Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2022 Update—Surveillance Report 3

Literature Update Period: Mid-October 2022 Through Late January 2023

Overview

This is the third surveillance report since the annual update of a living systematic review on cannabis and other plant-based treatments for chronic pain. Since the last surveillance report, inclusion criteria were expanded to also address subacute pain (4 to 12 weeks' duration) and pain in adolescents.[1]

The systematic review synthesizes evidence on the benefits and harms of plant-based compounds (PBCs), such as cannabinoids and kratom, used to treat chronic or subacute pain, and addresses 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-October 2022) and provide a synthesis of the accumulated evidence. Surveillance update reports are planned on a quarterly basis, and the systematic review will be updated annually. The systematic review is available on the Agency for Healthcare Research and Quality (AHRQ) website (https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review). 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)
Mid-January 2022	Surveillance Report 3 (May 2022)
March 2022	Surveillance Report 4 (August 2022)
April 2022	Systematic Review (August 2022)
Early July 2022	Surveillance Report 1 (September 2022)
Mid-October 2022	Surveillance Report 2 (January 2023)
Late January 2023	Surveillance Report 3 (April 2023)

Main Points

The Key Questions (KQs) for this review focus on the benefits (KQ1) and harms (KQ2) of cannabinoids for treating chronic or subacute pain, as well as the benefits (KQ3) and harms (KQ4) of other PBCs, such as kratom, for treating chronic or subacute pain. Studies of cannabis-related products were grouped based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio using the following categories: high THC to CBD ratio, comparable THC to CBD ratio, and low THC to CBD ratio. One new randomized trial of oral dronabinol (synthetic oral THC [high-

THC to CBD ratio]), CBD, or combined THC/CBD (low THC to CBD ratio) versus placebo for chronic neuropathic pain was identified for inclusion during this surveillance period.[2] The new trial slightly reduced the pooled effect size for improvement in pain intensity with synthetic high-THC to CBD ratio products versus placebo, crossing the threshold from moderate (prior pooled estimate −1.15 on a 0 to 10 scale, 95% confidence interval [CI −1.99 to −0.54) to small (updated pooled estimate −0.95, 95% CI −1.81 to −0.25) and changed the SOE for pain response from low to insufficient due to inconsistent results from two randomized trials. Although the new trial evaluated two cannabis products classified as low THC to CBD ratio, it was unclear if the CBD was synthetic or plant based. The evidence for low THC to CBD products remained insufficient due to heterogeneity in the products evaluated and some inconsistency.

Overall, in patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months):

- Comparable THC to CBD ratio oral spray is probably associated with small improvements in pain severity and overall function versus placebo. There was no increase in risk of serious adverse events or withdrawal due to 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 ratio) may be associated with small improvement in pain severity but with increased risk of sedation and potential increased risk of nausea versus placebo. 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 versus placebo; outcomes assessing benefit were not reported or insufficient.
- Evidence on whole-plant cannabis (including patient's choice of products), low THC to CBD ratio products (topical or oral CBD), and other cannabinoids (cannabidivarin), and comparisons with other active interventions or different cannabis-related products 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 or evidence was insufficient to draw conclusions.
- 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 (2022)	Findings From Surveillance to Date	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

Key Question[a]	Conclusions From Systematic Review (2022)	Findings From Surveillance to Date	Assessment
KQ1 and KQ2. Synthetic High THC to CBD Ratio Benefits and Harms	Benefits: small improvements in pain severity (SOE: low; 7 RCTs); no effect on overall function/disability (SOE: low; 3 RCTs) Harms: moderate increased risk of sedation (SOE: low; 4 RCTs); large increased risk of nausea (SOE: low; 3 RCTs); and moderate increased risk of dizziness (SOE: moderate; 3 RCTs)	1 new study[b]	Reduced effect size for pain intensity improvement for synthetic high THC versus placebo from moderate to small.
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 Ratio Benefits and Harms	Insufficient evidence (3 RCTs[c])	1 new study[b]	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
KQ1 and KQ2. Comparable THC to CBD Ratio Vs. Synthetic THC Benefits and Harms	Insufficient evidence (1 observational study)	No new studies	No change in conclusions
KQ1 and KQ2. Comparable THC to CBD Ratio Vs. LAOs	No studies	Insufficient evidence (1 observational study)	Insufficient evidence
KQ3 and KQ4. Kratom or Other Plant-Based Substances Benefits and Harms	Insufficient evidence (0 RCTs)	No new studies	No change in conclusions

Abbreviations: CBD = cannabidiol; KQ = Key Question; LAO = long-acting opioid; RCT = randomized controlled trial; SOE = strength of evidence; THC = tetrahydrocannabinol.

[a] For Key Question wording, see the Background section below.

[b] Newly included study had arms for both high THC to CBD ratio and low THC to CBD ratio products.

[c] Products varied regarding origin (synthetic or plant derived) and route (oral or topical), causing inconsistencies in the results.

Summary of Findings Tables

The 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, based on evidence reviewed to date. 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 Product	Pain Response Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD - Extracted From Whole Plant, Oromucosal Spray	Potential effect (4)[a] [+]	Small effect (7) [++]	Small effect (6) [++]
High THC – Synthetic, Oral	**Insufficient (2, 1 new)[c]**	**Small effect (7, 1 new)[c]** [+]	No effect (4, 1 new) [+]
High THC – Extracted From Whole Plant, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Topical CBD, Extracted From Whole Plant	No evidence	Insufficient (1)	No evidence
Low THC – Oral CBD, Synthetic	No evidence	Insufficient (1)	Insufficient (1)
Low THC – Oral CBD or CBD/THC, Unclear If Synthetic or Extracted From Whole Plant	**Insufficient (1 new)[c]**	**Insufficient (1 new)[c]**	**Insufficient (1 new)[c]**
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."
[c] Text is bolded to indicate that the strength of evidence has changed.
Text that is red indicates that a new study has been added. Color is used for visual emphasis only.
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 – Extracted From Whole Plant, Oromucosal Spray	No effect (5) [+]	No effect (3) [+]	Large effect (6) [+]	Moderate effect (6) [+]	Large effect (6) [+]
High THC – Synthetic, Oral	Potential effect[a] (5, 1 new) [+]	Insufficient (1)	Large effect (3, 1 new) [++]	Potential effect[a] (3, 1 new) [+]	Moderate effect (4, 1 new) [+]
High THC – Extracted From Whole Plant, Oral	Large effect (1) [+]	Insufficient (1)	Large effect (1) [+]	No evidence	No evidence
Low THC – Topical CBD, Extracted From Whole Plant	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Oral CBD, Synthetic	Insufficient (1)	Insufficient (1)	No evidence	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 – Oral CBD or CBD/THC, Unclear If Synthetic or Extracted From Whole Plant	**Insufficient (1, 1 new)[c]**	**Insufficient (1, 1 new)[c]**	**Insufficient (1, 1 new)[c]**	**Insufficient (1, 1 new)[c]**	**Insufficient (1, 1 new)[c]**
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."
[c] Text is bolded to indicate that the strength of evidence has changed.
Text that is red indicates that a new study has been added. Color is used for visual emphasis only.
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,[3,4] and it affects approximately 100 million people in the United States.[5] Chronic pain adversely affects physical and mental functioning, productivity, and quality of life, and is often refractory to treatment and associated with substantial costs.[6-8]

While opioids are often prescribed for chronic pain, a recent series of systematic reviews found that opioids,[9] several nonopioid drugs,[10] and some nonpharmacologic treatments[11] have small to moderate effects on pain and function, but also 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.[3,4] 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.[12]

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,[13,14] although its psychoactive effects and abuse potential may limit its suitability as an analgesic. CBD may also have some analgesic or anti-inflammatory properties and is thought to be less intoxicating and not addictive.[15,16] While not derived from plants, two synthetic cannabinoid products, dronabinol (a 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.[17]

Although the original review and prior surveillance reports and update focused on chronic pain in adults, subacute pain and pain in adolescents are also relevant. Subacute pain, often defined as pain lasting for 4 to 12 weeks, represents a transitional state between acute (<4 weeks) pain, which often resolves, and chronic pain, which is more likely to persist.[18] Effective

treatments for reducing the likelihood that subacute pain will become chronic are also needed. Adolescents also experience chronic pain and have a high prevalence of cannabis use (recreational or medical[19,20]).

Four KQs guide the review:

KQ1: In adults or adolescents with chronic or subacute pain, what are the benefits of cannabinoids for treatment of chronic or subacute pain?

KQ2: In adults or adolescents with chronic or subacute pain, what are the harms of cannabinoids for treatment of chronic or subacute pain?

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

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

The protocol for the systematic review can be found on the AHRQ website (https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol) and on the PROSPERO systematic reviews registry (registration number CRD42021229579). The scope of the review was reviewed with a Technical Expert Panel (TEP) following the prior annual update, including considerations for expansion of scope.[21] With TEP input, the protocol was amended to include adolescents and subacute pain. An updated protocol was submitted to PROSPERO,[1] and the title, key questions, and inclusion and exclusion criteria were revised to reflect the changes.

Methods

In brief, we searched Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases monthly through late January 2023 for studies of patients with chronic pain with at least 4 weeks of treatment or followup. Search strategies were updated to include terms for adolescents and subacute pain and applied to databases from inception to identify studies on adolescent and subacute pain. Additionally, we re-assessed previously excluded studies for eligibility based on revised inclusion criteria. For the period covered by this surveillance report (mid-October 2022 to late January 2023), one new study comparing dronabinol (synthetic oral THC), CBD, combined THC/CBD (low-THC to CBD ratio), and placebo for chronic neuropathic pain was identified.[2] 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. Briefly, we included randomized controlled trials (RCTs) and observational studies with a concurrent control group with a minimum of 4 weeks' followup assessing cannabis and other plant-based interventions in adults or adolescents with noncancer chronic or subacute pain. 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,[22] and abstracted key information and conducted risk-of-bias assessments using the Cochrane Back Pain Group's

version of the Cochrane guidance for randomized trials[23] and criteria developed by the U.S. Preventive Services Task Force[24] for observational studies for each included study. Our methods included categorizing studies based on the duration of followup 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. When studies were similar enough to provide a meaningful combined estimate, 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)	Source	Possible Derivatives	Example Products	U.S. Availability
High THC (THC to CBD ratio equals ≥2:1 ratio)	Synthetic	Synthetic THC (100% THC or analog)	Dronabinol (Marinol®) or nabilone (Cesamet®)	Available via prescription[a]
	Synthetic	Purified from whole-plant with close to 100% THC	Purified dronabinol (Namisol®)[b,c]	Not available in the U.S.
	Plant-based	Commercially marketed product extracted from whole-plant with known high ratio of THC/CBD	THC/CBD extracts with high THC/CBD ratio	Unknown – may be available at dispensaries where allowed
	Plant-based	Whole-plant with known high concentration of THC	Whole-plant cannabis with known high THC concentration	Unknown – may be available at dispensaries where allowed
Comparable THC to CBD (THC to CBD ratio is <2:1 and >1:2)	Plant-based	Extracted from whole-plant with comparable ratio of THC/CBD	Nabiximols (Sativex®)[d]	Not available in the U.S.
	Plant-based	Extracted from whole-plant with comparable ratio of THC/CBD	Oral tinctures with similar ratio of THC/CBD	Unknown – may be available at dispensaries where allowed
	Plant-based	Whole-plant with known comparable ratio of THC/CBD	Whole-plant with known comparable ratio of THC/CBD	Unknown – may be available at dispensaries where allowed
Low THC (THC to CBD ratio equals ≤1:2)	Plant-based	Extracted from whole plant with low ratio of THC/CBD	CBD topical or oral	Unknown – may be available at dispensaries where allowed
Low THC(THC to CBD ratio is ≤1:2)	Synthetic	Synthetic CBD	CBD oral tablets	Unknown

Intervention Category (Definition)	Source	Possible Derivatives	Example Products	U.S. Availability
Whole-Plant Cannabis Products (THC to CBD ratio categorized based on information provided [potentially unknown])	Plant-based	Whole-plant products	Cannabis flowers, resins, buds, leaves, hashish	Unknown – may be available at dispensaries where allowed.
Other Cannabinoids (Cannabinoids other than THC or CBD)	Plant-based	Extracted from whole-plant	Cannabidivarin (CBDV) extracted oil (oral)	Unknown – may be available at dispensaries where allowed

Abbreviations: CBD = cannabidiol; THC = tetrahydrocannabinol.
[a]These products are approved by the Food and Drug Administration for non-pain indications (anorexia related to HIV infection, nausea related to chemotherapy).
[b] Namisol® is chemically identical to dronabinol, and is therefore grouped together with synthetic dronabinol.
[c] Manufactured in The Netherlands, may be available in some European countries. Not currently FDA-approved.
[d] Manufactured and available in Canada and some European countries; not FDA-approved.

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

Results to Date

Results Overview

Across all of the monthly literature searches to date, 5,085 citations were screened, from which we included 31 studies.[2,25-54] For the period covered by this surveillance report, 1,517 citations were screened

One new low risk of bias study (n=115) met inclusion criteria for this update period. 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.

Table 6 summarizes the characteristics of included RCTs, and Table 7 summarizes the characteristics of included observational studies.

Table 6. Characteristics of included randomized controlled trials to date

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
THC to CBD Ratio	Comparable[a]	High	High	Low	NA - other cannabinoids
Source	Plant-extracted	Plant-extracted	Synthetic Nabilone Dronabinol Dronabinol/Namisol®[b]	Plant-extracted (1) Synthetic (1) Unclear (1)	Plant-extracted
N Studies	7	2	10[c]	3[c] (1 topical, 2 oral)	1

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Comparator (Study Count)	Placebo (7)	Placebo (2)	Placebo (7); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low THC to CBD ratio (CBD or Dronabinol/CBD[d]) (1)	Placebo (3); Dronabinol[d] (1); Dronabinol/CBD[d] (1)	Placebo
Route of Administration, Formulation (Study Count)	Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl	Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1) Oral capsule, 2.5 mg THC/0.8–1.8 mg CBD extract (1)	Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Dronabinol 2.5 mg oral capsule (2); Dronabinol 5 mg oral capsule (1); Namisol®[a] 3 mg oral tablet (1)	Topical oil, 83 mg CBD/fluid ounce (1), Oral tablet, 10 mg CBD (1) Oral capsule, 5 mg CBD (1) Oral capsule, 5 mg CBD/2.5 mg dronabinol (1)[d]	Oral oil, 50 mg/ml CBDV
Dosing Regimen	Final mean dose 23 mg THC/21 mg CBD daily.	Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily. Capsule: 2.5-12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily.	Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Dronabinol capsules: 2.5 -15 mg once or twice daily, titrated. Final dose range 15-25 mg/day Namisol®[a] tablet: 3 - 8 mg 3 times daily, titrated. Final dose NR.	Topical oil: applied locally 1-4 times/day (volume/dose, final dose NR). Oral tablet: 10 mg daily, titrated (max 3 times daily) Final dose NR. Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 50 mg CBD daily. Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 15 mg THC/30 mg CBD daily.	400 mg CBDV daily. Final dose NR.
Risk of Bias	29% high, 57% moderate, 14% low	50% moderate, 50% low	20% high, 40% moderate, 40% low	33% high, 33% moderate, 33% low	100% moderate
Total Randomized	882	297	592	252	34
Age, Mean Years	53	52	53	64	50
Female, %	66%	89%	61%	50%	3%
Non-White,[e] %	1.6% (2)	1% (1)	5.4% (3)	NR	NR
Primary Pain Type (Study Count)	NPP (6); Inflammatory arthritis (1)	NPP (1); Fibromyalgia (1)	NPP (7); Fibromyalgia (1); Headache (1); Visceral pain (1)	NPP (2); OA (1)	NPP (1)

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Baseline Pain Score, Mean (Range)[f]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.48 (4 to 8.1)[g]	5.67 (4.67 to 6.5)	6.28 (6.12 to 6.44)
Study Duration	4 to 15 weeks	8 to 12 weeks	4 to 47 weeks	4 to 12 weeks	4 weeks

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; NA = not applicable; NPP = neuropathic pain; NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; THC = tetrahydrocannabinol.

[a]All products were nabixiomols.

[b] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

[c]Includes one new RCT for this review.

[d]One new study compared THC to CBD, CBD/THC, and placebo.

[e](n) = number of studies reporting this characteristic at baseline.

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

[g] Weighted mean includes median scores for 1 study (6 vs. 6).

Table 7. Characteristics of included observational studies to date

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
THC to CBD Ratio	Unclear	High	High	Comparable vs. high	Comparable
Source	Any cannabis product (patient's choice)	Plant-based	Synthetic (nabilone)	Plant-based vs. synthetic	Plant-based
N Studies	5	1	1	1	1[b]
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (1)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)	Active comparator; oral mucosal spray vs. dronabinol	Long-acting opioids (MME 69.4 (SD 38.9) mg/day)
Route of Administration, Formulation	Unreported (any available allowed, patient's choice)	Whole-plant cannabis, "certified 12.5% THC" (CBD NR) route determined by patient: smoking 27%, oral 8%, vaporization 4%, combination 61%	Nabilone 0.5 mg oral capsule	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Dronabinol oral capsule (strength NR)	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Oral long-acting opioids (dose varied)
Dosing Regimen	None specified. Final dose NR	None specified; titrated to max dose 5 g/day. Final median dose 2.5 g/day	None specified; final mean dose 3 mg/day	None specified; final mean dose 16.6/15.4 mg THC/CBD/day vs. 17.2 mg THC/day	None specified; based on individual patient needs; final mean dose 16.7/15.5 mg THC/CBD/day vs. MME 69.4 mg/day
ROB	60% high, 40% moderate	100% high	100% moderate	100% moderate	100% moderate
N Total	12,508	431	156	674	1,310
Age, Mean Years	53	49	61	46	51
Female, %	55%	57%	59%	57%	57%
% Non-White (Study Count)	54% (1); NR (4)	NR	NR	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic non-cancer pain	Chronic non-cancer pain	NPP	Peripheral NPP	Peripheral neuropathic back pain

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
Baseline Pain Score, Mean (Range)[c]	5.35 (4.56 to 8.00)	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)	4.4 (4.39 to 4.41)	4.32 (4.31 to 4.33)
Study Duration, Weeks (Range)	12 to 208	52	26	24	24

Abbreviations: CBD = cannabidiol; LAO = long-acting opioid; MME = morphine milligram equivalents; NPP = neuropathic pain; NR = not reported; ROB = risk of bias; SD = standard deviation; THC = tetrahydrocannabinol.

[a] Patients could choose any medicinal product they preferred in these studies.

[b]Includes one new study for this review.

[c] 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. One new RCT (n=115) evaluated a high THC to CBD ratio product.[2] It was conducted in Denmark and compared oral THC (dronabinol) versus CBD, combined THC/CBD (low THC to CBD ratio), or placebo for neuropathic pain. Median daily doses were 25 mg for dronabinol, 50 mg for CBD, and 15 mg/30 mg for combined THC/CBD. Median age was 65, 64 percent were female, and the median duration of pain was 60 months. Race was not reported. The duration of followup was 8 weeks. Estimates favored placebo over dronabinol for improvement in pain intensity (mean difference for dronabinol vs. placebo 0.50 on 0 to 10 scale, 95% CI −0.58 to 1.58), likelihood of 30 percent or more improvement in pain (43% vs. 57%, risk ratio [RR] 0.76, 95% CI 0.45 to 1.28), and improvement in function (mean difference 0.36 on 0 to 10 scale, 95% CI −1.19 to 1.91), although estimates were imprecise and not statistically significant.

Based on an updated pooled analysis of seven RCTs (1 new RCT added[2]), synthetic high-THC to CBD ratio products were associated with a small improvement in pain severity (7 RCTs, N=448, 0 to 10 scale, mean difference [MD] –0.95, 95% CI –1.81 to –0.25, I^2=60%; Appendix E, Figure E-10).[2,28,37,40-42,45] The estimate was slightly reduced from the prior pooled estimate (MD –1.15, 95% CI –1.99 to –0.54, I^2=48%) and crossed the threshold from moderate to small. Two trials (including the new RCT) reported likelihood of pain response (≥30% improvement from baseline) for synthetic high THC to CBD ratio products but reported inconsistent findings.[2,41] An updated pooled analysis of three RCTs,[2,41,42] including the new trial,[2] found little difference between synthetic high THC versus placebo for function, although the estimate was imprecise (0 to 10 scale, MD −0.18, 95% CI −1.25 to 0.77, I^2=51%; Appendix E, Figure E-12).[2,41,42]

The new, low risk of bias RCT (n=58) found no differences between dronabinol versus placebo in sleep (0 to 10 scale, MD 0.36, 95% CI −1.31 to 2.03 on 0 to 10 scale), quality of life (0 to 10 scale, mean difference −0.35, 95% CI −1.66 to 0.97), Patient Reported Outcomes Measurement Information System [PROMIS] anxiety scores (MD 0.23, 95% CI −2.04 to 2.50), or PROMIS depression scores (MD 1.64, 95% CI −0.24 to 3.52).[2]

For adverse events, findings were similar with the addition of the new RCT.[2] The most commonly reported was withdrawals due to adverse events (WAEs). Updated pooled analysis of WAEs in five trials showed a statistically nonsignificant increase with synthetic THC versus placebo (14% vs. 7%, RR 1.75, 95% CI 0.95 to 4.11, I^2=0%, Appendix E, Figure E-13).[2,28,37,40,42] Of these five studies, two evaluated nabilone[40,42] (7% vs. 4%, RR 1.54, 95% CI 0.14 to 17.71, I^2=0%) and three evaluated dronabinol[2,28,37] (15% vs. 8%, RR 1.77, 95% CI 0.90 to 5.44, I^2=0%), with no statistically significant differences between subgroups (p=0.89). Synthetic THC was

associated with statistically significant increased risk of dizziness (3 dronabinol RCTs, 29% vs. 11%, RR 2.52, 95% CI 1.20 to 4.82, I^2=41%, Appendix E, Figure E-15)[2,28,37] and sedation (4 RCTs, 1 nabilone, 3 dronabinol, 19% vs. 12%, RR 1.60, 95% CI 1.01 to 2.95, I^2=7.7%, Appendix E, Figure E-16).[2,28,37,40] However, as in previous analyses, the confidence interval for sedation became very imprecise and nonstatistically significant when using the Bartlett correction. Synthetic THC (dronabinol) was also associated with increased risk of nausea, but the estimate was imprecise and the difference was not statistically significant (3 RCTs, 11% vs. 5%, RR 2.22, 95% CI 0.90 to 5.05, I^2=0%, Appendix E, Figure E-17).[2,28,37]

Based on the updated evidence (including the new trial), synthetic oral THC (high THC to CBD ratio) may be associated with a small improvement (downgraded from moderate) in pain severity (SOE: low) and no effect on overall function or disability (SOE: low). As in the prior update, synthetic THC treatments are associated with a moderate increase in risk of sedation (SOE: low) and dizziness (SOE: moderate), and there was a large increased risk of nausea (SOE: low). There were inconsistent effects on likelihood of experiencing a pain response (SOE: insufficient [downgraded from 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).

The new, low risk of bias RCT (n=87 for the low THC to CBD ratio arms) evaluated oral CBD (median 50 mg/day) or THC (dronabinol)/CBD in a 1:2 ratio (median 15/30 mg/day) versus placebo.[2] The trial did not report whether CBD was synthetic or plant based; the THC component of the combined product was synthetic (dronabinol). At 8 weeks, CBD was associated with increased pain intensity versus placebo (average weekly pain on 0 to 10 scale, MD 1.14, 95% CI 0.11 to 2.19), with no difference between THC/CBD versus placebo (MD −0.12, 95% CI −1.13 to 0.89). There were no statistically significant differences in likelihood of 30 percent or more improvement in pain (33% vs. 57%, RR 0.59, 95% CI 0.32 to 1.09 for CBD vs. placebo and 60% vs. 57%, RR 1.06, 95% CI 0.69 to 1.62 for THC/CBD vs. placebo). Estimates for low THC to CBD ratio products versus placebo and function (0 to 10 scale, MD 1.24, 95% CI −0.32 to 2.81 for CBD and MD 0.89, 95% CI −0.64 to 2.42 for THC/CBD) or secondary outcomes including sleep, quality of life, depression, or anxiety were imprecise. Estimates for adverse events were also imprecise. In the prior update, the SOE for low THC to CBD ratio products was insufficient, based on two trials that evaluated different types of products (topical, plant-extracted[46] or oral, synthetic[52]). The updated SOE remains insufficient, with additional heterogeneity in interventions and some inconsistency.

Conclusion

One new randomized trial was identified for this surveillance report. For synthetic high THC to CBD ratio products, addition of the new trial resulted in a slightly lower pooled estimate for improvement in pain severity versus placebo that crossed the effect size threshold from moderate to small; in addition, the SOE for likelihood of experiencing a pain response (≥30% improvement) was downgraded from moderate to insufficient due to inconsistency between two trials. For low THC to CBD ratio products, the SOE remained insufficient despite the new trial, due to heterogeneity in products and mode of administration, and some inconsistency.

Overall, this surveillance report found that evidence on cannabis-related interventions remains restricted to short-term outcomes, primarily in patients with neuropathic pain. Improvement in pain appears small with high and comparable THC to CBD ratio products.

Compared with placebo, cannabis-related interventions are associated with 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 Report

The next surveillance report update is scheduled for summer 2023.

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Disclaimers

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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 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.

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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 surveillance reports will provide up-to-date information following the last full systematic review 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 January 20, 2023

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 or subacute* or sub-acute*).ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory or subacute* or sub-acute) 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 December 2022

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 or subacute* or sub-acute*).ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory or subacute* or sub-acute*) 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 January Week 4, 2023

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 or subacute* or sub-acute*).ti,ab.
5 3 and 4
6 ((chronic or persistent or intractable or refractory or subacute* or sub-acute*) 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 January 22, 2023

('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 'subacute pain'/exp OR 'subacute 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 osteoarthrtis) NOT ((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*)) AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'preprint'/it OR 'review'/it) AND [english]/lim AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Database: Elsevier Scopus January 30, 2022

((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 "subacute 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"))) AND NOT (TITLE-ABS-KEY (
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*)) AND (LIMIT-TO (LANGUAGE , "English"))

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). In the winter of 2022, the protocol was amended to include adolescents and subacute pain.[1] These changes were documented on in a revised protocol submitted to PROSPERO,[2] the AHRQ Protocol, and the title, key questions, and inclusion and exclusion criteria were edited to reflect said changes. The changes expanded inclusion criteria to include subacute pain and adolescents.

KQ1: In adults or adolescents with chronic or subacute pain, what are the benefits of cannabinoids for treatment of chronic or subacute pain?
KQ2: In adults or adolescents with chronic or subacute pain, what are the harms of cannabinoids for treatment of chronic or subacute pain?
KQ3: In adults or adolescents with chronic or subacute pain, what are the benefits of kratom or other plant-based substances for treatment of chronic or subacute pain?
KQ4: In adults or adolescents with chronic or subacute pain, what are the harms of kratom or other plant-based substances for treatment of chronic or subacute pain?

Table B-1. PICOTS

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults or adolescents (including pregnant or breastfeeding women) with noncancer chronic pain (>12 weeks or pain persisting past the time for normal tissue healing) or subacute pain (pain lasting 4 weeks to 3 months). See categorization of specifically included pain populations below.	**All KQs:** Children; adults with acute 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

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, general function [e.g., Short-Form 36 Physical Functioning Scale] or pain-related [e.g., Oswestry Disability Index or Roland-Morris Disability Questionnaire, for low back pain] 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 (challenges in performing daily, social, or work-related tasks due to pain).

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 reports were published to the Agency for Healthcare Research and Quality (AHRQ) website, and evidence tables are 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,[3] and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force.[4] 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.[5] 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[6,7] 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).[6-10]

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.[11] 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 based on the profile likelihood method,[12] and statistical heterogeneity was assessed using the I^2 method. Publication bias (small sample size bias) was 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[6-10] 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 = risk ratio; 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)[13]
- If the magnitude of effect is below the threshold for a small effect, the finding is considered to have "No effect"[6]
- 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."[14]

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.[5] 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 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."[15]

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,[16] 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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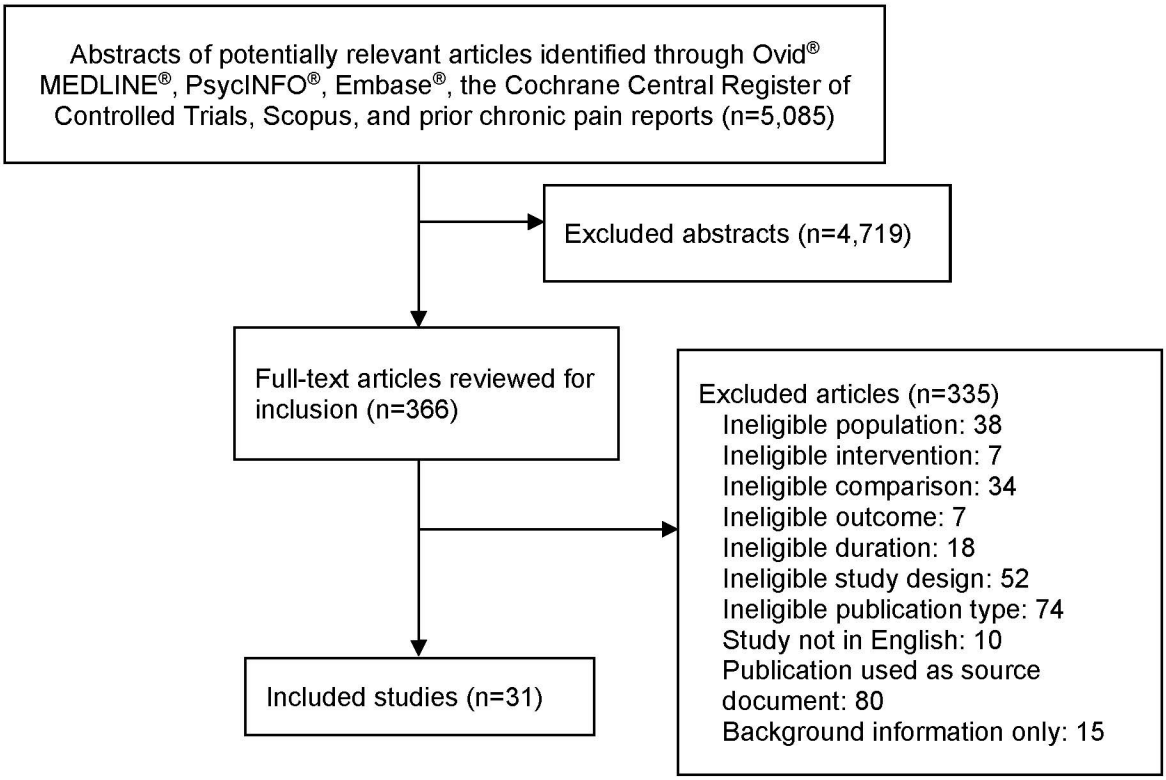
Appendix D. Literature Flow Diagram

Figure D-1. Literature flow diagram



Note: Numbers in parenthesis indicate all records identified up to late January 2023.

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%), RR 0.18 (95% CI 0.01 to 3.49) WAE: 0/31 (0%) vs. 3/27 (11.11%), RR 0.13 (95% CI 0.01 to 2.32)	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%), RR 1.60 (95% CI 0.71 to 3.60)	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%), RR 1.00 (95% CI 0.02 to 45.13) WAE: 0/8 (0%) vs. 0/8 (0%), RR 1.00 (95% CI 0.02 to 45.13)	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%), RR 2.95 (95% CI 0.12 to 71.13) WAE: 11/63 (17.46%) vs. 2/62 (3.23%), RR 5.41 (95% CI 1.25 to 23.43)	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%), RR 0.94 (95% CI 0.02 to 46.16) WAE: 2/34 (5.88%) vs. 0/32 (0%), RR 4.71 (95% CI 0.23 to 94.58)	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. 7/118 (6%), RR 1.32 (95% CI 0.52 to 3.35) WAE: 25/128 (19.53%) vs. 25/118 (21.19%), RR 0.92 (95% CI 0.56 to 1.51)	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 = risk ratio; 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%), RR 1.11 (95% CI 0.02 to 50.43)	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%), RR 3.73 (95% CI 0.84 to 16.57)	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%), RR 1.00 (95% CI 0.02 to 49.39) WAE: 2/48 (4%) vs. 6/48 (12.5%), RR 0.33 (95% CI 0.07 to 1.57)	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%), RR 1.00 (95% CI 0.07 to 15.26)	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%), RR 0.71 (95% CI 0.06 to 8.91) WAE: 1/7 (14.29%) vs. 0/5 (0%), RR 2.25 (95% CI 0.11 to 46.13)	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%), RR 1.53 (95% CI 0.63 to 3.76) WAE: 19/124 (15.32%) vs. 12/116 (10.34%), RR 1.48 (95% CI 0.75 to 2.91)	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%), RR 1.19 (95% CI 0.02 to 56.54) WAE: 1/20 (5%) vs. 1/20 (5%), RR 1.00 (95% CI 0.07 to 14.90)	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%), RR 0.89 (95% CI 0.02 to 39.84) WAE: 1/8 (12.5%) vs. 0/7 (0%), RR 2.67 (95% CI 0.13 to 56.63)	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%), RR 5.00 (95% CI 0.26 to 95.02)	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%), RR 2.19 (95% CI 0.58 to 8.28) WAE: 30/143 (20.98%) vs. 9/134 (6.72%), RR 3.12 (95% CI 1.54 to 6.33)	NR
Zubcevic, 2022 Low RCT Peripheral neuropathic pain	A: THC 2.5 mg capsule (dronabinol), max dose 25 mg/day (28) B: CBD 5 mg capsule (unknown if synthetic or plant-derived), max dose 50 mg/day (27) C: CBD/THC capsule, max dose 50 mg CBD (unknown of synthetic or plant-derived)/25 mg THC (dronabinol)/day (30) D: Placebo (30)	Pain response ≥30% (NRS scale): 12/28 (42.86%) vs. 9/27 (33.34%) vs. 18/30 (60.00%) vs. 17/30 (56/67%), RR (95% CI) A vs. B: 1.29 (0.65 to 2.55) A vs. C: 0.71 (0.43 to 1.20) A vs. D: 0.76 (0.45 to 1.28) B vs. C: 0.56 (0.30 to 1.02) B vs. D: 0.59 (0.32 to 1.09) C vs. D: 1.06 (0.69 to 1.62) Pain severity change from baseline (mean [95% CI] 0 to 10 NRS scale): −1.4 (-2.2 to -0.7) vs. -0.6 (-1.2 to 0.1) vs. -1.9 (-2.7 to -1.2) vs. -1.9 (-2.7 to -1.0)	Pain interference (mean [SD] 0 to 10 Pain Impact on Daily Activities Scale): MD (95% CI) A vs. D: 0.36 (-1.19 to 1.91) B vs. D: 1.24 (-0.32 to 2.81) C vs. D: 0.89 (-0.64 to 2.42)	SAE: 0/28 (0%) vs. 0/27 (0%) vs. 1/30 (3.3%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.96 (0.02 to 47.01) A vs. C: 0.36 (0.02 to 8.40) A vs. D: 1.07 (0.02 to 52.14) B vs. C: 0.37 (0.02 to 8.70) B vs. D: 1.11 (0.02 to 53.97) C vs. D: 3.00 (0.13 to 70.83) WAE: 1/28 (3.57%) vs. 2/27 (7.41%) vs. 4/30 (13.33%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.48 (0.05 to 5.01) A vs. C: 0.27 (0.03 to 2.25) A vs. D: 3.21 (0.14 to 75.62) B vs. C: 0.56 (0.11 to 2.80) B vs. D: 5.54 (0.28 to 110.42) C vs. D: 9.00 (0.51 to 160.18)

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 = risk ratio; 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%), RR 1.05 (95% CI 0.15 to 7.22) WAE: 0/70 (0%) vs. 2/66 (3%), RR 0.19 (95% CI 0.01 to 3.86)	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; CI = confidence interval; 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%), RR 3.00 (95% CI 0.13 to 68.57) WAE: 1/16 (6.25%) vs. 0/16 (0%), RR 3.00 (95% CI 0.13 to 68.57)	Pain interference (0 to 10 BPI−SF scale): MD −0.35 (95% CI −1.36 to 0.43)

Abbreviations: BPI-SF = Brief Pain Inventory – Short Form; CBDV = cannabidivarin; CI = confidence interval; MD = mean difference; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; SAE = serious adverse event; SD = standard deviation; WAE = study withdrawals due to adverse events.

[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%), RR 0.44 (95% CI 0.17 to 1.16 for A vs. B, RR 1.12 (95% CI 0.34 to 3.65) for A vs. C, RR 2.54 (95% CI 0.96 to 6.71) for B 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, MD 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, MD 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 to 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
Ueberall, 2022a Moderate Retrospective cohort Peripheral neuropathic pain	A: Nabiximols as an add-on treatment; 16.6 (SD 6.5) mg THC/15.4 (SD 4.1) mg CBD/day (337) B: Dronabinol as an add-on treatment; 17.2 (SD 7.6) mg THC/day (337) 24 weeks Whole plant extracted vs. synthetic	A vs. B Pain intensity index (VAS 0-100 scale) mean relative change (improvement) rates at week 24 83.4% vs. 75.9%, p<0.001 Pain intensity index (VAS 0-100 scale, converted to 0-10) mean difference: 3.50 (95% CI 1.6 to 5.4)	NR	A vs. B Pain-related disabilities (VAS 0-100 scale) mean relative change (improvement) rates at week 24 76.0% vs. 68.3%, p<0.001

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)
Ueberall, 2022b Moderate Retrospective cohort Peripheral neuropathic back pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 16.7 mg THC/15.5 mg CBD/day (655) B: Long-acting opioid, MME 69.4 mg/day 24 weeks Whole plant extracted and long-acting opioid	Pain intensity index (mean relative change from baseline at week 24, 0 to 100 VAS scale): −72.3% (SD 30.5) vs. −49.2% (SD 39.9) Pain intensity index (VAS 0-100 scale, converted to 0-10) mean difference: 9.90 (95% CI 8.05 to 11.75)	Pain-related disabilities (mean relative change [improvement] rates at week 24, 0 to 100 VAS scale): −66.1 (28.7) vs. −42.9 (34.5), p<0.001	WAE: 7.9% vs. 29.3%, RR 0.27 (95% CI 0.20 to 0.36)
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%), RR 0.67 (95% CI 0.43 to 1.04) 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.

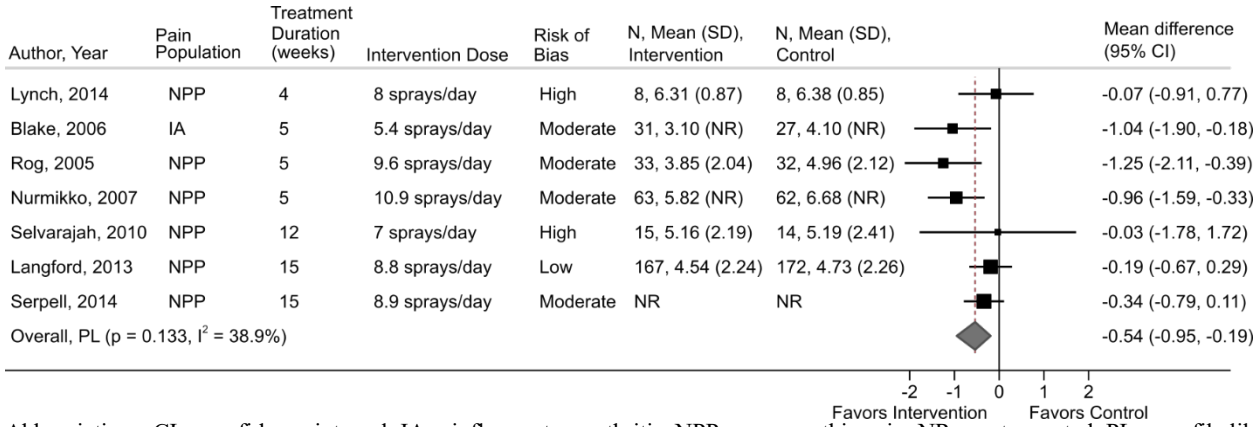
[b]Only included outcome reported was opioid-use.

Meta-Analysis Results

Comparable THC to CBD Ratio Studies

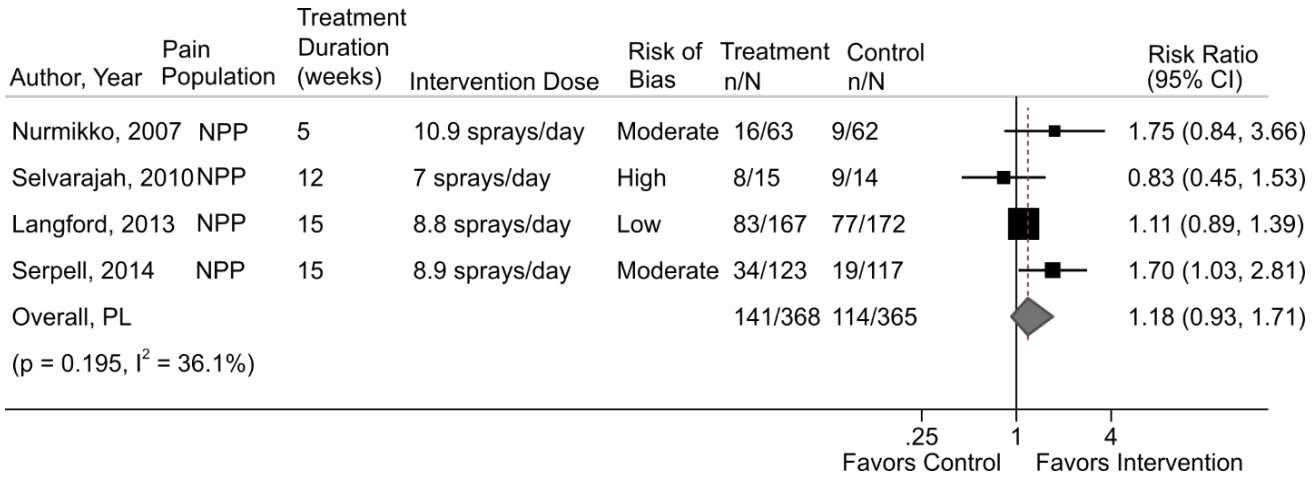
Pooled results and the forest plot for the sensitivity analysis conducted for improvement in pain severity are available upon request by emailing ahmedaz@ohsu.edu.

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



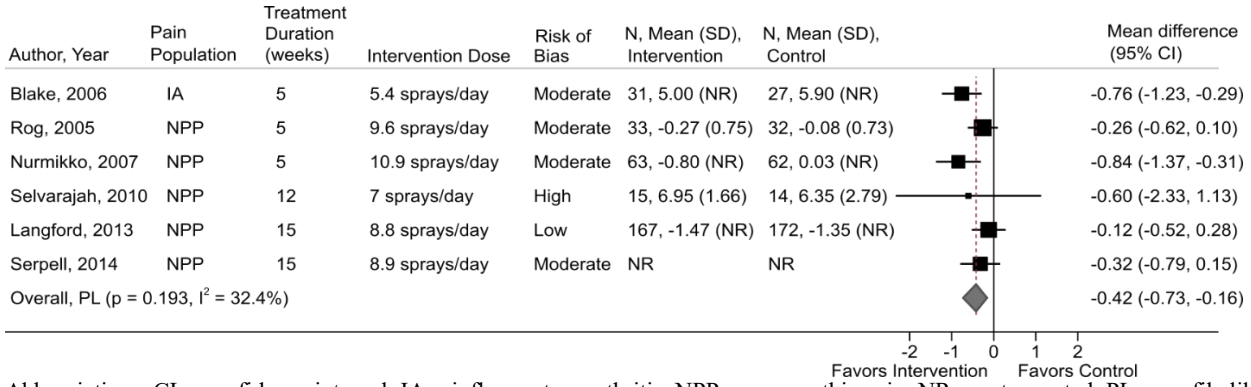
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation.

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)



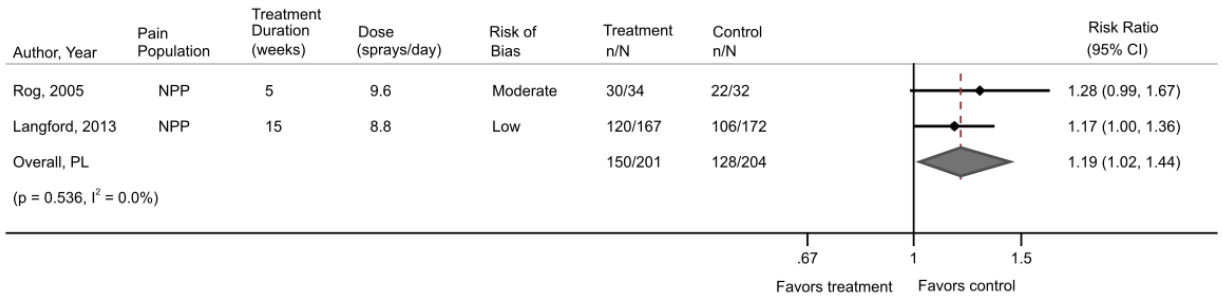
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood.

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



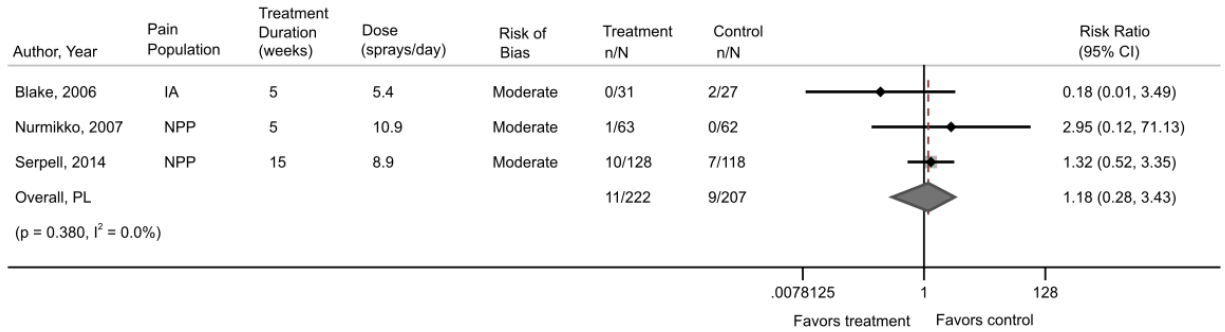
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation.

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



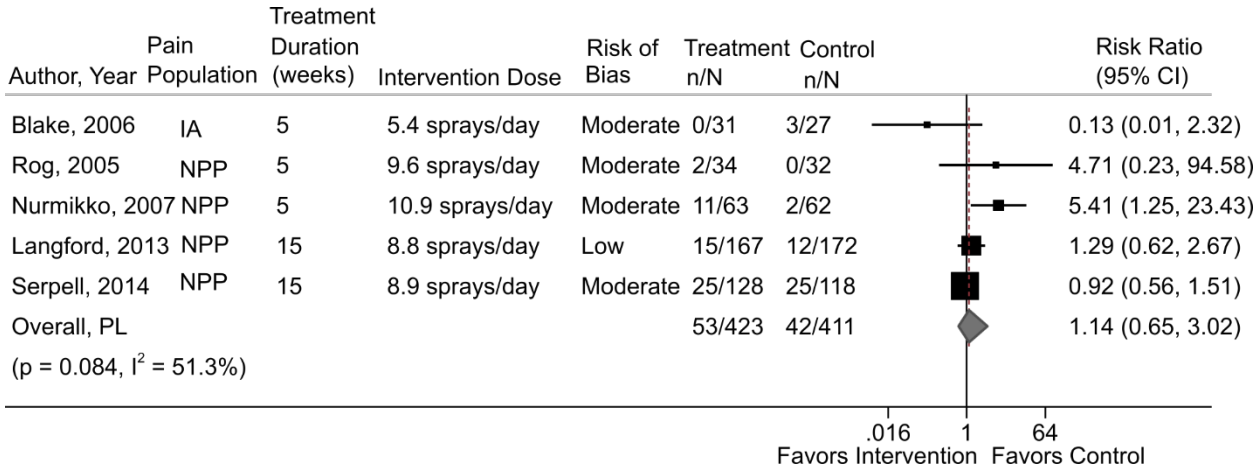
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile-likelihood.

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



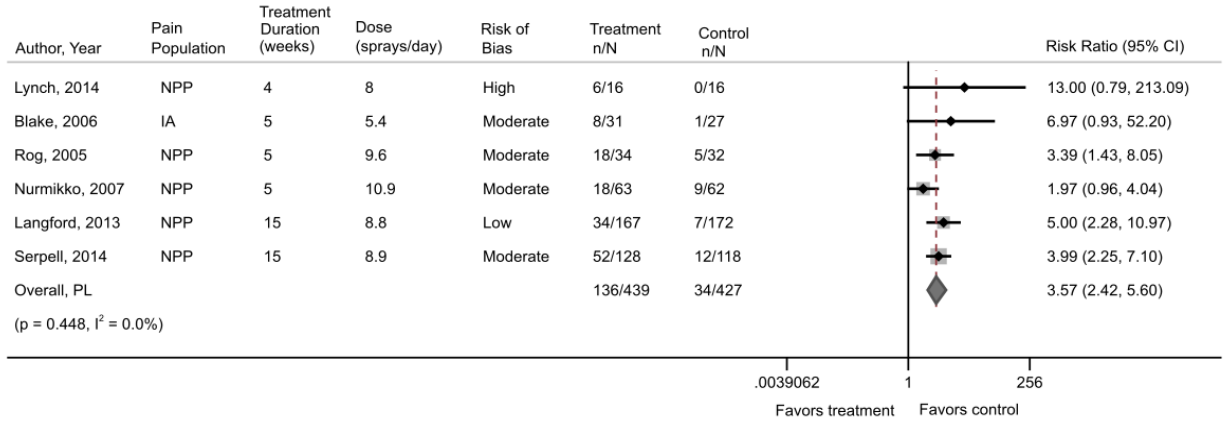
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile-likelihood.

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



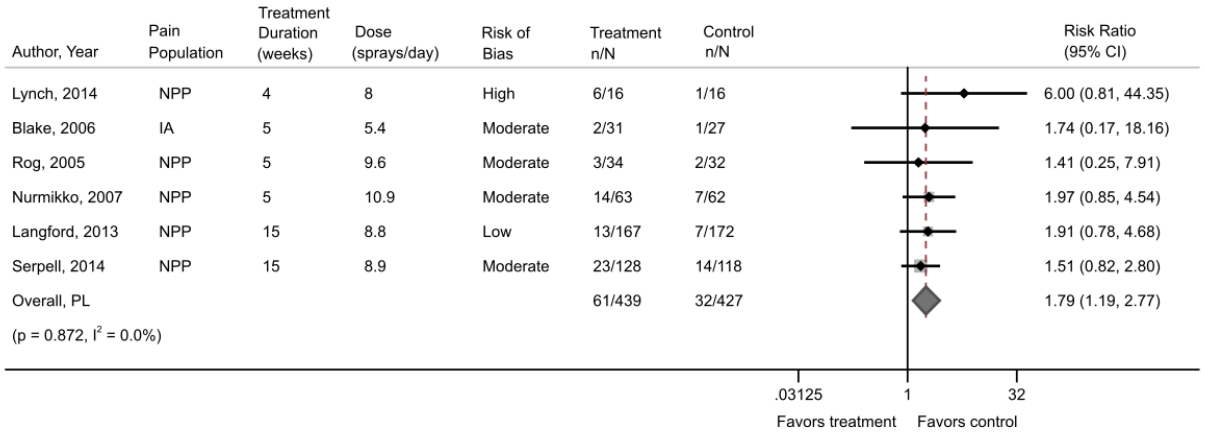
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile-likelihood.

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



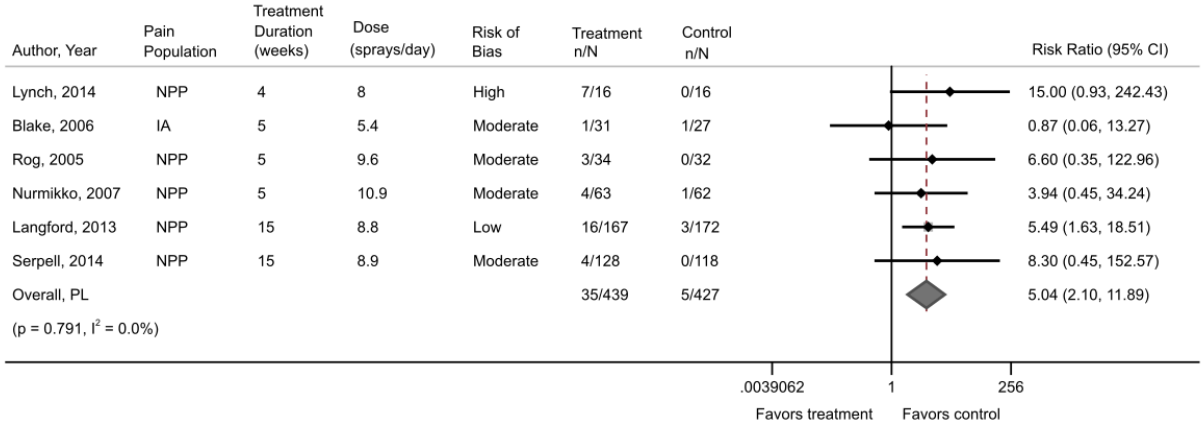
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood.

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; PL = profile likelihood.

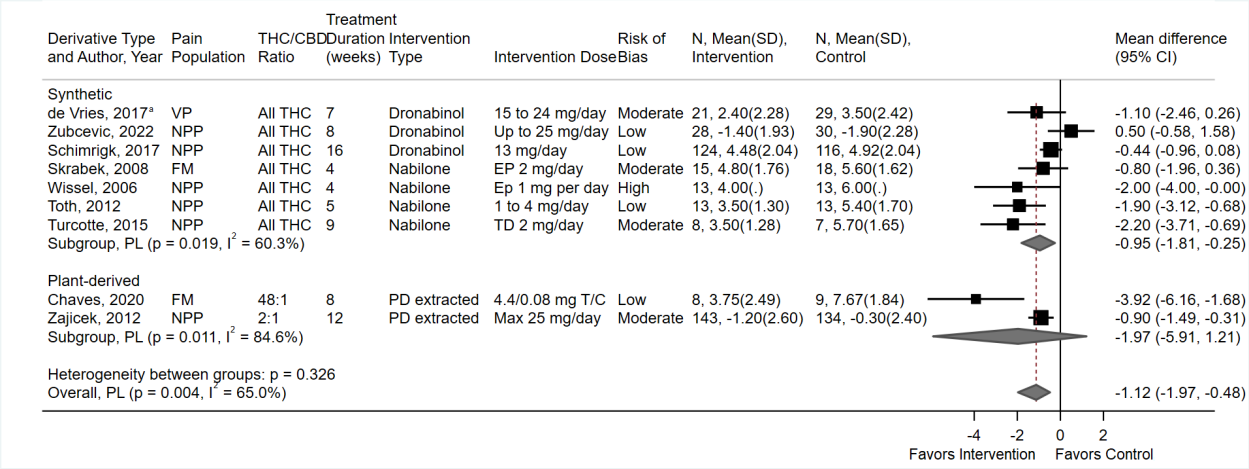
Figure E-9. Sedation for comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)



Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood.

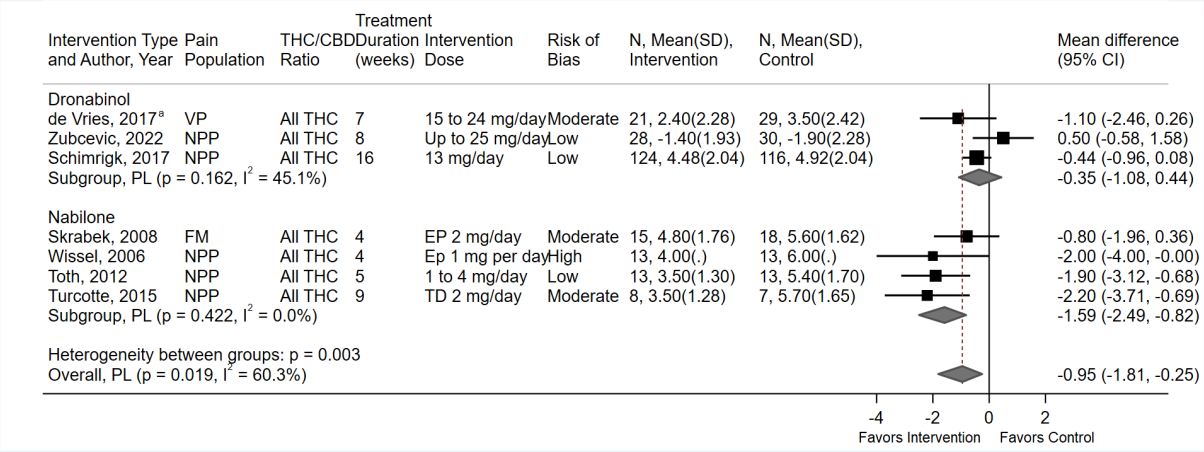
High THC to CBD Ratio Studies

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; NA = not applicable; NPP = neuropathic pain; PD = plant-derived; PL = profile likelihood; SD = standard deviation; TD = total dose; T/C = THC/CBD; THC = tetrahydrocannabinol; VP = visceral pain.
[a]Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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; NR = not reported; PL = profile likelihood; RCT = randomized controlled trials; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain.
[a]Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

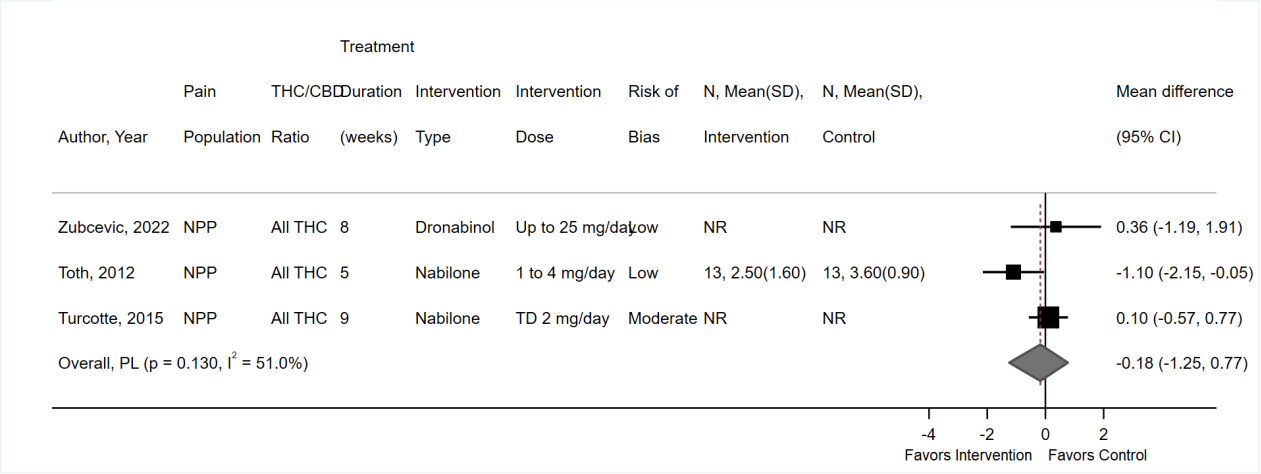
Table E-6. Interaction effect of RCTs assessing synthetic cannabinoids: nabilone versus dronabinol

Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−1.29	0.510	−2.53	0.053	−2.60 to 0.022

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

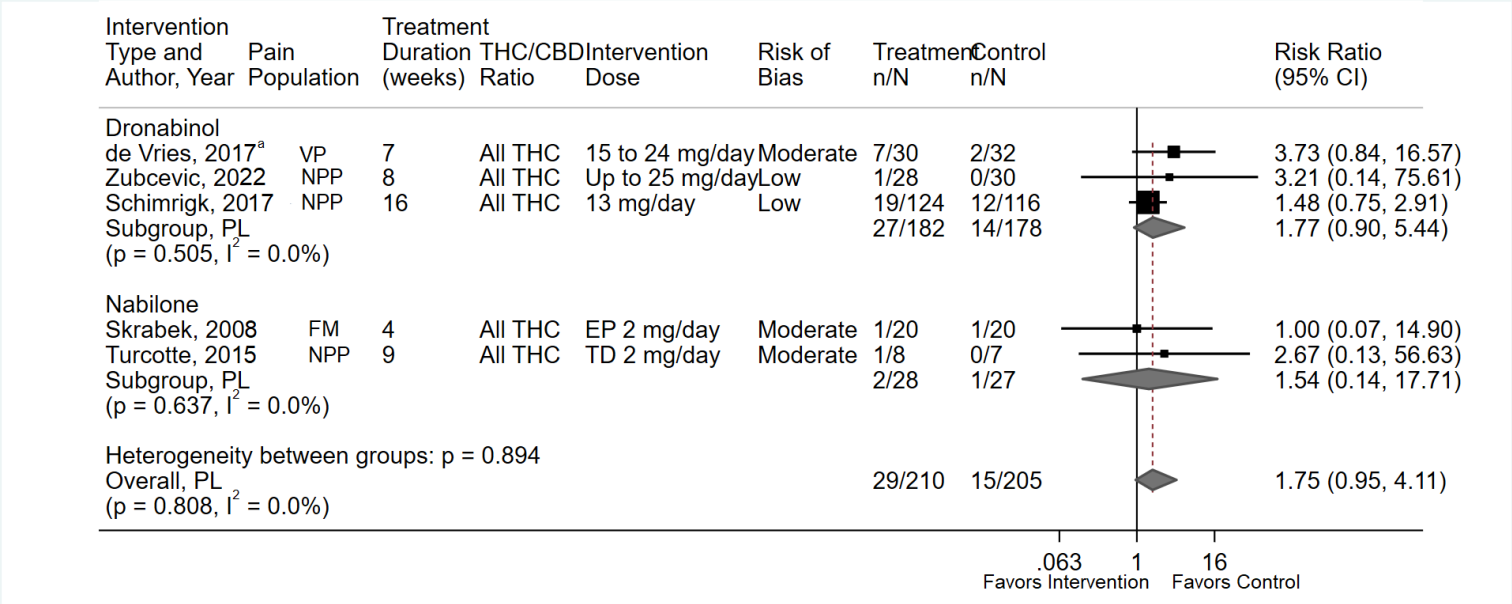
Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−0.986	0.85	−1.16	0.272	−2.87 to 0.90

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



Abbreviations: CBD = cannabidiol; CI = confidence interval; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol.

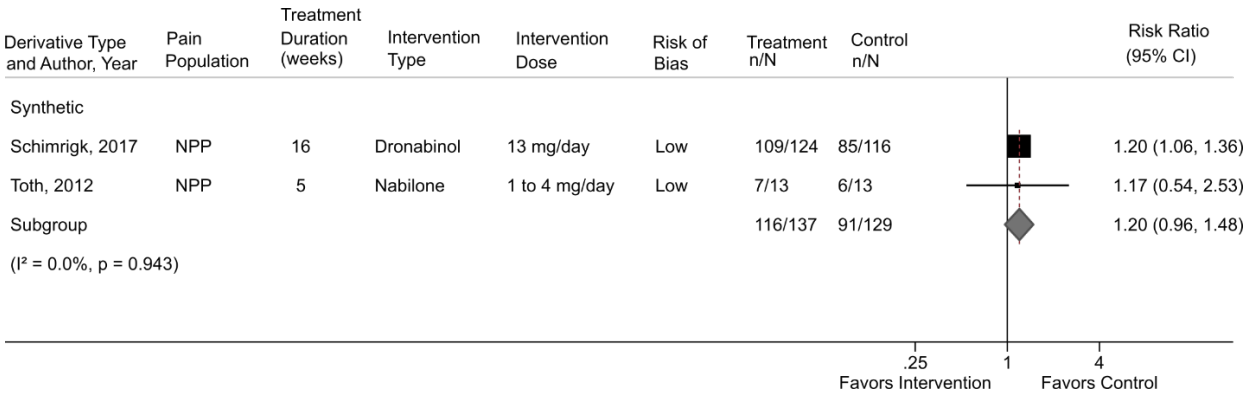
Figure E-13. Withdrawal due to adverse events for high THC versus placebo (short-term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NA = not applicable; NPP = neuropathic pain; PL = profile likelihood; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain.

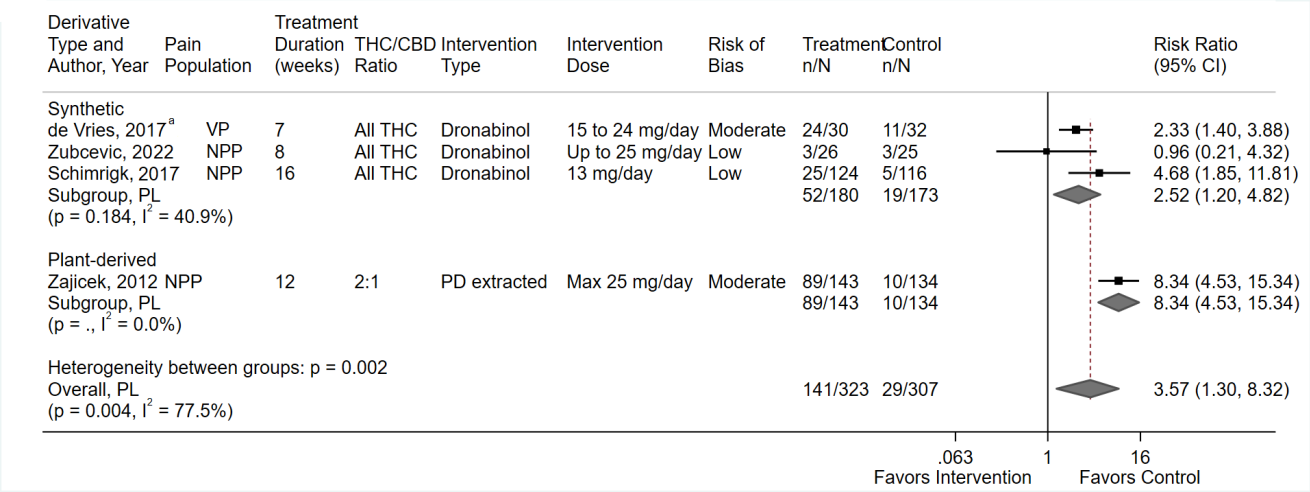
[a]Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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.

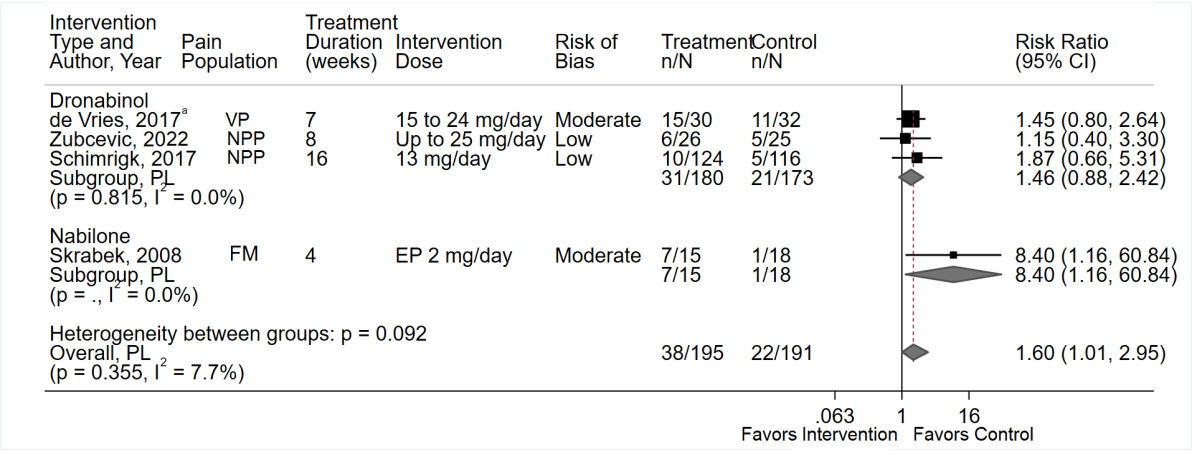
Figure E-15. Dizziness for high THC versus placebo (short-term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; NA = not applicable; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol; VP = visceral pain.

[a]Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

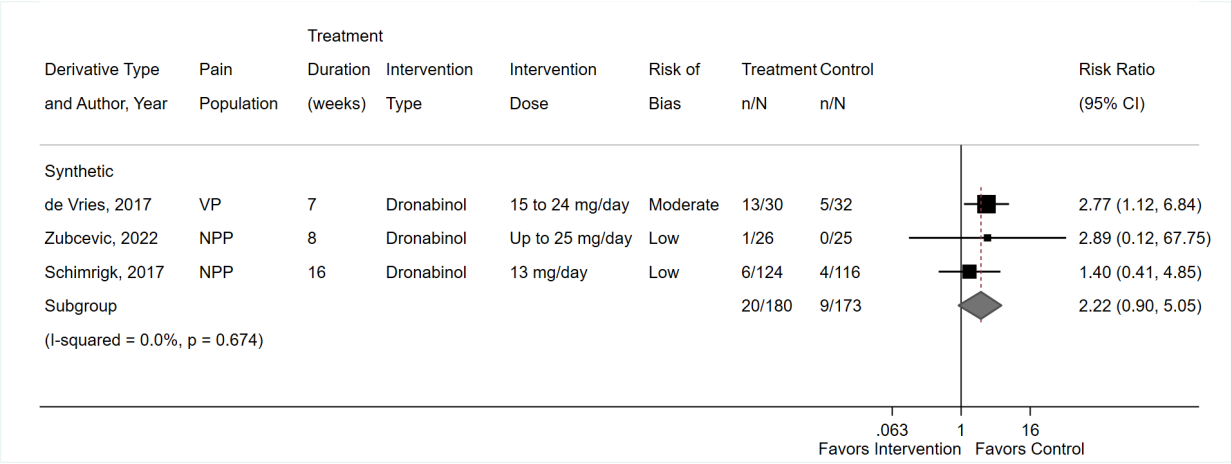
Figure E-16. Sedation for high THC versus placebo (short-term, 4 weeks to 6 months followup)



Abbreviations: CI = confidence interval; EP = end point; FM = fibromyalgia; NA = not applicable; NPP = neuropathic pain; PL = profile likelihood; VP = visceral pain.

[a]Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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.
[a]Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

Table E-8. Meta-analysis results and sensitivity analysis using the Bartlett's Correction

THC to CBD Ratio	Outcome	N; k Studies	Point Estimate	PL 95% CI	BC 95% CI	I-Squared
Comparable	Pain severity	N=702; k=7	MD −0.54	−0.95 to −0.19	−1.03 to −0.11	39%
Comparable	Pain response (≥30% improvement)	N=733; k=4	RR 1.18	0.93 to 1.71	0.67 to 2.43	36%
Comparable	Function	N=616; k=6	MD −0.42	−0.73 to −0.16	−0.80 to −0.10	32%
Comparable	Adverse events	N=405; k=2	RR 1.19	1.02 to 1.44	0.74 to 2.03	0%
Comparable	SAEs	N=427; k=3	RR 1.18	0.26 to 3.43	0.02 to 35.25	0%
Comparable	WAEs	N=834; k=5	RR 1.19	0.60 to 3.72	0.25 to 8.29	54%
Comparable	Dizziness	N=866; k=6	RR 3.57	2.42 to 5.60	2.15 to 6.62	0%
Comparable	Nausea	N=866; k=6	RR 1.79	1.19 to 2.77	1.06 to 3.32	0%
Comparable	Sedation	N=866; k=6	RR 5.04	2.10 to 11.89	1.41 to 17.29	0%
High	Pain severity	N=742; k=9	MD −1.12	−1.97 to −0.48	−2.08 to −0.40	65%
High (synthetic)	Pain severity	N=448; k=7	MD −0.95	−1.81 to −0.25	−1.95 to −0.13	60%

THC to CBD Ratio	Outcome	N; k Studies	Point Estimate	PL 95% CI	BC 95% CI	I-Squared
High (synthetic - dronabinol)	Pain severity	N=348; k=3	MD −0.35	−1.08 to 0.44	−2.21 to 1.54	45%
High (synthetic - nabilone)	Pain severity	N=100; k=4	MD −1.59	−2.49 to −0.82	−2.21 to −0.39	0%
High (plant-derived)	Pain severity	N=294; k=2	MD −1.97	−5.91 to 1.21	−11.33 to 6.53	85%
High	Function	N=unclear; k=3	MD −0.18	−1.25 to 0.77	−2.23 to 1.78	51%
High	WAEs	N=692; k=6	RR 2.21	1.27 to 4.14	0.96 to 5.58	0%
High (synthetic)	WAEs	N=415; k=5	RR 1.75	0.95 to 4.11	0.50 to 8.88	0%
High (synthetic - dronabinol)	WAEs	N=360; k=3	RR 1.77	0.90 to 5.44	0.25 to 24.91	0%
High (synthetic - nabilone)	WAEs	N=55; k=2	RR 1.54	0.14 to 17.71	0.01 to 280.12	0%
High	Any adverse event	N=266; k=2	RR 1.20	0.96 to 1.48	0.42 to 3.36	0%
High	Dizziness	N=637; k=4	RR 3.57	1.30 to 8.32	0.90 to 11.47	78%
High (synthetic)	Dizziness	N=360; k=3	RR 2.52	1.20 to 4.82	0.42 to 12.00	41%
High	Sedation	N=335; k=3	RR 1.73	1.03 to 4.63	0.44 to 15.71	28%
High (synthetic - dronabinol)	Sedation	N=360; k=3	RR 1.46	0.88 to 2.42	0.59 to 3.66	0%
High	Nausea	N=360; k=3	RR 2.22	0.90 to 5.05	0.40 to 11.80	0%

Abbreviations: BC = Bartlett's correction; CBD = cannabidiol; CI = confidence interval; MD = mean difference; PL = profile likelihood; RR = risk ratio; SAEs = serious adverse events; THC = tetrahydrocannabinol; WAEs = study withdrawals due to adverse events.

Appendix F. Evidence Tables

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

Appendix G. Risk of Bias Assessment

Shown in associated Excel files 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% vs. 31%, RR 1.18 (0.93 to 1.71); I^2=36%	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=40%) 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=32% (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=51%	Insufficient
Comparable THC to CBD Ratio vs. Placebo	SAEs	3 RCTs (N=429)[2,4,5]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 5.0% vs. 4.3%, RR 1.18 (0.28 to 3.43; I^2=0%)	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 = risk ratio; 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)	2 RCTs (N=84)[8,9]	Low	Direct	Very serious inconsistency	Imprecise	Unknown	Unable to assess, due to inconsistency from two trials (one trial of nabilone, 85% vs. 38%, RR 2.20 [1.06 to 4.55] and one trial of dronabinol, 43% vs. 57%, RR 0.76 [0.45 to 1.28])	Insufficient (previously low)
Synthetic THC vs. Placebo	Pain severity	7 RCTs (N=448)[8-14]	Moderate	Direct	Consistent	Imprecise	Unknown	Small effect with synthetic THC 0 to 10 scale, MD −0.95 (−1.81 to −0.25; I^2=60%)	Low
Synthetic THC vs. Placebo	Function/disability	3 RCTs (N=unclear)[8,9,13] 1 RCT (N=13) not Included in meta-analysis[14]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect (scale 0 to 10) MD: −0.18, −1.25 to 0.77, I^2=51%)	Low
Synthetic THC vs. Placebo	WAEs	5 RCTs (N=415)[9-13]	Moderate	Direct	Consistent	Imprecise	Unknown	Potential moderate effect, not statistically significant 14% vs. 7%, RR 1.75 (0.95 to 4.11; I^2=0%)	Low
Synthetic THC vs. Placebo	SAEs	1 RCT (N=240)[11]	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

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	Dizziness	3 RCTs (N=360)[9-11]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 29% vs. 11%, RR 2.52 (1.20 to 4.82; I^2=41%)	Moderate
Synthetic THC vs. Placebo	Nausea	3 RCTs (N=302)[9-11]	Low	Direct	Consistent	Imprecise	Unknown	Potential large effect with dronabinol, not statistically significant 11% vs. 5%, RR 2.22 (0.90 to 5.05; I^2=0%)	Low
Synthetic THC vs. Placebo	Sedation	4 RCTs (N=335)[9-12]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with dronabinol 19% vs. 12%, RR 1.60 (1.01 to 2.95; I^2=7.7%)	Low

Abbreviations: CBD = cannabidiol; CI = confidence interval; KQ = Key Question; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; 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 High THC vs. Placebo	Pain severity	2 RCTs (N=297)[15,16]	Moderate	Direct	Inconsistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD −1.97 (−5.91 to 1.21; I^2=85%)	Insufficient
	Function/disability	1 RCT (N=18)[16]	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)[15]	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)[15]	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)[15]	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 = risk ratio; 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	9 RCTs (N=742)[8-16]	Moderate	Direct	Consistent	Precise	Unknown	Moderate effect MD −1.12 (−1.97 to −0.48; I^2=65%)	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)[17]	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)[17]	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)[17]	High	Direct	Unknown	Imprecise	Unknown	No effect 13% vs. 19%, OR 0.64 (0.38 to 1.04)	Insufficient
	Dizziness	1 (N=431)[17]	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)[17]	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)[17]	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)[17]	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 = risk ratio; 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, Plant-Extracted CBD vs. Placebo	Pain severity (change)	1 RCT (N=29)[18]	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)[19]	Moderate	Direct	Unknown	Imprecise	Unknown	No effect with oral synthetic CBD RR 1.01 (0.66 to 1.55)	Insufficient
Oral CBD or THC/CBD (Unknown If Synthetic or Plant-extracted vs. Placebo[a]	Pain severity (change)	1 RCT (N=87)[9]	Low	Unclear	Unknown	Imprecise	Unknown	Potential increase in pain for CBD (MD 1.14 [0.11 to 2.19]) and no difference but imprecise for THC/CBD (MD -0.12 [-1.13 to 0.89])	Insufficient
	Pain response (≥30% improvement)	1 RCT (N=87)[9]	Low	Unclear	Unknown	Imprecise	Unknown	Imprecise estimates for CBD (RR 0.59 [0.32 to 1.09]) and THC/CBD (RR 1.06 [0.69 to 1.62])	Insufficient
	Function/disability	1 RCT (N=87)[9]	Low	Unclear	Unknown	Imprecise	Unknown	Imprecise estimates for CBD (MD 1.24 [-0.32 to 2.81]) and THC CBD (MD 0.89 [-0.64 to 2.42])	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

[a]Study did not report whether CBD was synthetic or plant-extracted, and did not provide any details about the product composition.

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)[20]	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)[20]	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 = risk ratio; SOE = strength of evidence.

Table H-8. KQ1 and 2: Observational studies of cannabinoids to treat chronic pain – unknown THC to CBD ratio (patient-choice)

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Unknown THC to CBD Ratio vs. Usual Care	Pain response (≥30% improvement from baseline)	No studies	NA	NA	NA	NA	NA	NA	No evidence
Unknown THC to CBD Ratio vs. Usual Care	Pain severity (change) Short-term (3 months)	2 cohort studies: short- to intermediate-term (N=202)[21,22]	High	Direct	Inconsistent	Imprecise	Unknown	VAS (0-100): 41.5 vs. 43.6 at 3 months[21] 34.1 vs. 48.8; mean difference −14.71 (95% CI, −32.71 to 3.29)[22]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Long-term (12 months)	1 cohort (N=1,514)[23]	High	Direct	Unknown	Precise	Unknown	Adjusted mean; BPI, 0-10 scale) 5.2 vs. 4.9; Beta: 0.37 (95% CI −0.23 to 1.10), p=0.20[23]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Function or Disability (SF-36 Physical Function)	2 cohorts = short to medium-term (N=202)[21,22]	High	Direct	Consistent	Imprecise	Unknown	SF-36 Physical Functioning (mean, 0 to 100 scale) 46.5 vs. 43.7 at 6 months[21] 70.0 vs. 69.4; MD 0.56 (95% CI −17.2 to 18.3) at 3 months[22]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	WAEs	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	6 months: 23% (12/52) vs. 9% (5/55), RR 2.54 (95% CI 0.95 to 6.71)	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	SAEs	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	None in any group	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + gabapentin vs. Gabapentin Alone)	Dizziness	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	3 months: 33% (17/52) vs. 29% (16/55), RR 1.12 (95% CI 0.64 to 1.98) 6 months: 39% (20/52) vs. 33% (18/55), RR 1.17 (95% CI 0.70 to 0.91)	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + gabapentin vs. Gabapentin Alone)	Nausea	No studies	NA	NA	NA	NA	NA	NA	No evidence
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	Sedation	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	3 months: 54% (28/52) vs. 33% (18/55) RR 1.65 (95% CI 1.04 to 2.59) 6 months: 60% (31/52) vs. 36% (20/55) RR 1.64 (95% CI 1.08 to 2.48)	Insufficient

Abbreviations: BPI-SF = Brief Pain Inventory (Short Form); CBD = cannabidiol; CI = confidence interval; KQ = Key Question; MD = mean difference; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Appendix H References

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Appendix I. Excluded Studies List

1. Vaporized Cannabis for chronic pain associated with Sickle Cell Disease. Cannabinoid-based therapy and approaches to quantify pain in Sickle Cell disease. 2013. **Exclusion Reason:** Ineligible publication type
2. Cannabis-opioid interaction in the treatment of Fibromyalgia pain â“ an open label proof of concept study with randomization between treatment groups: Cannabis, Oxycodone or Cannabis/Oxycodon combination. 2019. **Exclusion Reason:** Ineligible study design
3. Proof of concept trial of Cannabis derivatives in neuropathic pain. Proof of Concept Trial of Cannabis Derivatives in Neuropathic Pain. 2022. **Exclusion Reason:** Ineligible publication type
4. Topical CBD for musculoskeletal pain. Immediate effect of topical CBD for Musculoskeletal pain. 2022. **Exclusion Reason:** Ineligible population
5. Cannabinoids for the Reduction of Inflammation and Sickle Cell Related Pain. Dronabinol for the Reduction of Chronic Pain and Inflammation in People With Sickle Cell Disease. 2022. **Exclusion Reason:** Ineligible publication type
6. A Phase III study to investigate the effect of EMD-RX5 on symptoms of psychological distress in adults with chronic pain. A multi-site, parallel-arm, randomised, double blind, placebo-controlled study to investigate the effect of EMD-RX5 on symptoms of psychological distress in adults with chronic pain. 2022. **Exclusion Reason:** Ineligible publication type
7. Comparison of VER-01 to Opioids in Patients With Chronic Non-specific Low Back Pain. Multicentre, Randomized, Open-label Study to Prove an Additional Benefit of the Full-spectrum Cannabis Extract VER-01 Over Opioids in the Treatment of Patients With Chronic Non-specific Low Back Pain. 2022. **Exclusion Reason:** Ineligible publication type
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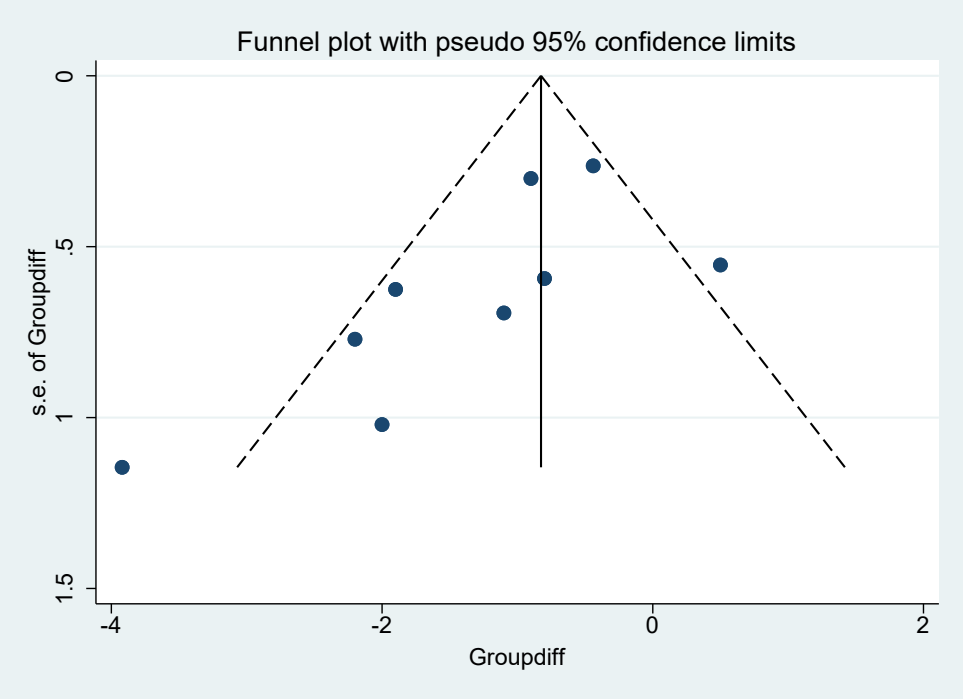
Appendix J. Funnel Plot of High THC Ratio Studies Included in Meta-Analysis for Pain Severity

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



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