vs. 3/134 (2.24%) WAE: 30/143 (20.98%) vs. 9/134 (6.72%)	NR

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 E-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)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
Vela, 2021 Moderate RCT Musculoskeletal - hand osteoarthritis and psoriatic arthritis	A: CBD oral tablet (20 to 30 mg/day) (68) B: Placebo (61) 12 weeks Synthetic CBD	Pain response ≥30% (VAS 0 to 100 scale): 27/68 (39.7%) vs. 24/61 (39.3%), RR 1.01 (95% CI 0.66 to 1.55) Pain severity (0 to 100 VAS scale): mean NR, MD 0.23 (95% CI −9.41 to 9.9)	SAE: 2/58 (3.4%) vs. 2/61 (3.3%) WAE: 0/70 (0%) vs. 2/66 (3%)	Function/disability (0 to 3 HAQ-DI scale): mean NR, MD 0.03 (95% CI −0.11 to 0.18)
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)	SAE: 0/15 (0%) vs. 0/14 (0%)	NR

Abbreviations: CBD = cannabidiol; HAQ-DI = Health Assessment Questionnaire Disability Index; 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 E-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)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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)	SAE: 1/16 (6.25%) vs. 0/16 (0%) WAE: 1/16 (6.25%) vs. 0/16 (0%)	Pain interference (0 to 10 BPI−SF scale): MD −0.35 (95% CI −1.36 to 0.43)

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 E-5. Observational study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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	SAE: 0/49 (0%) vs. 0/52 (0%) vs. 0/55 (0%) WAE: 5/49 (10%) vs. 12/52 (23%) vs. 5/55 (9%)	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[a]): 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
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)	NR	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)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]	Other Primary Outcomes (Function/Disability, Pain Interference)
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
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	SAE: 28/215 (13%) vs. 42/216 (19.4%) WAE: 10/215 (4.65%) vs. NR (assumed 0)	NR

Abbreviations: BPI = brief pain inventory; CBD = cannabidiol; CI = confidence interval; MD = mean difference; NA = not applicable; NR = not reported; PDI = Pain Disability Index; 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.

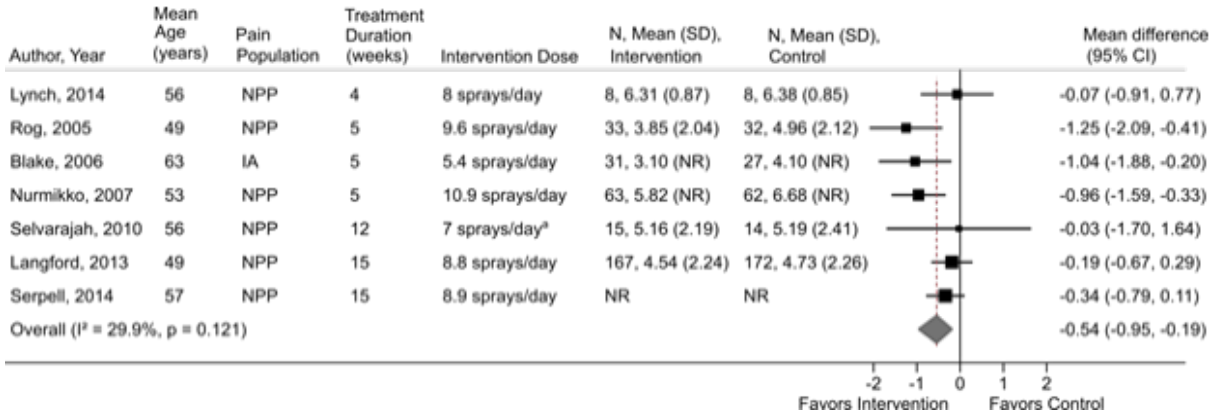
[a] Higher scores indicate better outcomes.
[b] Only included outcome reported was opioid-use.

Forest Plots

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.

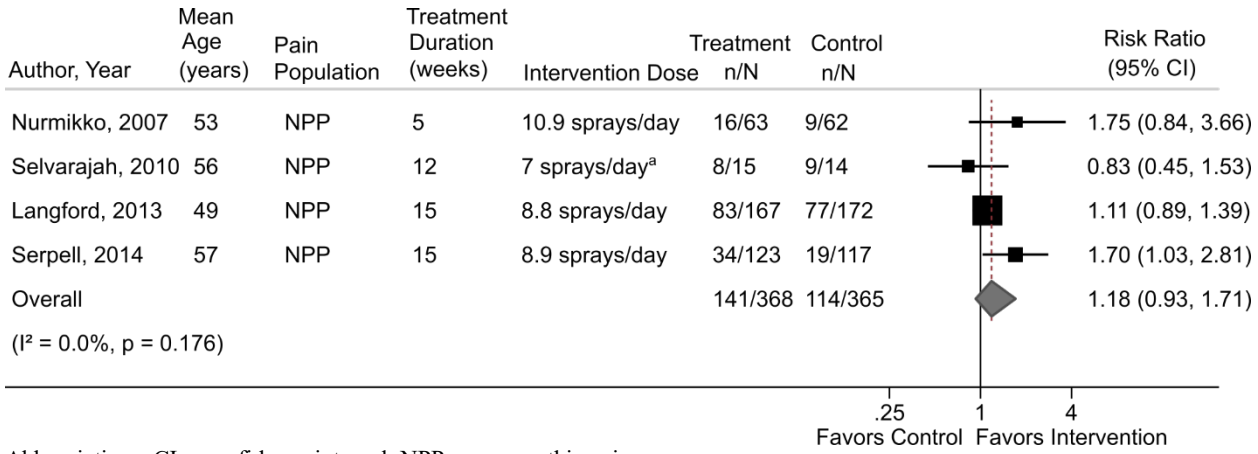
Figure E-1. Change in pain severity with comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



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

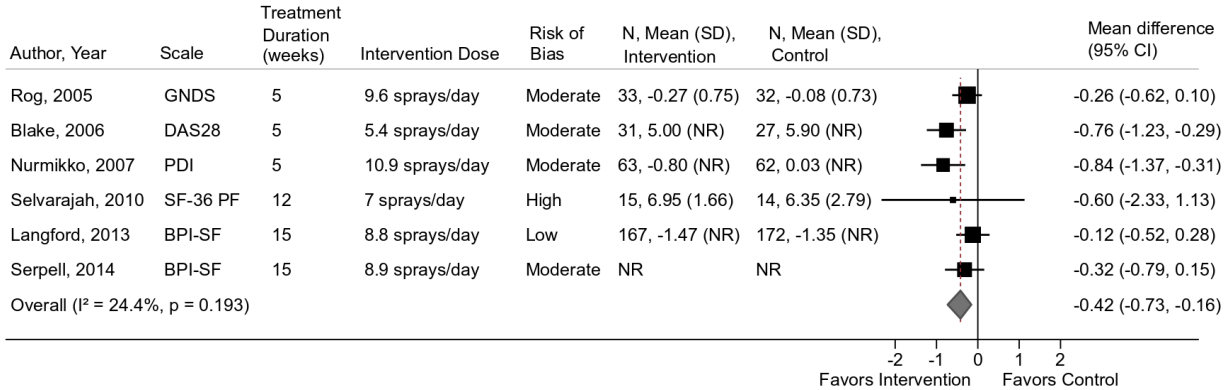
[a] Calculated by review team

Figure E-2. Proportion of patients with pain response (≥30% improvement) with comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



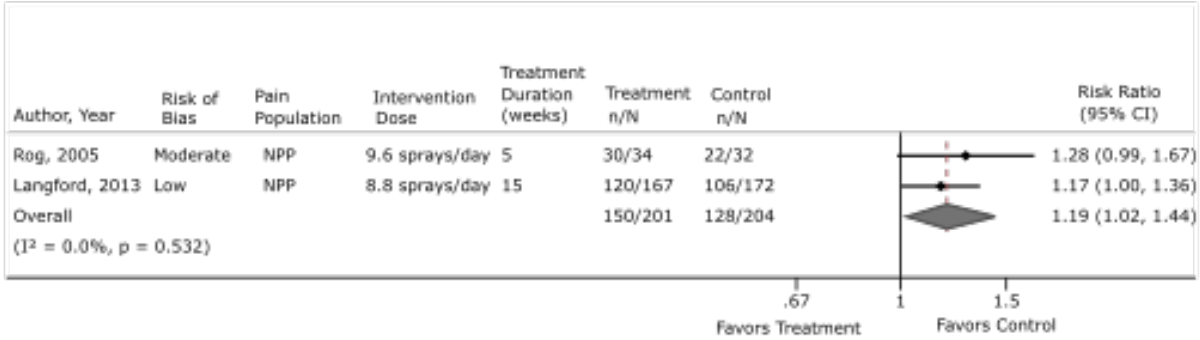
Abbreviations: CI = confidence interval; NPP = neuropathic pain
[a] Calculated by review team

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



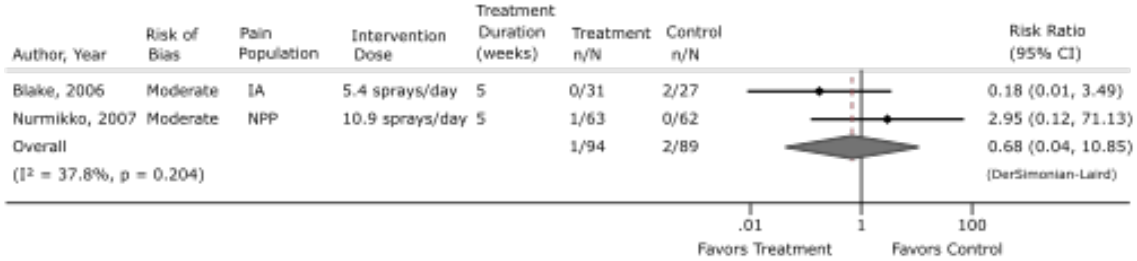
Abbreviations: BPI-SF = Brief Pain Inventory- Short Form; CBD = cannabidiol; CI = confidence interval; DAS28 = 28-Joint Disease Activity Scale; GNDS = Guy's Neurological Disability Scale; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PDI = Pain Disability Index; SD = standard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

Figure E-4. Adverse events for comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



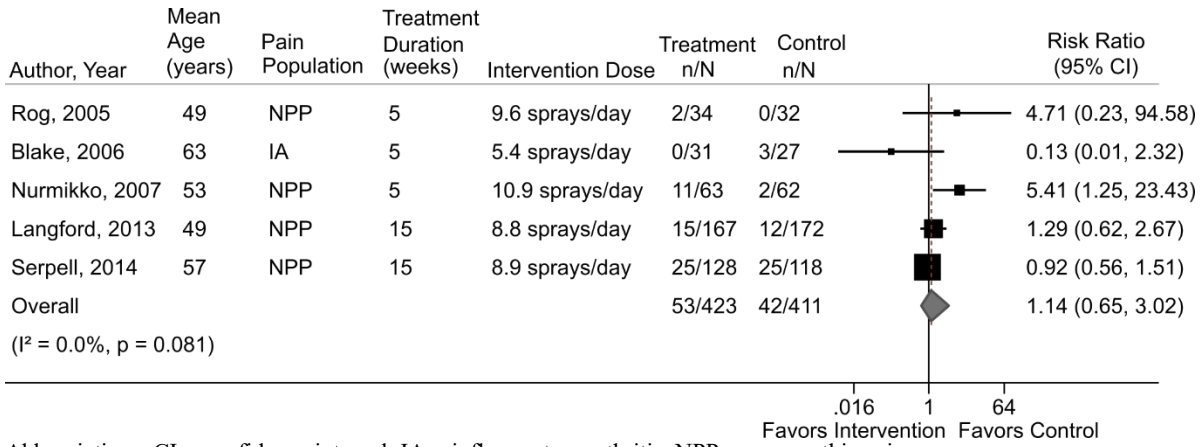
Abbreviations: CI = confidence interval; NPP = neuropathic pain

Figure E-5. Serious adverse events for comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



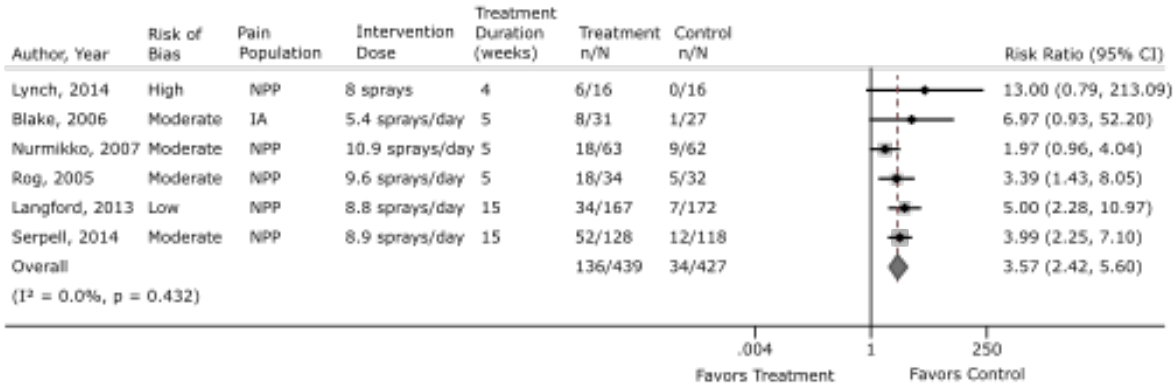
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

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



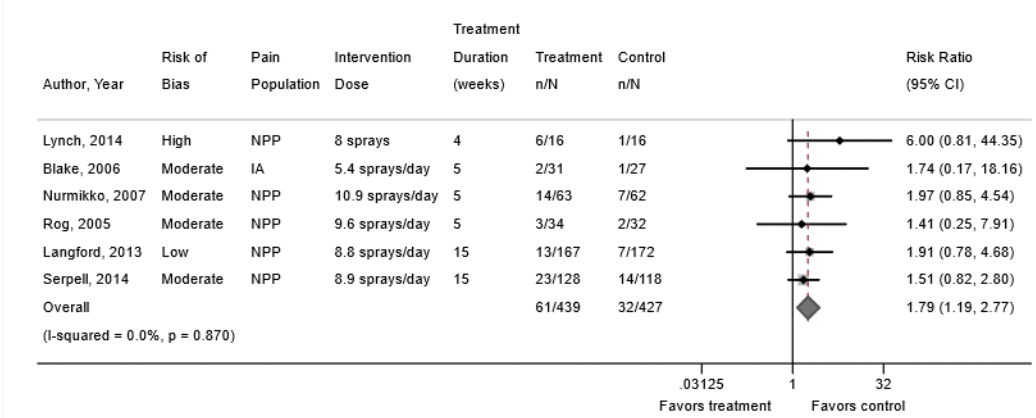
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

Figure E-7. Dizziness for comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



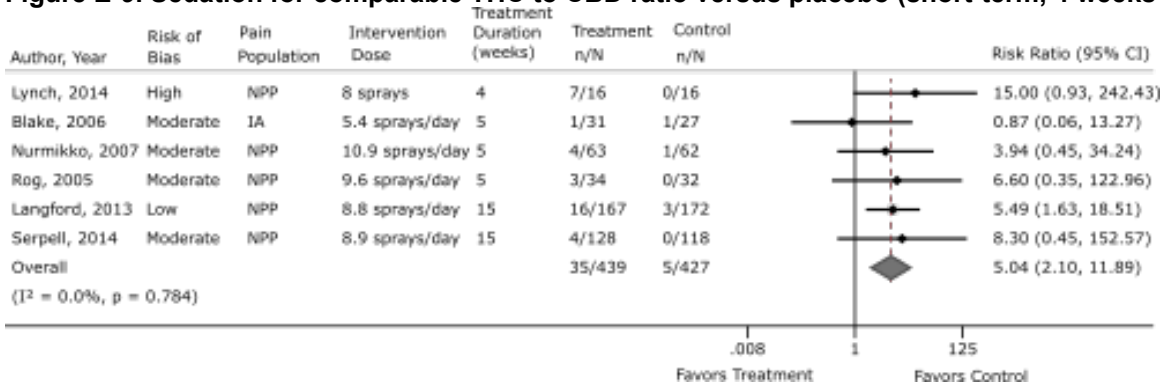
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

Figure E-8. Nausea for comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



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

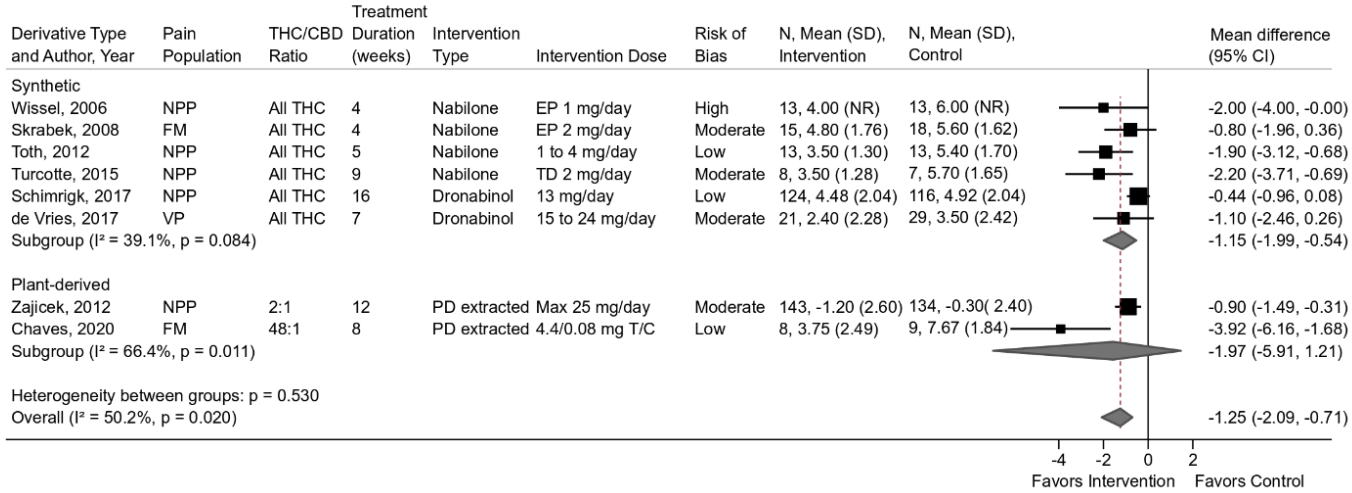
Figure E-9. Sedation for comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



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

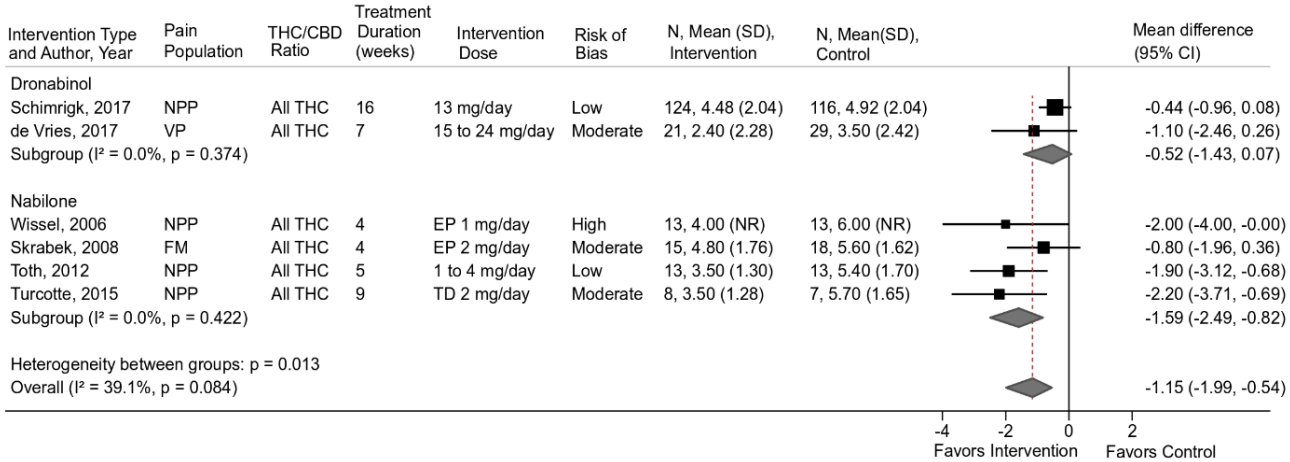
High THC to CBD Ratio Studies

Figure E-10. Change in pain severity with high THC ratio versus placebo (short-term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; SD = standard deviation; T/C = THC/CBD; TD = twice daily; THC = tetrahydrocannabinol; VP = visceral pain; WP = whole plant

Figure E-11. Stratified results on pain severity of RCTs using dronabinol and nabilone (short term, 4 weeks to 6 months followup)



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

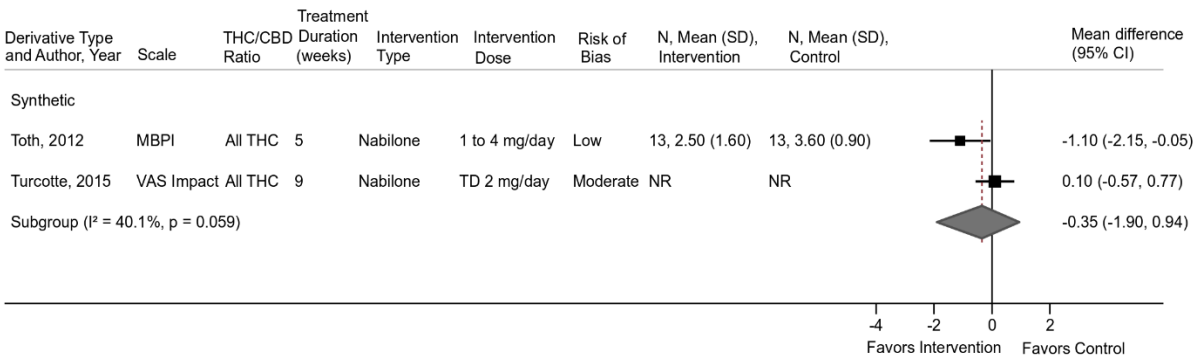
Table E-6. Interaction effect of RCTs assessing synthetic cannabinoids: nabilone versus dronabinol

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

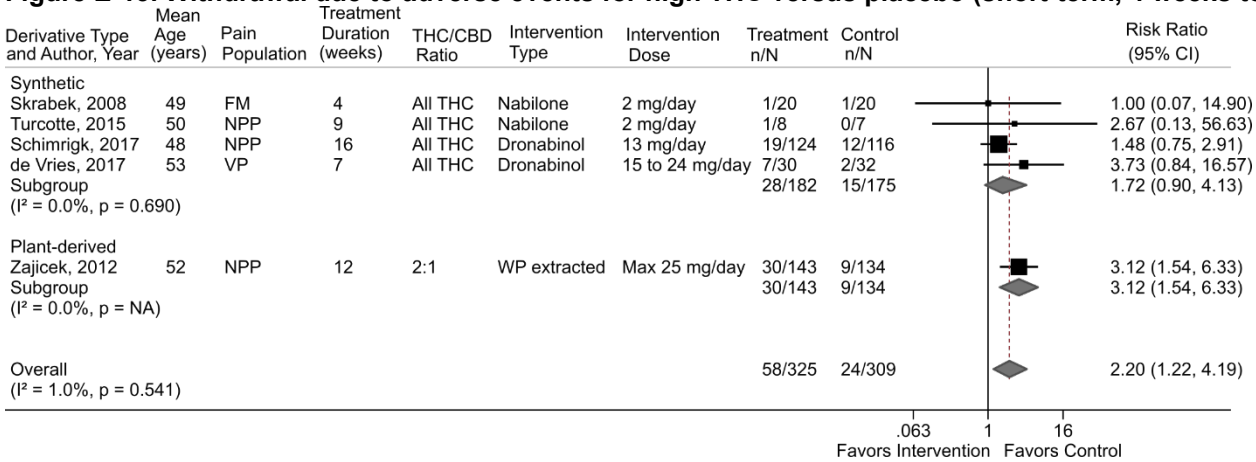
Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−0.682	0.81	−0.84	0.423	−2.55 to 1.18

Figure E-12. Overall function for high-THC versus placebo (short term, 1-6 months followup)



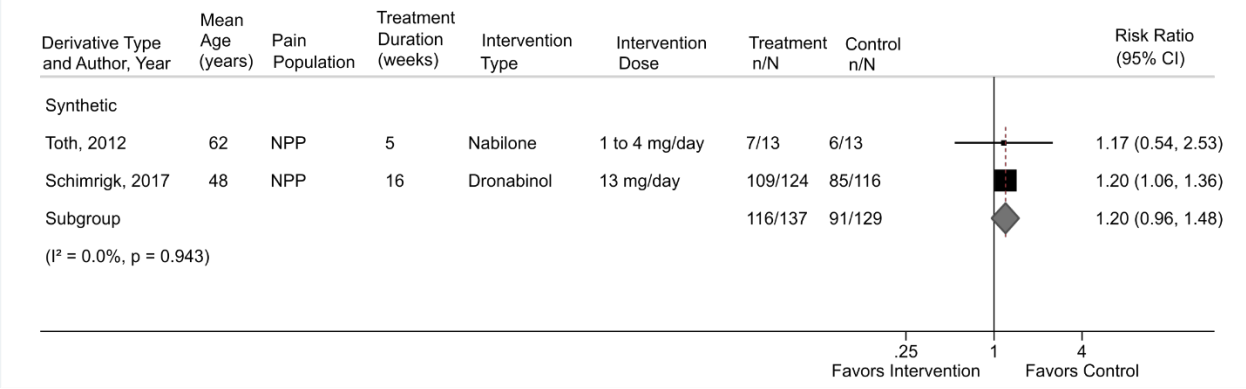
Abbreviations: CBD = cannabidiol; CI = confidence interval; MBPI = Modified Brief Pain Inventory; NPP = neuropathic pain; NR = not reported; SD = standard deviation; THC = tetrahydrocannabinol; VAS = Visual Analogue Scale

Figure E-13. Withdrawal due to adverse events for high THC versus placebo (short-term, 4 weeks to 6 months followup)



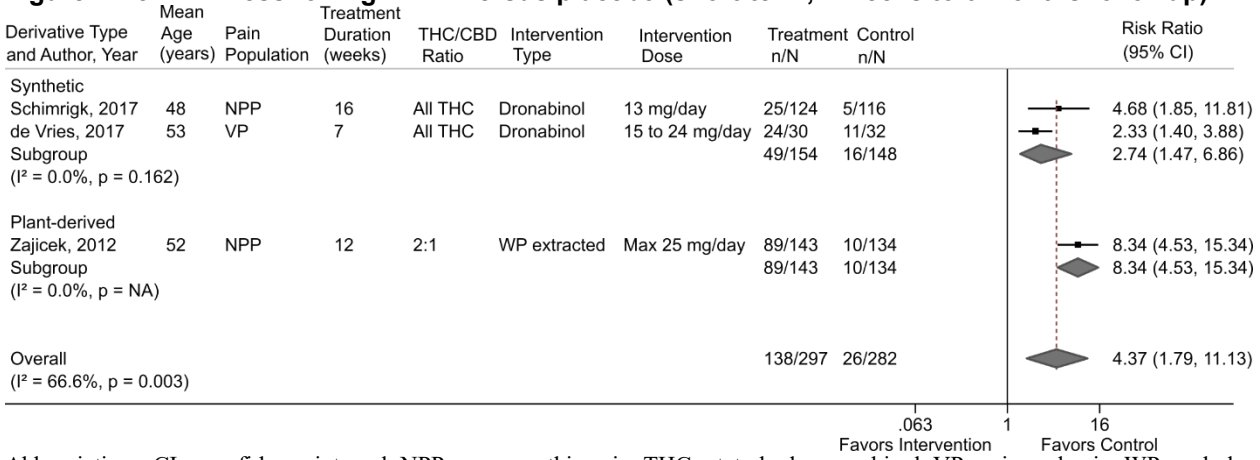
Abbreviations: CI = confidence interval; FM = fibromyalgia; NPP = neuropathic pain; THC = tetrahydrocannabinol; WP = whole plant

Figure E-14. Any adverse event for high THC versus placebo (short-term, 4 weeks to 6 months followup)



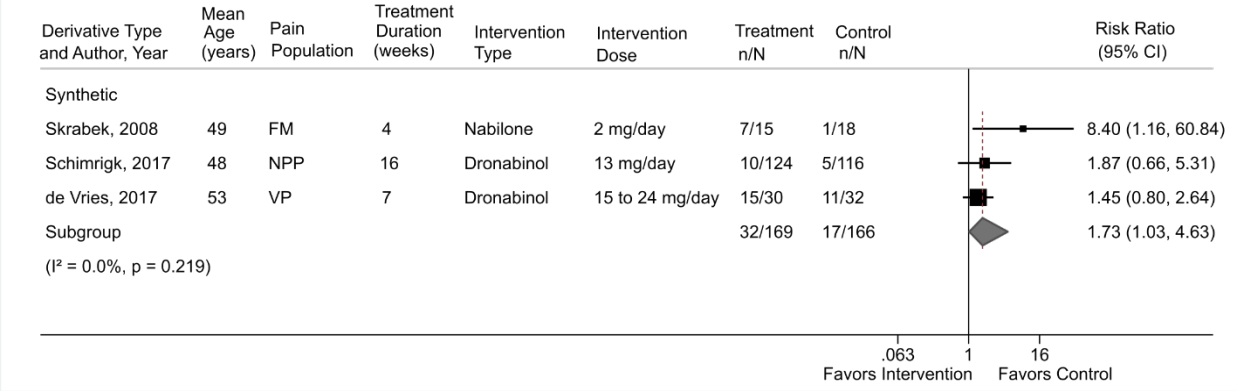
Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol

Figure E-15. Dizziness for high THC versus placebo (short-term, 4 weeks to 6 months followup)



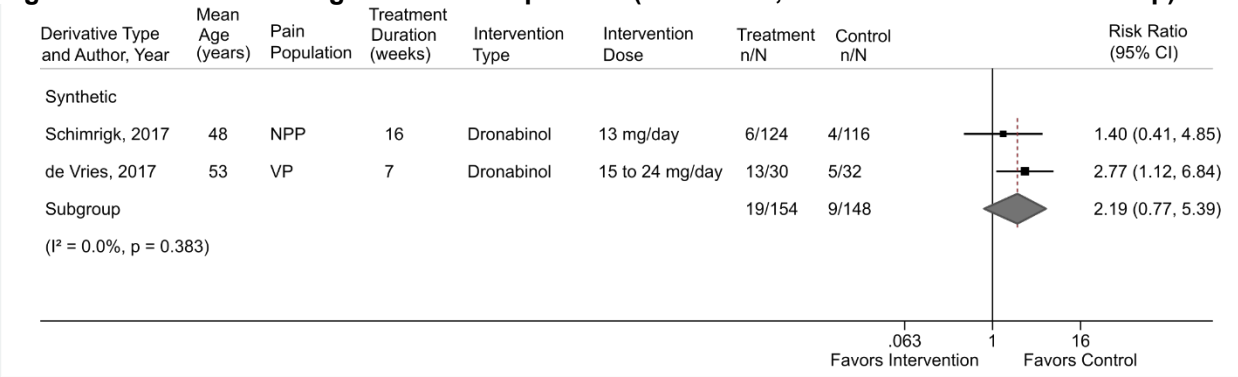
Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol; VP = visceral pain; WP = whole plant

Figure E-16. Sedation for high THC versus placebo (short-term, 4 weeks to 6 months followup)



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

Figure E-17. Nausea for high THC versus placebo (short-term, 4 weeks to 6 months followup)



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

Appendix F. Evidence Tables

Shown in associated Excel files for Surveillance Report 2 at https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review.

Appendix G. Risk of Bias Assessment

Shown in associated Excel files for Surveillance Report 2 at https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review.

Appendix H. Details on Strength of Evidence

Table H-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); I^2=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%	Insufficient
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 (1.19 to 2.77; 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 H-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
Synthetic THC vs. Placebo	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
Synthetic THC vs. Placebo	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, −1.9 to 0.94, 0 to 10 scale, I^2=40%	Low
Synthetic THC vs. Placebo	WAEs	4 RCTs (N=357)[9-12]	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
Synthetic THC vs. Placebo	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
Synthetic THC vs. Placebo	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

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	Nausea	2 RCTs (N=302)[9,10]	Low	Direct	Consistent	Imprecise	Unknown	Potential large effect with dronabinol, not statistically significant 12% vs. 6%, RR 2.19 (0.77 to 5.39; I^2=0%)	Low
Synthetic THC vs. Placebo	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 H-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 H-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	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 H-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. Usual Care	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 H-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
Oral Synthetic CBD vs. Placebo	Pain response (≥30% improvement)	1 RCT (N=136)[18]	Moderate	Direct	Unknown	Imprecise	Unknown	No effect with oral synthetic CBD RR 1.01 (0.66 to 1.55)	Insufficient

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

Table H-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)[19]	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)[19]	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 H References

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Appendix I. Excluded Studies List

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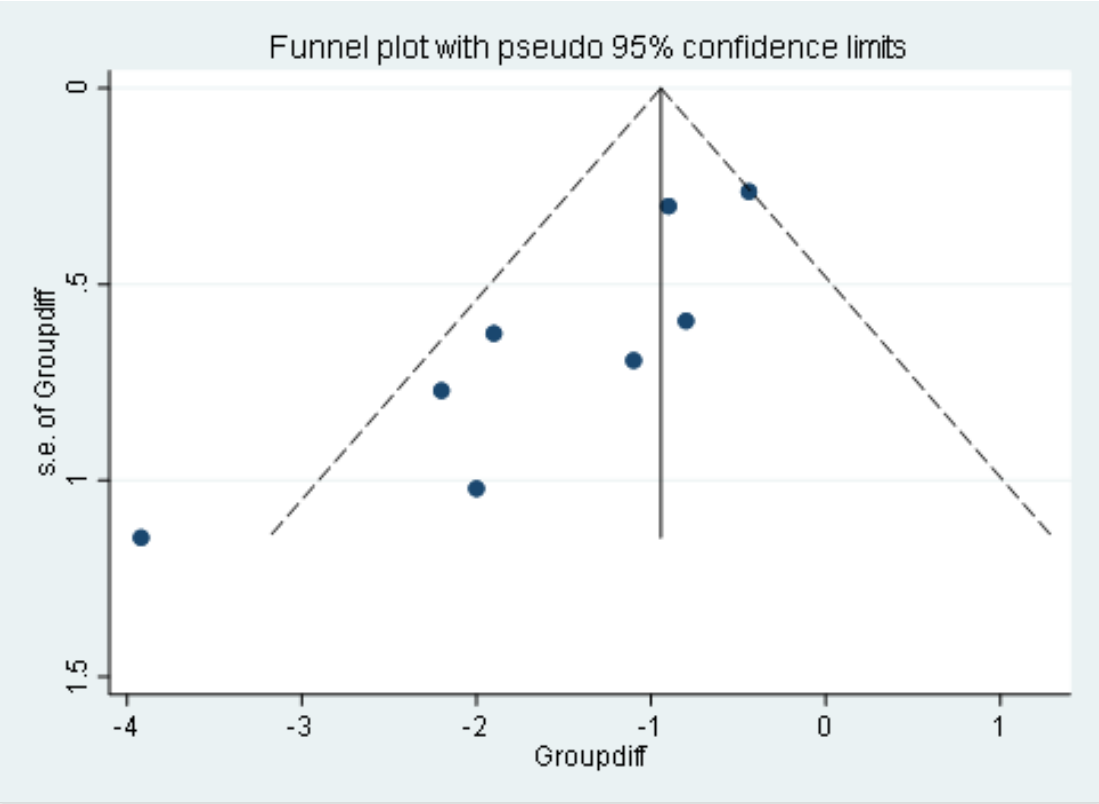
Appendix J. Funnel Plot of High-THC Ratio Studies Included in Meta-Analysis for Pain Severity

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



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