Comparative Effectiveness Review

Number 250

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2024 Update

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

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Preface

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

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

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

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Technical Expert Panel

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

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

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

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Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2024 Update

Structured Abstract

Objectives. To update the evidence on benefits and harms of cannabinoids and other plant-based compounds to treat subacute and chronic pain in adults and adolescents using a living systematic review approach.

Data sources. Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases, and reference lists of included studies were searched to June 30, 2024.

Review methods. We grouped studies based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio and by product type: *synthetic, purified (plant-derived product consisting of a single cannabinoid, e.g. dronabinol or CBD), or extracted (from whole plant, containing multiple cannabinoids)*. We conducted random effects meta-analyses and categorized magnitude of benefit (large, moderate, small, or no effect [less than small]).

Results. Three new randomized controlled trials (RCTs) in four publications (n=134, 86, and 60) and two new observational studies (N=296 and 32,332) were added for this annual update; no study addressed subacute pain or adolescents. One new RCT compared high THC, low THC, and combination THC to CBD ratio products versus placebo in patients with neuropathic pain; one new RCT evaluated oral CBD plus paracetamol versus paracetamol alone for knee osteoarthritis; and one new RCT evaluated a topical (intraoral) THC to CBD product versus placebo for temporomandibular disorders. Since the inception of this living review, from 5,894 total abstracts identified, 26 RCTs (in 27 publications) (N=2,315) and 12 observational studies (N=48,468) assessing different cannabinoids have been included; no study evaluated kratom. Studies were primarily short term, and 53 percent enrolled patients with neuropathic pain. Comparators were primarily placebo or usual care. Strength of evidence (SOE) was low unless indicated otherwise.

Compared with placebo, extracted, comparable ratio THC to CBD oral spray was associated with a small decrease in pain severity (7 RCTs, N=878, 0 to 10 scale, mean difference [MD] −0.54, 95% confidence interval [CI] −0.95 to −0.19, I^2=39%; SOE: moderate); improvement in overall function favored the cannabis product but was slightly below the threshold for small (negative values for function indicate improved function; 6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI −0.73 to −0.16, I^2=32%; SOE: moderate) versus placebo. There was no effect on study withdrawals due to adverse events (WAEs). There was a large increased risk of dizziness and sedation, and a moderate increased risk of nausea (dizziness: 6 RCTs, N=866, relative risk [RR] 3.57, 95% CI 2.42 to 5.60, I^2=0%; sedation: 6 RCTs, N=866, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%; and nausea: 6 RCTs, N=866, RR 1.79, 95% CI 1.19 to 2.77, I^2=0%).

Synthetic and purified high THC to CBD ratio products were associated with a small improvement in pain severity, with no effect on overall function or disability. There was a moderate increase in risk of WAEs, a moderate increase in sedation, and a large increase in risk of nausea (pain: 8 RCTs, N=507, 0 to 10 scale, MD −0.78, 95% CI −1.59 to −0.08, I^2=64%;

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WAEs: 6 RCTs, N=487, RR 1.92, 95% CI 1.10 to 4.80, I^2=0%; sedation: 5 RCTs, N=458, RR 1.57, 95% CI 1.11 to 2.29, I^2=0%; nausea: 4 RCTs, N=425, RR 2.12, 95% CI 1.09 to 3.96; I^2=0%). There was also moderate SOE for a large increased risk of dizziness (4 RCTs, N=425, RR 2.30, 95% CI 1.53 to 3.52, I^2=22%).

Synthetic or purified oral CBD alone was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale, MD 0.40, 95% CI −0.14 to 1.00, I^2=20%; SOE: moderate), greater likelihood of pain response (4 RCTs, N=334, RR 0.84, 95% CI 0.62 to 1.10; I^2=0%; SOE: moderate), or improved function (3 RCTs, N=272, standardized mean difference [SMD] 0.11, 95% CI −0.14 to 0.41, I^2=0%; SOE: moderate) versus placebo, and combined oral THC plus CBD (~1:2 ratio) was not associated with decreased pain intensity (2 RCTs, N=123, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I^2=0%), greater likelihood of experiencing ≥30 percent improvement in pain (2 RCTs, N=123, RR 1.07, 95% CI 0.73 to 1.57, I^2=0%), or improved function (1 RCT, n=60, SMD 0.29, 95% CI −0.21 to 0.80) versus placebo.

Evidence (including observational studies) on whole-plant cannabis, topical CBD, other cannabinoids, comparisons with active noncannabis treatments or between cannabis-related products, and impact on use of opioids remained insufficient. Evidence was not available on important harms such as psychosis, cannabis use disorder, and cognitive effects.

Conclusions. Low- to moderate-strength evidence suggests small improvements in pain (mostly neuropathic), and moderate to large increases in common adverse events (dizziness, sedation, nausea) with extracted, comparable THC to CBD ratio and synthetic or purified high THC to CBD ratio products versus placebo during short-term treatment (1 to 6 months). Low- to moderate-strength evidence suggests that low THC to CBD ratio products may not be associated with improved outcomes versus placebo. Evidence for whole-plant cannabis and other comparisons, outcomes, and plant-based compounds was unavailable or insufficient to draw conclusions.

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Executive Summary

Main Points

This is the third annual update of a living systematic review addressing the effectiveness and harms of plant-based treatments for chronic and subacute pain in adults and adolescents. The first systematic review was published in October of 2021, and the first and second updates were published in September of 2022 and August of 2023, respectively. As this review is "living," it uses methods to identify and synthesize recently published literature and adapt its scope on an ongoing basis. Included plant-based compounds are those that have potential analgesic effects as well as the potential for addiction, misuse, and serious adverse effects.

Studies of cannabis-related products were grouped based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio using the following categories: comparable THC to CBD, high THC to CBD (including THC only), and low THC to CBD (including CBD only). Since the second annual update of the systematic review published in August 2023, three new placebo-controlled randomized controlled trials (RCTs) in four publications and two new observational studies were added, for a total of 26 RCTs (in 27 publications) and 12 observational studies. One of the new RCTs evaluated oral purified THC (dronabinol), synthetic CBD, or both; one new RCT evaluated purified CBD; and one new RCT evaluated topical (intraoral) CBD (unclear if synthetic or plant-derived). The new observational studies evaluated various (low, comparable, or high THC to CBD ratio) products. In patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months):

- Extracted, comparable THC to CBD ratio oral spray is probably associated with small improvements in pain severity (strength of evidence [SOE]: moderate) and overall function versus placebo (SOE: moderate). There may be no increase in risk of serious adverse events (SAEs) (SOE: low) or withdrawal due to adverse events (WAEs) (SOE: low). There may be a large increased risk of dizziness and sedation (SOE: low) and a moderate increased risk of nausea (SOE: low).
- Synthetic and purified THC (high THC to CBD) may be associated with small improvement in pain severity (SOE: low), but with increased risk of WAEs (SOE: low), sedation (SOE: low), and nausea (SOE: low) versus placebo. Synthetic and purified THC is probably associated with a large increased risk of dizziness (SOE: moderate).
- Low THC to CBD ratio oral products (synthetic or purified CBD alone, or combined purified THC plus synthetic CBD in ratio ~1:2) may not be associated with improved pain and function versus placebo (SOE: moderate for CBD alone and low for THC/CBD). THC plus CBD is probably associated with large increased risk of nausea (SOE: moderate).
- 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.
- We did not identify any evidence on other plant-based compounds such as kratom that met criteria for this review.

Background and Purpose

Cannabinoids are a group of compounds that are active in cannabis; the two main cannabinoid are THC and CBD. THC has demonstrated analgesic properties,[1,2] although its

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psychoactive effects and the potential for development of use disorder may limit its suitability as an analgesic. It may also be associated with serious harms, including those related to potential for use disorder or physiological withdrawal. The purpose of the systematic review is to evaluate the evidence on benefits and harms of cannabinoids and similar plant-based substances (e.g., kratom) to treat chronic or subacute pain on an ongoing basis. This report updates the original 2021 systematic review on cannabis and other plant-based treatments for chronic pain in adults.[3] In the 2023 update, the scope was expanded to include subacute pain and adolescents. Using a living review approach, the literature continues to be monitored quarterly for new studies, and the systematic review may be updated annually.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Effective Health Care Program Methods Guide (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), as described in the full report. Searches for this update covered publication dates from database inception to June 30, 2024. The original review focused on adults with chronic pain.[4] With input from a Technical Expert Panel, the scope in the 2023 update was expanded to include adolescents and subacute pain. We included RCTs and comparative observational studies with a minimum of 4 weeks duration that assessed cannabinoids or kratom for noncancer chronic and subacute pain. Cannabinoids were categorized according to their THC to CBD ratio (comparable, high, low) and type (whole-plant [included extracted or purified products] or synthetic). Strength of evidence was assessed as low, moderate, high, or insufficient, and magnitude of effect was assessed according to Table ES-1. Estimates that were below the threshold for a small effect were categorized as "no effect."[5,6]

Table ES-1. Definitions of effect sizes

Effect Size	Definition
No effect/trivial effect	• Below thresholds for small effect
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.
Note: For pain and function, negative values for MD indicate improved outcomes; for other outcomes, positive values for MD indicate improved outcomes.

Results

The included RCTs are described in Table ES-2 and the included observational studies are described in Table ES-3. There were five new studies in six publications added since the prior annual update. One new RCT in two publications (n=134) compared plant-derived synthetic equivalent THC (dronabinol; high THC to CBD ratio), synthetic CBD (low THC to CBD ratio), or both (low THC to CBD ratio) versus placebo for neuropathic pain;[7,8] one new RCT (n=86) evaluated a plant-derived CBD (low THC to CBD ratio) versus placebo for knee osteoarthritis;[9] and one new RCT (n=60)

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evaluated topical (intraoral) CBD (unclear if synthetic or plant-derived) for temporomandibular pain.[10] Both of the new observational studies (n=296 and n=32,332)[11,12] included patients with various chronic pain conditions and evaluated low, comparable, or high THC to CBD ratio cannabis products; one of the studies[12] (n=32,332) focused on the association between cannabis use and on risk of arrhythmia and acute coronary syndrome. Evidence added for this update enabled a new meta-analysis which found that low THC to CBD ratio products (CBD alone or the combination of THC and CBD in a 1:2 ratio) were not associated with improvement in pain or function versus placebo, but some imprecision was present. For synthetic and purified THC (high THC to CBD ratio) versus placebo, updated meta-analyses changed pooled estimates for nausea (large increase in risk) and WAEs (moderate increase in risk) from nonstatistically significant to statistically significant; however, the SOE for these outcomes remained low. For other comparisons and outcomes, the new studies did not change main findings.

Table ES-2. Characteristics of included randomized controlled trials of cannabinoids

Characteristic	THC/CBD	THC	CBD	CBDV
THC to CBD Ratio	Comparable[a]	High	Low	NA - other cannabinoids
Source	Extracted	Synthetic Purified Extracted	Synthetic Purified Extracted Unclear	Extracted
N Studies	7	13[b]	7[b] (1 topical, 1 sublingual, 4 oral, 1 unclear)	1
Comparator (Study Count)	Placebo (7)	Placebo (10); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low THC to CBD ratio (CBD or purified THC/CBD) (2)	Placebo (7); Dronabinol (2); Low THC to CBD ratio (CBD or purified THC/CBD (2); ≥97% purified low THC to CBD (1:6) sublingual oil (1); 5% or 10% CBD gel (unclear if synthetic or plant-based) (1)	Placebo
Route of Administration, Formulation (Study Count)	Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl	Dronabinol 3 mg oral tablet (1); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Purified dronabinol oral 2.5 mg capsule (2); Oral capsule, 2.5 mg purified THC/0.8 – 1.8 mg CBD extract (1); Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)	Oral capsule, 5 mg synthetic CBD (2); Oral tablet, 10 mg synthetic CBD (1); Oral capsule, 200 mg purified CBD (1); Oral capsule, 5 mg CBD extract/2.5 mg dronabinol (2); Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1); Topical cream, 83 mg CBD/fluid ounce (1) 5% or 10% CBD gel, unclear if local or systemic (1)	Oral oil, 50 mg/ml CBDV

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Characteristic	THC/CBD	THC	CBD	CBDV
Dosing Regimen	Final mean dose 23 mg THC/21 mg CBD daily.	Dronabinol capsules: 2.5 to 5 mg, titrated. Final dose range 13 - 25 mg/day Dronabinol (Namisol®[a]) tablet: 3 to 8 mg 3 times daily, titrated. Final dose NR Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Capsule: 2.5 -12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily	Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 45 to 50 mg CBD daily (2) Oral tablet: 10 mg daily, titrated (max 3 times daily) Final dose NR Oral CBD capsule: 200 mg 3 times daily. Final dose 600 mg/day Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 12.5 to 15 mg THC/30 to 45 mg CBD daily (2) Sublingual oil, titrated to max daily dose of 6 drops 3 times daily (15 mg THC/90 mg CBD) Topical cream: applied locally 1-4 times/day (volume/dose, final dose NR) CBD gel: 20 mg of 5% or 10% gel applied on each side, total dose 20-40 mg daily	400 mg CBDV daily. Final dose NR.
Risk of Bias	29% high, 57% moderate, 14% low	8% high, 46% moderate, 46% low	43% high, 43% moderate, 14% low	100% moderate
Total Randomized	882	1,028	568	34
Age, Mean Years	53	54	54	50
Female, %	66%	62%	60%	3%
Non-White,[c] %	1.6% (2)	5.3% (4)	NR	NR
Primary Pain Type (Study Count)	NPP (6); Inflammatory arthritis (1)	NPP (9); Fibromyalgia (2); Visceral pain (1); Headache (1);	NPP (3); MS (1); OA (2); Temporomandibular (1); Unspecified (1)	NPP (1)
Baseline Pain Score, Mean (Range)[d]	6.59 (5.3 to 7.3)	6.75 (4.00 to 8.67)[e]	6.01 (4.67 to 7.4)[f]	6.28 (6.12 to 6.44)
Study Duration	4 to 15 weeks	4 to 47 weeks	4 to 16 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 nabiximols.

[b] Two trials are included in both the THC and CBD columns, as they compared THC to CBD, CBD/THC, and placebo.

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

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

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

[f] Weighted mean includes median scores for 1 study (5.2 vs. 6.1).

Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

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Table ES-3. Characteristics of included observational studies of cannabinoids

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
THC to CBD Ratio	Unclear or mixed	High	High	Comparable vs. high	Comparable
Source	Any cannabis product (patient's choice) or mixed cannabinoids	Extracted	Synthetic (nabilone)	Extracted vs. synthetic	Extracted
N Studies	8[b]	1	1	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (2); other cannabinoids (2)	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) (6); inhaled or oral prescribed cannabis (2)	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 (7) Final median dose 85 mg CBD vs. 7.8/20 mg THC/CBD vs. 20/25 mg THC/CBD vs. 42 mg THC/day (1)	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	50% high, 50% moderate	100% high	100% moderate	100% moderate	100% moderate
N Total	45,897	431	156	674	1,310
Age, Mean Years	54	49	61	46	51
Female, %	52%	57%	59%	57%	57%
% Non-White (Study Count)	54% (1); NR (7)	NR	NR	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic noncancer pain	Chronic noncancer pain	NPP	Peripheral NPP	Peripheral neuropathic back pain
Baseline Pain Score, Mean (Range)[c]	5.75 (4.56 to 7.00)	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 two new studies for this review.

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

Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

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Tables ES-4 and ES-5 summarize the findings of the review. Other prioritized adverse events (cannabis use disorder [CUD], psychosis, cognitive deficits) and the impact on the use of opioids for chronic pain, were not reported in the RCTs.

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

Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD - Extracted, Oromucosal Spray	Potential effect (4)[b] [✓]	Small effect (7) [✓✓]	No effect[c] (6) [✓✓]
High THC – Synthetic or Purified, Oral	Insufficient (3, 1 new)	Small effect (8, 1 new) [✓]	No effect (3) [✓]
High THC – Extracted, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Extracted CBD, Topical	No evidence	Insufficient (1)	No evidence
Low THC – Synthetic or Purified, Oral[d]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (3, 1 new)[e]** [✓✓]
Low THC – Synthetic CBD Plus Purified THC, Oral[f]	**No effect (2, 1 new)[e]** [✓]	**No effect (2, 1 new)[e]** [✓]	**No effect (1)** [✓]
Low THC – Sublingual CBD/THC, Extracted	No evidence	Insufficient (1)	No evidence
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	**Insufficient (1 new)**	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[g]	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] ≥30% improvement from baseline
[b] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[c] The pooled difference of -0.42 (95% CI -0.73 to -0.16) was just below the threshold for a small effect.
[d] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.
[e] Text is bolded to indicate that the strength of evidence has changed.
[f] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.
[g] Comparison was "usual care."
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 ES-5. 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, Oromucosal Spray	No effect (5) [✓]	No effect (3) [✓]	Large effect (6) [✓]	Moderate effect (6) [✓]	Large effect (6) [✓]
High THC – Synthetic or Purified, Oral	Moderate effect[a] (6, 1 new) [✓]	Insufficient (2, 1 new)	Large effect (4, 1 new) [✓✓]	Large effect[a] (4, 1 new) [✓]	Moderate effect (5, 1 new) [✓]

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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]
High THC – Extracted, Oral	Large effect (1) [✓]	Insufficient (1)	Large effect (1) [✓]	No evidence	No evidence
Low THC – Extracted CBD, Topical	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Synthetic or Purified CBD, Oral[b]	Insufficient (4, 2 new)	Insufficient (2, 1 new)	**No effect (3, 2 new)[c]** [✓]	**Insufficient (2 new)[c]**	**No effect (3, 2 new)[c]** [✓]
Low THC – Synthetic CBD plus Purified THC, Oral[d]	**Insufficient (2, 1 new)**	**Insufficient (2, 1 new)**	**Potential effect (2, 1 new)[c]** [✓]	**Large effect (2, 1 new)** [✓✓]	**Potential effect (2, 1 new)[c]** [✓]
Low THC – Sublingual CBD/THC, Extracted	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC)[e]	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] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.

[c] Text is bolded to indicate that the strength of evidence has changed.

[d] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.

[e] Comparison was "usual care."

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.

Limitations

Key limitations of the evidence base relate to the limited ability to provide strong, reliable, estimates of effect due to: (1) inadequate sample sizes or numbers of studies, (2) narrowness of enrolled populations (primarily chronic neuropathic pain, with mean age 54 years; see Tables ES-2 and ES-3) with no evidence on subacute pain or adolescents, (3) lack of evidence or inadequate evidence on extracted high THC to CBD products, whole-plant cannabis products, and extracted or nonoral low THC to CBD products; comparisons with other active interventions or different cannabis-related products; and other plant-based compounds including kratom, and (4) inconsistent reporting of important outcomes such as dosage, pain response, overall function or disability, effect on opioid use, and longer-term adverse events, such as CUD, psychosis, and cognitive deficits. In addition, generalizability of findings may be reduced in specific settings

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due to the unavailability or unclear availability of studied cannabis products. These limitations affect both the stability and applicability of the findings.

Implications and Conclusions

Select individuals with chronic neuropathic pain may experience small short-term improvements in pain with some cannabis products, but the impact on moderate or long-term outcomes is unknown. Improvement in pain intensity was small with high and comparable THC to CBD ratio products, though there was insufficient evidence to determine effects on likelihood of a pain response (e.g., ≥30% improvement in pain). Compared with placebo, these interventions resulted in greater risk of common adverse events (dizziness, nausea, sedation); high THC to CBD products were also associated with increased risk of study WAEs. Low THC to CBD products, including CBD alone, were not associated with improved pain or function. Evidence for other interventions, including kratom, was insufficient or not found. As the strength of this evidence was mostly low, more data are needed to confidently recommend cannabis as a treatment for various chronic pain-related conditions, for specific cannabis products (e.g., whole plant cannabis), and for patients with diverse demographic or clinical characteristics. Recommendations for future research include studies evaluating appropriately representative and diverse populations (including adolescents), studies evaluating specific cannabis-based products available in the United States, studies on long-term outcomes, studies on nonneuropathic chronic pain, studies comparing effects of cannabis-based products versus other treatments for chronic pain, head-to-head studies of different cannabis products, and studies on subacute pain.

References

1. Elikkottil J, Gupta P, Gupta K. The analgesic potential of cannabinoids. J Opioid Manag. 2009 Nov-Dec;5(6):341-57. doi: 10.5055/jom.2009.0034. PMID: 20073408.
2. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73. doi: 10.1001/jama.2015.6358. PMID: 26103030.
3. McDonagh M, Wagner J, Ahmed A, et al. Living systematic review on cannabis and other plant-based treatments for chronic pain. Comparative effectiveness review no. 250. (Prepared by Pacific Northwest Evidence-based Practice Center under contract no. 75Q80120D00006.). AHRQ Publication No. 21(22)-EHC036. 2021 Oct Rockville, MD: Agency for Healthcare Research and Quality. doi: 10.23970/AHRQEPCCER250.
4. Agency for Healthcare Research and Quality. Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain Research Protocol. 2020. https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/protocol. Accessed Nov 28 2022.
5. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283-93. doi: 10.1016/j.jclinepi.2011.01.012. PMID: 21839614.
6. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2 Suppl):53s-70s. doi: 10.1378/chest.11-2288. PMID: 22315256.

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7. Hansen JS, Gustavsen S, Roshanisefat H, et al. Cannabis-based medicine for neuropathic pain and spasticity—A multicenter, randomized, double-blinded, placebo-controlled trial. Pharmaceuticals (Basel). 2023a;16(8):1079. doi: 10.3390/ph16081079. PMID: 37630995.

8. Hansen JS, Boix F, Hasselstrom JB, et al. Pharmacokinetics and pharmacodynamics of cannabis-based medicine in a patient population included in a randomized, placebo-controlled, clinical trial. Clin Transl Sci. 2023b;06:06. doi: https://dx.doi.org/10.1111/cts.13685. PMID: 38054364.

9. Pramhas S, Thalhammer T, Terner S, et al. Oral cannabidiol (CBD) as add-on to paracetamol for painful chronic osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Lancet Reg Health Eur. 2023;35doi: 10.1016/j.lanepe.2023.100777. PMID: 38033459.

10. Walczyńska-Dragon K, Kurek-Górecka A, Niemczyk W, et al. Cannabidiol Intervention for Muscular Tension, Pain, and Sleep Bruxism Intensity—A Randomized, Double-Blind Clinical Trial. J Clin Med. 2024;13(5)doi: 10.3390/jcm13051417.

11. Schubert EA, Johnstone MT, Benson MJ, et al. Medicinal cannabis for Australian patients with chronic refractory pain including arthritis. Br J Pain. 2023;17(2):206-17. doi: 10.1177/20494637221147115. PMID: 37057257.

12. Holt A, Nouhravesh N, Strange JE, et al. Cannabis for chronic pain: cardiovascular safety in a nationwide Danish study. European Heart Journal. 2024. doi: 10.1093/eurheartj/ehad834. PMID: 38200679.

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1. Introduction

1.1 Background

Chronic pain, defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,[1,2] is a serious public health issue in the United States, affecting approximately 100 million people[3] and resulting in over $560 billion annually in costs.[4] Chronic pain substantially impacts physical and mental functioning, reducing productivity and quality of life. It is the leading cause of disability and is often refractory to treatment.[5,6] Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015;[7] although opioid prescribing rates have declined since 2016, they remain substantially higher than pre-1999 levels.[8] The increase in opioid prescribing was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[7,9,10] involving prescription opioids. From 1999 to 2021, approximately 280,000 people died from overdoses related to prescription opioids in the United States, with an estimated 14,716 prescription opioid overdose deaths in 2022.[11] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[12]

While opioids are often prescribed for chronic pain, they are associated with small to moderate effects on pain and overall function and frequent adverse effects.[13] The 2022 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends nonopioid therapy as preferred treatment for chronic pain.[14] Recent systematic reviews found that several nonopioid drugs,[15] and some nonpharmacologic treatments,[16] also have small to moderate effects on chronic pain and overall function. Some nonopioid pharmacological treatments had frequent overall adverse events and some less frequent but serious adverse effects, while nonpharmacological treatments typically reported few adverse events.[15]

The challenges of treating chronic pain in light of the limited benefits of commonly prescribed prescription medications and potential harms of opioids have catalyzed a search for alternative pain treatments, including cannabis. Ideally, alternative treatments would have equal or better benefits for pain while avoiding potential unintended consequences that could result in harms. Plants have historically been evaluated for medicinal properties, with some being developed into drug therapies (i.e., the field of pharmacognosy). Some preclinical data suggest that cannabinoids may have analgesic properties, though research in this area is mixed.[17] Tetrahydrocannabinol (THC), one of over 140 cannabinoids in cannabis,[18] has demonstrated analgesic properties,[19,20] though its psychoactive effects and the potential for development of use disorder may increase its risk and lessen its suitability as an analgesic. Other cannabinoids (e.g., cannabidiol [CBD], cannabigerol [CBG], and cannabichromene [CBC]) may also have some analgesic or anti-inflammatory properties and are not thought to be intoxicating or addictive,[21,22] but may not be as potent as THC. Observational studies indicate that some patients use cannabis and related compounds as a substitute for opioids.[23-26]

Other plant-based compounds (PBCs) such as kratom, though pharmacologically distinct from cannabis, may be considered as analgesics, in part due to use in the community as substitutes for opioids.[27,28] They may also have serious harms, such as dependence, addiction, and physiological withdrawal potential.[29] Although some PBCs thought to reduce pain are currently classified as Schedule I by the Drug Enforcement Administration, there is disagreement on scheduling others, such as kratom.[30] Recent legalization of cannabis by several states[31] may

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lead to more and higher quality research on PBCs with potential for treating chronic pain.[32] Initiatives to develop and study alternative interventions for chronic pain are expected to contribute to this increase in research on PBCs, specifically for pain. This living review was initiated in response to a request from Congress on PBCs for chronic pain.[32,33]

Although the original review and prior surveillance reports and updates focused on chronic pain in adults, subacute pain as well as the adolescent population 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.[34] Effective treatments for reducing the likelihood of subacute pain becoming chronic are also needed. Adolescents also experience chronic pain and have a high prevalence of cannabis use (recreational or medical).[35,36]

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

1.2 Purpose and Scope of the Systematic Review

This is an update of a "living systematic review" originally addressing the effectiveness and harms of plant-based treatments for chronic pain in adults, now also addressing subacute pain and adolescents. The review is living, meaning that it uses methods to identify and synthesize recently published literature and adapt its scope on an ongoing basis. For the purposes of this review, included PBCs are those that have potential analgesic effects as well as the potential for addiction, misuse, and serious adverse effects; other PBCs, such as herbal treatments are not included. The intended audience includes policy and decision makers, funders and researchers of treatments for pain, and clinicians who treat pain.

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2. Methods

2.1 Review Approach

This Systematic Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter "AHRQ Methods Guide").[37] All methods were determined a priori, and the original protocol was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/protocol and on the PROSPERO systematic reviews registry (registration no. CRD42021229579).[38] Based on input from a Technical Expert Panel, the protocol was expanded for the 2023 update to include adolescents and subacute pain.[39] Below is a summary of the specific methods used in this review. Search strategies appear in Appendix A, and a complete description of methods is presented in Appendix B.

2.2 Key Questions

This review will address the following Key Questions:

1. In adults or adolescents with chronic or subacute pain, what are the benefits of cannabinoids for treatment of chronic or subacute pain?
2. In adults or adolescents with chronic or subacute pain, what are the harms of cannabinoids for treatment of chronic or subacute pain?
3. 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?
4. 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?

2.3 Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through June 30, 2024, with ongoing, automated monthly searches to identify newly published studies. Search strategies were updated for the 2023 review to include terms for subacute pain and applied to databases from inception to identify studies on subacute pain. The original search terms did not exclude adolescents, though, though we did reassess previously excluded studies for eligibility based on the revised inclusion criteria. The search strategies are shown in **Appendix A**. Electronic searches were supplemented with review of reference lists of relevant studies and two prior AHRQ pain reports[13,15] for studies that met the inclusion criteria for this review. For the original 2021 review, a Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies. Pre-established criteria were used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ Methods Guide, based on the Key Questions and populations, interventions, comparators,

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outcomes, timing, and settings (PICOTS; Table 1).[37] See **Appendix B** for more details on eligibility criteria and methods for study selection, including dual review of studies screened.

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults or adolescents (including pregnant or breastfeeding women) with noncancer chronic (>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:** Nonplant-based interventions, capsaicin, herbal supplements
Comparators	**All KQs:** Any comparator, or usual care	**All KQs:** No comparison
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, 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).

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2.4 Data Extraction and Risk of Bias Assessment

After studies were selected for inclusion, data were abstracted into evidence tables in categories that included but not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results. Information relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention (including regulatory status and availability in the United States), and care settings. All study data were verified for accuracy and completeness by a second team member.

The risk of bias of individual studies was assessed using methods consistent with the AHRQ Methods Guide.[37] Separate criteria were used for randomized controlled trials and observational studies. Two reviewers independently assessed risk of bias, resulting in final ratings of low, moderate, or high, with any disagreements resolved by consensus. For full details about data extraction, risk of bias assessment, and other methods, please see **Appendix B**.

2.6 Data Synthesis and Analysis

To assist with narrative synthesis, we constructed summary tables of the abstracted study characteristics, results, and risk of bias ratings for all included studies. Data were additionally summarized in in-text tables, using ranges and descriptive analysis and interpretation of the results. We assessed the persistence of benefits or harms by evaluating the three periods consistent with prior AHRQ pain reports (1 to <6 months, 6 to 12 months, and ≥12 months).[13,15,16,40,41]

Based on input from a Technical Expert Panel regarding potential differences in cannabis products that could impact estimates of benefits and harms, we organized cannabis interventions into three prespecified categories based on their ratios of tetrahydrocannabinol (THC) to cannabidiol (CBD) (Table 2). The first category, high THC, includes products with a ratio of THC to CBD of at least 2 to 1, and includes products consisting of THC alone. This category was further stratified based on whether interventions were synthetic or plant-derived. Plant-derived products can be extracted with limited purification or undergo additional purification, depending on the process used. We classified products as extracted if they contained multiple cannabinoids; in addition to THC and CBD, such products may contain additional cannabinoids and other compounds (e.g., terpenes) present in whole-plant cannabis that may or may not affect the impact of the intervention. We classified purified products as pharmaceutical grade products considered free of contaminants and consisting of only a single cannabinoid (i.e., only THC [or THC analogue] or CBD). Although purified dronabinol and CBD are plant derived, they are chemically identical to synthetic dronabinol and CBD.[42] Therefore, we grouped purified with synthetic THC and CBD in primary analyses. However, due to the potential for differential effects of synthetic and purified products, we also performed secondary analyses in which purified dronabinol and CBD were evaluated as a separate category from synthetic dronabinol and CBD.

The second category, low THC, contains a ratio of THC to CBD of less than 1 (i.e., lower THC than CBD, with ratio less than 1 to 2). These may be either extracted or purified products.

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

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

Within the same THC to CBD category, we analyzed oral and oromucosal (e.g., sublingual or oromucosal spray) or topical products separately from topical products, unless the oromucosal or topical product was clearly designed to produce systemic (rather than local) effects. In such cases, the oromucosal or topical product with systemic effects was analyzed together with oral products.

After our categorization scheme was developed and utilized in the original report and annual updates, the U.S. Food and Drug Administration (FDA) released a document summarizing the

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research and drug approval process for cannabis. The FDA document categorized cannabis products as "cannabis-derived compounds" occurring naturally in the plant (corresponding to the "plant-derived" category in this report) and "cannabis-related compounds" (corresponding to the "synthetic" category in this report). The FDA document did not describe categories based on THC to CBD ratio or product formulation; in addition, it did not describe separate categories for subcategories of plant-derived products (i.e., extracted and purified). Due to the potential importance of these factors when evaluating cannabis products and potential confusion due to the similarity of the terms "cannabis-derived" and "cannabis-related", we elected (in consultation with the Technical Expert Panel) to retain our original categorization scheme.

Table 2. 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]
	Purified	Purified from whole-plant with close to 100% THC	Purified dronabinol[b,c] (e.g., Namisol®)	Not available in the U.S.
	Extracted	Commercially marketed product extracted from whole-plant with known high ratio of THC/CBD	THC/CBD extracts with high THC/CBD ratio	May be available at dispensaries where allowed
	Extracted	Whole-plant with known high concentration of THC	Whole-plant cannabis with known high THC concentration	May be available at dispensaries where allowed
Comparable THC to CBD (THC to CBD ratio is <2:1 and >1:2)	Extracted	Extracted from whole-plant with comparable ratio of THC/CBD	Nabiximols (Sativex®)[d]	Not available in the U.S.
	Extracted	Extracted from whole-plant with comparable ratio of THC/CBD	Oral tinctures with similar ratio of THC/CBD	May be available at dispensaries where allowed
	Extracted	Whole-plant with known comparable ratio of THC/CBD	Whole-plant with known comparable ratio of THC/CBD	May be available at dispensaries where allowed
Low THC (THC to CBD ratio is ≤1:2)	Synthetic	Synthetic CBD	CBD oral tablets	Not available in the U.S.
	Purified	Purified from whole-plant with close to 100% CBD	Purified CBD	May be available at dispensaries where allowed
	Extracted	Extracted from whole plant with low ratio of THC/CBD; may undergo further purification	CBD topical, sublingual or oral	May be available at dispensaries where allowed
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	May be available at dispensaries where allowed.
Other Cannabinoids (Cannabinoids other than THC or CBD)	Extracted	Extracted from whole-plant	Cannabidivarin (CBDV) extracted oil (oral)	May be available at dispensaries where allowed

Abbreviations: CBD = cannabidiol; THC = tetrahydrocannabinol.

[a] These products are approved by the Food and Drug Administration for nonpain indications (anorexia related to HIV infection, nausea related to chemotherapy).

[b] These plant-derived, purified products are chemically identical to dronabinol, and are therefore grouped together with synthetic dronabinol.

[c] Manufactured in the Netherlands and Denmark, may be available in some European countries. Not currently FDA-approved.

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[d] Manufactured and available in Canada and some European countries; not FDA-approved.

Meta-analyses were conducted to summarize randomized controlled trial (RCT) data and obtain more precise estimates on outcomes for which studies were similar enough to provide a meaningful combined estimate.[43] The decision to conduct quantitative synthesis depended on the presence of at least two studies with similar cannabis-related products, methodology, completeness of reported outcomes, and a lack of statistical heterogeneity among the reported results. Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic.[44] Pain intensity scales were converted to a standardized 0 to 10 scale and the mean difference was used as the effect measure for change in pain. For function or disability, the standardized mean difference (SMD) was used as the effect measure, due to differences in the scales and measures used. For other continuous outcomes, the mean difference on the original scale was used if all studies used the same measure; otherwise, the SMD was used. When the standard deviation for continuous outcomes was not reported or could not be calculated from the reported data, it was imputed using the average coefficient of variation from other included studies. For primary binary outcomes (pain response and adverse events), relative risk was used as the effect measure. See **Appendix B** for more details.

We used a random effects model based on the profile likelihood method[45] to combine interventions with comparable THC to CBD ratios, high-THC trials, and low-THC trials. The primary analysis was stratified by the type of product evaluated. Synthetic and purified products were analyzed together, based on their identical chemical composition, and extracted products were analyzed separately. Sensitivity analysis was conducted by excluding studies rated as high risk of bias and evaluating purified products separately from synthetic products. For meta-analyses with more than 5 but fewer than 20 studies, we also performed sensitivity analyses by repeating analyses using the Bartlett's correction, which can provide improved confidence interval coverage probabilities (i.e., wider confidence intervals) in these situations.[46,47] Meta-analyses were conducted using command *metan* and *admetan* in Stata/SE 16.1 (StataCorp, College Station, TX). Publication bias (small study effect) was assessed using both funnel plots and the Egger test when there were eight or more studies included in a meta-analysis.

The magnitude of effects for primary outcomes were classified according to the same definitions used in other recent AHRQ reviews on chronic pain[13,15,16,40,41] to provide a consistent benchmark for evaluating results of pain interventions across reviews. The findings were categorized as small, moderate, and large magnitudes of effect based on the criteria shown in Table 3. Results that were below the threshold for a small effect were considered to reflect "no effect" or a trivial effect. Results with a small, medium, or large effect that were not statistically significant were considered to have "potential effects."

Table 3. Definitions of effect sizes

Effect Size	Definition
No effect/trivial effect	• Below the threshold for a small effect
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

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Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.
Note: For pain and function, negative values for MD indicate improved outcomes; for other outcomes, positive values indicate improved outcomes.

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

When data were available, we conducted subgroup analysis based on duration (short-, medium-, long-term followup), type of pain (e.g. neuropathic, visceral, joint), and excluding high risk of bias studies.

2.7 Grading the Strength of the Body of Evidence

We assessed the strength of evidence for all primary comparisons and outcomes listed above. The strength of evidence was based on the cumulative evidence (evidence identified for the original report plus new evidence added for the update). Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence for each Key Question/body of evidence was initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.[37,48] To ensure consistency and validity of the evaluation, the strength of evidence was reviewed by the entire team of investigators prior to assigning a final grade, based on the following domains:

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

For description of the overall grade categories, see **Appendix B**.

In narratively describing the findings on the strength of the evidence, we followed the principles outlined in recent guidance to improve clarity.[49-51] Using these principles, evidence that is low-strength is described as "may" have an effect, moderate strength evidence is described as "probably" has an effect, and high-strength evidence is described as having an effect.

2.8 Living Systematic Review Methods

This is an annual update of a systematic review originally published in 2021[52] and updated in 2022[53] and 2023.[54] Quarterly surveillance of the literature conducted prior to this full update and describing new evidence as it is identified can be found at: https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review. Due to the relatively small volume of new studies, the quarterly report format was abridged in late 2023. The new format consists of an updated literature flow diagram, a table of studies included since the 2023 review, and a brief description of whether new studies would impact findings. The availability of new studies likely to significantly impact findings would trigger a more detailed report.

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3. Results

3.1 Description of Included Evidence

The results of this systematic review are organized first by Key Questions, with evidence on Key Questions 1 and 2 (benefits and harms of cannabinoids) reported together. The evidence is then organized according to the categories described in the Methods, comparable tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio extracted interventions, high THC to CBD ratio interventions (synthetic, purified, or extracted), low THC to CBD ratio interventions (synthetic, purified, or extracted), and other cannabinoids. No eligible studies were identified for the Key Questions examining kratom (Key Questions 3 and 4). No studies addressed subacute pain or adolescents.

After screening a cumulative total of 5,894 abstracts, 507 full-text publications of studies were dually reviewed, resulting in 26 randomized controlled trials (RCTs) in 27 publications and 12 observational studies being included in this review. One new RCT in two publications (n=134) compared plant-derived synthetic equivalent THC (dronabinol; high THC to CBD ratio), synthetic CBD (low THC to CBD ratio), or both (low THC to CBD ratio) versus placebo for neuropathic pain;[55,56] one new RCT (n=86) evaluated a plant-derived CBD (low THC to CBD ratio) versus placebo for knee osteoarthritis;[57] and one new RCT (n=60) evaluated topical (intraoral) CBD for temporomandibular pain, although the origin of CBD (synthetic or plant-derived) was not reported and it was unclear whether its effects were meant to be systemic or local.[58]Both of the new observational studies (n=296 and n=32,332)[57Schubert, 2023 #7541,59] included patients with various chronic pain conditions and evaluated low, comparable, or high THC to CBD ratio cannabis products; one of the studies[59] (n=32,332) focused on the association between cannabis use and on risk of arrhythmia and acute coronary syndrome.

The search results and selection of studies are summarized in the literature flow diagram (Figure 1). **Appendix C** provides a list of all included studies. In total, seven placebo-controlled RCTs evaluated products that contain a combination of extracted THC and CBD in a comparable ratio.[60-66] Two RCTs evaluated the effects of extracted high THC to CBD ratio products.[67,68] Eleven placebo-controlled RCTs evaluated synthetic or purified THC (high THC to CBD ratio).[55,69-78] Eight placebo-controlled RCTs evaluated low THC to CBD ratio products.[55,57,58,78-82] Six of these evaluated CBD alone: three,[55,78,81] including one new RCT,[55] evaluated synthetic oral CBD; one new RCT[58] evaluated topical intraoral CBD (unclear if synthetic or plant-derived);[58] one new RCT evaluated purified oral CBD;[57] and one RCT evaluated extracted topical CBD.[82] Two of the RCTs of oral synthetic CBD (including one new RCT) also evaluated the combination of purified THC plus synthetic CBD (1:2 ratio)[55,78] and one prior RCT assessed extracted sublingual THC/CBD oil [1:6 ratio].[80] One other trial evaluated the phytocannabinoid cannabidivarin (CBDV), administered as an oral oil.[79] Seven RCTs reported prior cannabis use in 3 to 47 percent of participants[60,62-65,81,82] and two RCTs reported cannabis use in the past year in 6 and 10 percent of participants.[61,66] Nine RCTs excluded patients with any cannabis use or recent cannabis use (and did not report the proportion of patients with any prior use),[68-70,73-76,79,80] and seven RCTs did not report prior cannabis use.[55-57,67,71,72,77,78]

Appendix D summarizes key outcomes from each RCT and results of meta-analyses. Detailed evidence tables for included studies and risk of bias assessments are available in **Appendixes E and F**. **Appendix G** contains details on the strength of evidence, and **Appendix H** lists excluded studies at the full-text level and their reasons for exclusion.

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3.1 Results, Description of Included Evidence

Figure 1. Literature flow diagram

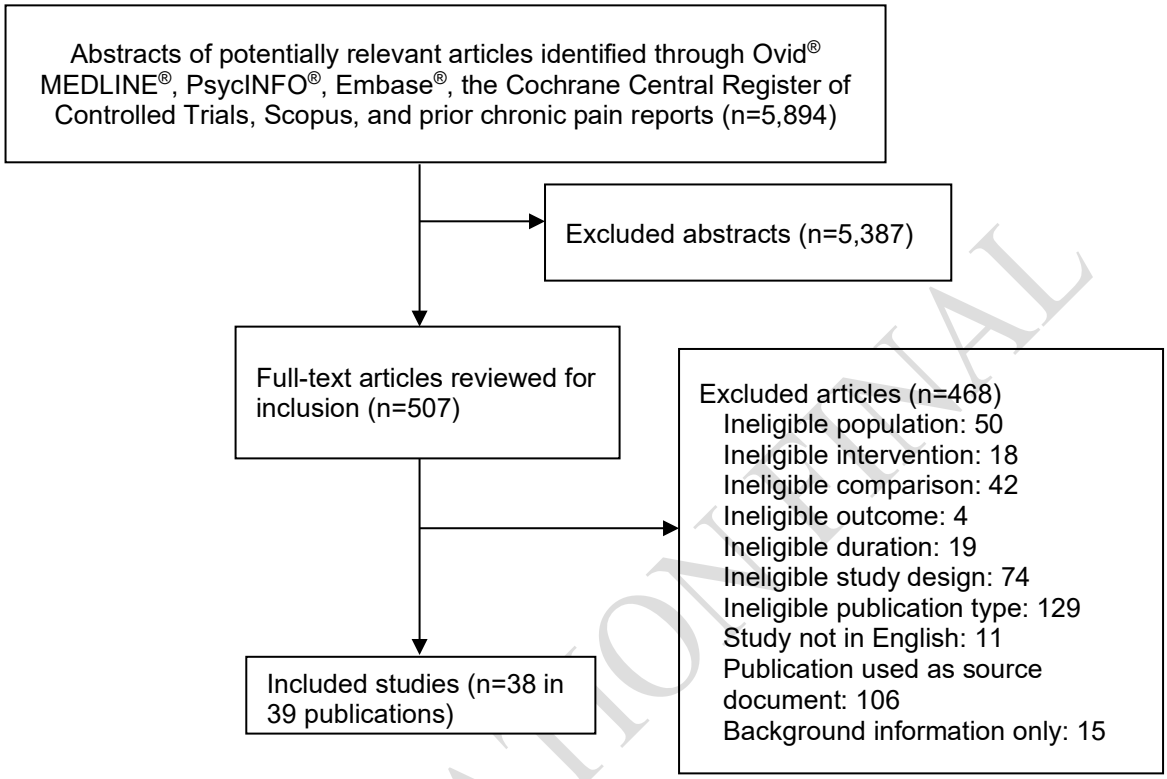

Table 4 summarizes the characteristics of the included trials, and Table 5 provides details on included observational studies.

Table 4. Characteristics of included randomized controlled trials of cannabinoids for chronic pain in adults

Characteristic	THC/CBD	THC	CBD	CBDV
THC to CBD Ratio	Comparable[a]	High	Low	NA - other cannabinoids
Source	Extracted	Synthetic Purified Extracted	Synthetic Purified Extracted Unclear	Extracted
N Studies	7	13[b]	7[b] (1 topical, 1 sublingual, 4 oral, 1 unclear)	1
Comparator (Study Count)	Placebo (7)	Placebo (10); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low THC to CBD ratio (CBD or purified THC/CBD) (2)	Placebo (7); Dronabinol (2); Low THC to CBD ratio (CBD or purified THC/CBD (2); ≥97% purified low THC to CBD (1:6) sublingual oil (1); 5% or 10% CBD gel (unclear if synthetic or plant-based) (1)	Placebo

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3.1 Results, Description of Included Evidence

Characteristic	THC/CBD	THC	CBD	CBDV
Route of Administration, Formulation (Study Count)	Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl	Dronabinol 3 mg oral tablet (1); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Purified dronabinol oral 2.5 mg capsule (2); Oral capsule, 2.5 mg purified THC/0.8 – 1.8 mg CBD extract (1); Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)	Oral capsule, 5 mg synthetic CBD (2); Oral tablet, 10 mg synthetic CBD (1); Oral capsule, 200 mg purified CBD (1); Oral capsule, 5 mg CBD extract/2.5 mg dronabinol (2); Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1); Topical cream, 83 mg CBD/fluid ounce (1) 5% or 10% CBD gel, unclear if local or systemic (1)	Oral oil, 50 mg/ml CBDV
Dosing Regimen	Final mean dose 23 mg THC/21 mg CBD daily.	Dronabinol capsules: 2.5 to 5 mg, titrated. Final dose range 13 - 25 mg/day Dronabinol (Namisol®[a]) tablet: 3 to 8 mg 3 times daily, titrated. Final dose NR Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Capsule: 2.5 -12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily	Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 45 to 50 mg CBD daily (2) Oral tablet: 10 mg daily, titrated (max 3 times daily) Final dose NR Oral CBD capsule: 200 mg 3 times daily. Final dose 600 mg/day Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 12.5 to 15 mg THC/30 to 45 mg CBD daily (2) Sublingual oil, titrated to max daily dose of 6 drops 3 times daily (15 mg THC/90 mg CBD) Topical cream: applied locally 1-4 times/day (volume/dose, final dose NR) CBD gel: 20 mg of 5% or 10% gel applied on each side, total dose 20-40 mg daily	400 mg CBDV daily. Final dose NR.
Risk of Bias	29% high, 57% moderate, 14% low	8% high, 46% moderate, 46% low	43% high, 43% moderate, 14% low	100% moderate

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3.1 Results, Description of Included Evidence

Characteristic	THC/CBD	THC	CBD	CBDV
Total Randomized	882	1,028	568	34
Age, Mean Years	53	54	54	50
Female, %	66%	62%	60%	3%
Non-White,[c] %	1.6% (2)	5.3% (4)	NR	NR
Primary Pain Type (Study Count)	NPP (6); Inflammatory arthritis (1)	NPP (9); Fibromyalgia (2); Visceral pain (1); Headache (1);	NPP (3); MS (1); OA (2); Temporomandibular (1); Unspecified (1)	NPP (1)
Baseline Pain Score, Mean (Range)[d]	6.59 (5.3 to 7.3)	6.75 (4.00 to 8.67)[e]	6.01 (4.67 to 7.4)[f]	6.28 (6.12 to 6.44)
Study Duration	4 to 15 weeks	4 to 47 weeks	4 to 16 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 nabiximols.

[b] Two trials are included in both the THC and CBD columns, as they compared THC to CBD, CBD/THC, and placebo.

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

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

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

[f] Weighted mean includes median scores for 1 study (5.2 vs. 6.1).

Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

Table 5. Characteristics of included observational studies of cannabinoids for chronic pain in adults

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
THC to CBD Ratio	Unclear or mixed	High	High	Comparable vs. high	Comparable
Source	Any cannabis product (patient's choice) or mixed cannabinoids	Extracted	Synthetic (nabilone)	Extracted vs. synthetic	Extracted
N Studies	8[b]	1	1	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (2); other cannabinoids (2)	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) (6); inhaled or oral prescribed cannabis (2)	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 (7) Final median dose 85 mg CBD vs. 7.8/20 mg THC/CBD vs. 20/25 mg THC/CBD vs. 42 mg THC/day (1)	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

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3.1 Results, Description of Included Evidence

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
ROB	50% high, 50% moderate	100% high	100% moderate	100% moderate	100% moderate
N Total	45,897	431	156	674	1,310
Age, Mean Years	54	49	61	46	51
Female, %	52%	57%	59%	57%	57%
% Non-White (Study Count)	54% (1); NR (7)	NR	NR	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic noncancer pain	Chronic noncancer pain	NPP	Peripheral NPP	Peripheral neuropathic back pain
Baseline Pain Score, Mean (Range)[c]	5.75 (4.56 to 7.00)	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 two new studies for this review.

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

Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

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3.2 Key Question 1 and Key Question 2. In adults or adolescents with chronic or subacute pain, what are the benefits (Key Question 1) and harms (Key Question 2) of cannabinoids for treatment of chronic or subacute pain?

3.2.1 Key Points for Comparable THC to CBD Ratio

- All results are short term (4 weeks to <6 months) in duration.
- Comparable extracted THC to CBD ratio oromucosal spray was associated with small improvements in pain severity (7 RCTs, N=878, 0 to 10 scale, mean difference [MD] −0.54, 95% confidence interval [CI], −0.95 to −0.19, I^2=39%) versus placebo (strength of evidence [SOE]: moderate), and was just below the threshold for a small improvement for overall function (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI –0.73 to −0.16, I^2=32%) versus placebo (SOE: moderate). While more patients experienced a pain response (≥30% improvement from baseline), fewer trials reported this outcome and the difference was small and did not reach statistical significance (4 RCTs, N=733, 38% vs. 31%, relative risk [RR] 1.18, 95% CI 0.93 to 1.71, I^2=36%) (SOE: low).
- Compared with placebo, comparable extracted THC to CBD oromucosal spray was associated with a large increase in risk of dizziness (6 RCTs, N=866, 30.0% vs. 8.0%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%) (SOE: low) and sedation (6 RCTs, N=866, 8.0% vs. 1.2%, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%) (SOE: low), and a moderate increased risk of nausea (6 RCTs, N=866, 14% vs. 7.5%, RR 1.79, 95% CI 1.19 to 2.77, I^2=0%) (SOE: low). There was no effect on study withdrawal due to adverse events (WAEs) (SOE: low).

3.2.2 Summary of Findings for Comparable THC to CBD Ratio

Seven RCTs (N=882, range 18 to 339)[60-66] included in prior updates compared extracted THC and CBD in a comparable THC to CBD ratio versus placebo in patients experiencing chronic pain. All used nabiximols, which are extracted from whole-plant cannabis with 2.7 mg of THC and 2.5 mg of CBD per 100 mcl oromucosal spray (specified as the product Sativex® in 7 studies). Sativex® is manufactured and available in Canada and some European countries. Other comparable THC to CBD products are available in the United States where allowed, though the availability of specific products is unknown. Six trials enrolled patients with neuropathic pain[61-66] and one trial included patients with rheumatoid arthritis.[60] Studies ranged from 4 to 15 weeks in duration of active treatment; all were short-term followup (1 to <6 months). Across trials, the weighted mean daily dose was 8.4 sprays (23 mg THC/21 mg CBD) for patients assigned to THC/CBD and 12.7 sprays for those assigned to placebo. One study did not specify the product name, strength or dosing in milligrams, but the number of sprays per day (8 vs. 11 for intervention vs. placebo), were similar to other trials.[62] Two trials were high risk of bias: one was a small (n=16), 4-week, crossover trial, and the other was a small (n=29), 12-week, parallel design trial.[62,65] The rest were parallel design trials; four were rated moderate risk of bias[60,63,64,66] and one low risk of bias.[61] One trial used an enriched enrollment randomized withdrawal design.[61] The mean age of participants in the trials was 53 years, and 62 percent were female. Race was poorly reported, with two trials reporting 1.2 percent of participants being non-White, and the others not reporting it at all. Four trials allowed patients using opioids and other analgesics to enroll and to continue using them during the study period.[61-63,66] The proportion of

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patients taking opioids was low in two studies (11% to 24%)[61,66] and much greater in the third study (63% in the cannabis group vs. 74% in the placebo group).[63] The other three trials did not report opioid use. All of the RCTs of comparable THC to CBD ratio products allowed prior cannabis use; the proportion of patients that used cannabis previously ranged from 5 to 64 percent. No study analyzed results according to prior cannabis use.

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

Four RCTs[61,63,65,66] found comparable extracted THC/CBD oromucosal spray associated with a nonstatistically significant increased likelihood of pain response (≥30% reduction in pain) versus placebo (38% vs. 31%, RR 1.18, 95% CI 0.93 to 1.71, I^2=36%; Appendix D, Figure D-1). Based on pooled analysis of all seven RCTs, comparable THC/CBD was associated with a small, statistically significant reduction in pain severity versus placebo (7 RCTs, 0 to 10 scale, MD −0.54, 95% CI −0.95 to −0.19, I^2=39%; Figure 2).[60-66] Figure 2 shows that, except for the small, high risk of bias, crossover study, the effect size was larger and statistically significant in shorter studies (4 to 5 weeks) compared with longer studies (12 to 15 weeks); however, all studies met the definition for short duration (1 to <6 months). Sensitivity analysis excluding two high risk of bias studies[62,65] did not alter the findings (0 to 10 scale, MD −0.63, 95% CI −1.15 to −0.24, I^2=52%).[61,66] One trial that used an enriched enrollment randomized withdrawal design reported worse results for comparable THC/CBD compared with the pooled estimate (MD −0.19, 95% CI −0.67 to 0.29).[61]

Six studies (N=616) with 5 to 15 weeks followup reported overall function or disability (including measures of pain interference).[60,61,63-66] Pooled analysis favored nabiximols versus placebo, but the difference was slightly below the threshold for a small effect (negative values indicate improved function; 6 RCTs, 0 to 10 scale, MD −0.42, 95% CI –0.73 to −0.16, I^2=32%; Figure 3).

For secondary outcomes, all of the trials reported quality of life. Overall, there were no statistically significant differences in quality of life between groups. Three used the EQ-5D scale (0 to 100), with none finding a significant difference between groups.[61,65,66] One used the Short General Health Questionnaire (GHQ-12; 0 to 36 scale), and found a small but nonstatistically significant difference between groups.[63] Three studies reported on the Short Form-36 (SF-36) Physical and Mental scales (0 to 100).[61,62,65] Two did not find statistically significant between-group differences. The third study, a high risk of bias crossover trial (n=16), reported that the SF-36 Physical scale scores improved with placebo, with little change in the THC/CBD group, while the SF-36 Mental scale scores remained similar in the THC/CBD group and decreased (worsened) in the placebo group.[62] Five RCTs assessed sleep quality or sleep disturbance using a 0 to 10 scale and four reported statistically significantly better sleep outcomes in the THC/CBD groups versus placebo groups.[60,61,63,64,66] The studies did not report on other secondary outcomes (e.g., depression or anxiety).

The four RCTs that allowed opioid use did not report on changes in opioid used during the study period.[61,63,66]

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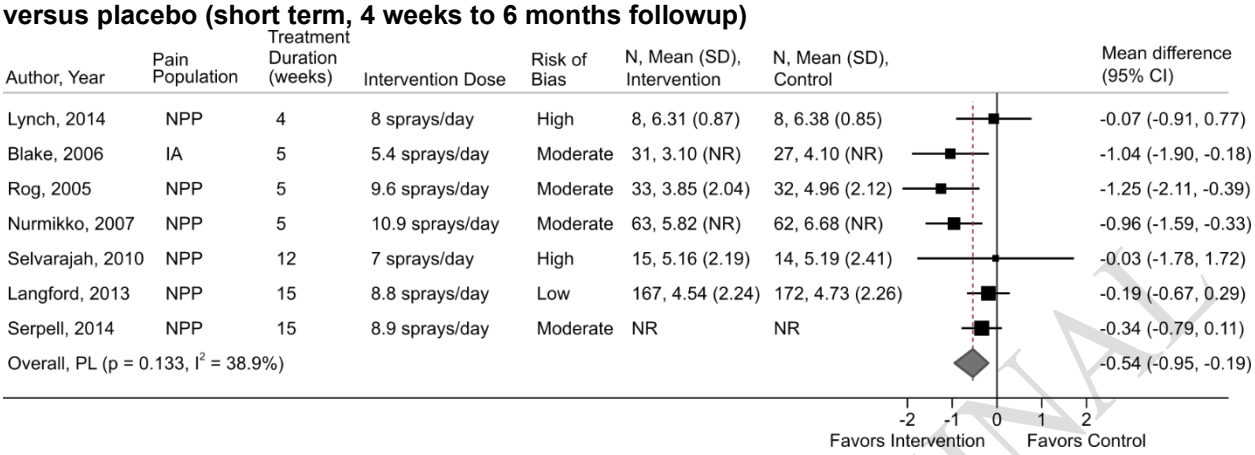
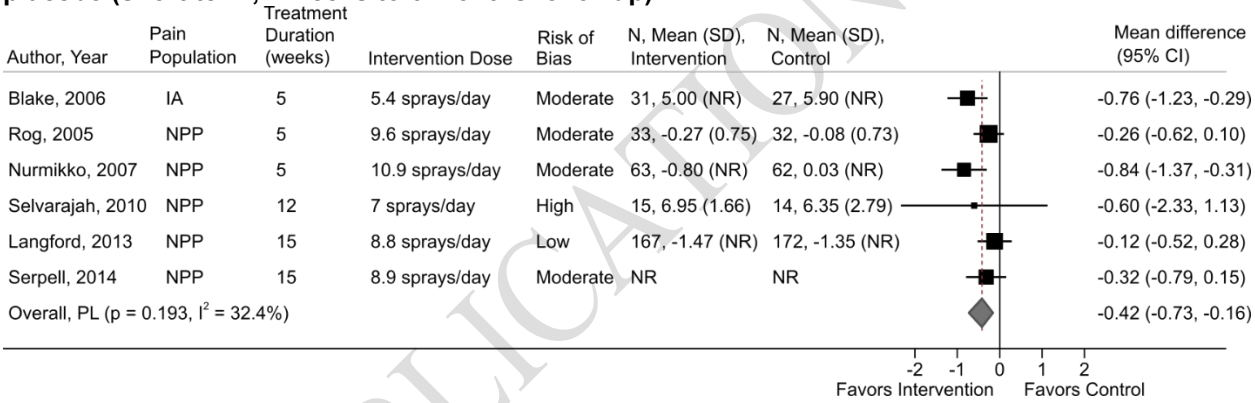
3.2 Results, Key Question 1 and Key Question 2. Benefits and harms of cannabinoids for treatment of chronic or subacute pain

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



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

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



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

Adverse events were reported in all the trials. Based on two RCTs, rates of any adverse event were significantly higher in the THC/CBD groups than placebo (2 RCTs, 75% vs. 63%, RR 1.19, 95% CI 1.02 to 1.44, I^2=0%, Appendix D, Figure D-2).[61,64]

Serious adverse events (SAEs) were reported in five studies, with two reporting that none occurred.[62,64] Pooling results from the other three studies found no effect on SAEs with comparable THC/CBD products (3 RCTs, 5.0% vs. 4.3%, RR 1.18, 95% CI 0.26 to 3.4, I^2=0%, Appendix D, Figure D-3).[60,63,66]

Five RCTs reported on study WAEs. Pooled analysis found no difference between extracted comparable THC to CBD ratio products versus placebo in risk of WAEs, though the estimate was imprecise (5 RCTs, 12.3% vs. 9.5%, RR 1.14, 95% CI 0.65 to 3.02, I^2=51%, Appendix D, Figure D-4).[60,61,63,64,66]

Statistically significant differences in specific adverse events of interest occurred more often in the THC/CBD groups than placebo across six RCTs (one did not report specific adverse events).[65] Dizziness occurred significantly more in the THC/CBD groups than placebo groups (6 RCTs, 31.0% vs. 8.0%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%, Appendix D, Figure D-5).[60-64,66] Nausea was reported in 13 percent of THC/CBD patients compared with 7.5 percent of placebo

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patients (6 RCTs, RR 1.79, 95% CI 1.19 to 2.77, I^2=0%, Appendix D, Figure D-6).[60-64,66] Sedation was reported in 8 percent of THC/CBD patients compared with 1.2 percent of placebo patients (6 RCTS, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%, Appendix D, Figure D-7).[60-64,66]

A previously included retrospective cohort study (n=1,310) provided insufficient evidence to compare outcomes of nabiximols oromucosal spray (plant-based extracted comparable THC to CBD ratio product) versus long-acting opioids when administered as add-on therapy in patients with neuropathic pain, due to methodological limitations.[83]

3.2.3 Key Points for High THC to CBD Ratio

- All RCT results were short term (4 weeks to <6 months) in duration.
- Synthetic or purified high THC to CBD ratio (100% THC or THC analogue) products were associated with a small improvement in pain severity (8 RCTs, N=507, 0 to 10 scale, MD −0.78, 95% CI −1.59 to −0.08, I^2=64%) (SOE: low) and no effect on overall function or disability (3 RCTs, N=unclear, 0 to 10 scale, MD −0.18, 95% CI −1.25 to 0.77, I^2=51%) (SOE: low).
- Synthetic or purified high THC to CBD ratio (100% THC or THC analogue) products were associated with a moderate increase in risk of study withdrawal due to adverse events (WAEs) (6 RCTs, N=487, 14% vs. 6%, RR 1.92, 95% CI 1.10 to 4.80, I^2=0%) (SOE: low), moderate increase in risk of sedation (5 RCTs, N=458, 24% vs. 16%, RR 1.57, 95% CI 1.11 to 2.29, I^2=0%) (SOE: low), a large increase in risk of dizziness (4 RCTs, N=425, 33% vs. 15%, RR 2.30, 95% CI 1.53 to 3.52, I^2=22%) (SOE: moderate), and a large increase in risk of nausea (4 RCTs, N=425, 12% vs. 6%, RR 2.12, 95% CI 1.09 to 3.96, I^2=0%), but the differences did not reach statistical significance (SOE: low).
- Synthetic or purified high THC to CBD ratio (100% THC or THC analogue) products were associated with inconsistent effects on likelihood of experiencing a pain response (≥30% improvement) (3 RCTs) (SOE: insufficient).
- Extracted high THC to CBD ratio products (not 100% THC) were associated with a large increased risk of study WAEs (1 RCT, N=277, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33) (SOE: low) and dizziness (1 RCT, N=277, 62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34) (SOE: low). Outcomes assessing benefit were not reported or evidence was insufficient.
- The combined evidence for synthetic or purified and extracted high THC to CBD ratio products indicated moderate improvement in pain severity versus placebo (10 RCTs, N=801, −0.98, 95% CI −1.80 to −0.32, I^2=68%) (SOE: moderate).

3.2.4 Summary of Findings for High THC to CBD Ratio

One new, low risk of bias RCT (n=134) evaluated a high THC to CBD ratio product.[55,56] It was conducted in Denmark and compared the purified THC analogue dronabinol versus synthetic CBD, combined THC/CBD (low THC to CBD ratio), or placebo for chronic (duration ≥3 months) neuropathic (multiple sclerosis or spinal cord injury) pain. Median daily doses were 9 mg per day for dronabinol, 45 mg per day for CBD, and 17.5 mg/35 mg per day for combined THC/CBD. Median age was 52 and 74 percent were female; average pain duration was not reported. Race was not reported. The duration of treatment was 7 weeks.

With the new trial, a total of 13 RCTs evaluated high THC to CBD ratio products.[55,67-78] Eleven evaluated synthetic THC (dronabinol, 2 RCTs),[72,73] a synthetic THC analog (nabilone, 6

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RCTs),[70,71,74-77] or purified dronabinol (3 RCTs).[55,69,78] Two other RCTs evaluated extracted products with both THC and CBD (THC to CBD ratio 48:1 in one study and 2:1 in the other).[67,68] Synthetic dronabinol and nabilone are available by prescription and approved by the U.S. Food and Drug Administration (FDA) for nonpain indications. The availability of purified dronabinol is unclear though it is manufactured in the Netherlands and Denmark and may be available in some European countries. Other extracted and high THC whole-plant products are available in the United States, where allowed, though the availability of specific products is unclear.

Seven of the previously included trials of synthetic or purified RCTs were placebo-controlled,[55,69,73-78] and three were active-controlled crossover trials.[70-72] The new trial of purified THC included both a placebo arm as well as active comparisons with low THC to CBD ratio products.[55] Both trials of extracted THC were placebo-controlled. All of the RCTs were short duration (4 weeks to 6 months followup). Additionally, two short duration observational studies,[84,85] one[85] comparing a synthetic THC versus extracted comparable THC to CBD ratio product, were included.

3.2.4.1 Synthetic or Purified THC

Eleven RCTs (N=659; 5 dronabinol, 6 nabilone)[55,69-78] evaluated synthetic or purified THC for treating chronic pain. Eight trials enrolled patients with neuropathic pain (4 multiple sclerosis [MS], 2 mixed neuropathic pain conditions, and 1 each painful diabetic neuropathy and spinal cord injury),[55,70,72,73,75-77] and one trial each enrolled patients with chronic abdominal pain,[69] medication overuse headache,[71] and fibromyalgia.[74] All studies had short duration of treatment, ranging from 4 to 14 weeks. All medications were titrated upward, with a maximum dose of 15 to 25 mg per day of dronabinol, and 0.5 to 2 mg per day of nabilone. The mean dose received at endpoint was inconsistently reported.

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

Seven trials used a parallel design and were placebo-controlled, with one adding nabilone or placebo to gabapentin treatment in patients who had not achieved pain relief (visual analog scale [VAS] score for pain >50).[76] Three RCTs were crossover trials with different active controls: diphenhydramine,[72] ibuprofen,[71] and dihydrocodeine.[70] As described above, the new RCT was placebo-controlled, and also included two low THC to CBD ratio product arms (CBD alone or the combination of THC and CBD in a ratio of ~1:2).[55] Risk of bias was high in two trials,[72,77] moderate in four trials,[69,70,74,76] and low in five trials,[55,71,73,75] including the new RCT.[55] Across trials, the mean age of participants was 54 years, and 60 percent were female. Race was poorly reported; three trials that described race reported that 5.4 percent of participants were non-White. Three studies allowed patients to continue taking their current medication for pain, not specifically excluding opioids or requiring their discontinuation,[69,73,74] with one RCT specifically allowing tramadol as rescue medication for acute pain during the trial.[73] The other studies required patients to discontinue opioid use[70,72,78] or did not report opioid use at baseline or during the study.[71,75-77] Six parallel design placebo-controlled trials (3 dronabinol, 3 nabilone) excluded

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patients with prior cannabis use.[55,69,73-76] One crossover designed trial (nabilone vs. dihydrocodeine) excluded patients with prior cannabis use.[70]

A previously included, small (n=156), moderate risk of bias cohort study evaluated nabilone and gabapentin in patients with neuropathic pain of various types for 6 months.[84]

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

Placebo-controlled trials of synthetic and purified THC. Based on an updated pooled analysis of eight RCTs (1 new RCT added),[55] synthetic and purified high THC to CBD ratio products were associated with a small improvement in pain severity versus placebo (8 RCTs, N=507, 0 to 10 scale, MD –0.78, 95% CI –1.59 to –0.08, I^2=64%; Figure 4).[55,69,73-78] However, statistical heterogeneity was present. The estimate was similar to the prior pooled estimate (MD –0.95, 95% CI –1.81 to –0.25, I^2=60%). Results were similar when the analysis was restricted to trials of patients with neuropathic pain (7 RCTs, MD –0.77, 95% CI –1.67 to 0.00, I^2=70%). However, statistical heterogeneity remained present. Excluding the small (n=26), enriched enrollment randomized withdrawal trial[75] also resulted in a similar pooled estimate and did not resolve statistical heterogeneity. Stratified analysis indicated that the pooled effect estimate for nabilone (MD −1.59, 95% CI −2.49 to −0.82, I^2=0%) was larger than with dronabinol (MD −0.23, 95% CI −0.82 to 0.54, I^2=45%; Appendix D, Figure D-8, Table D-6); this difference was statistically significant (p=0.027).[55,69,73-78] Analyzing purified THC as a separate category from synthetic THC did not resolve statistical heterogeneity among the high THC trials, although results suggested discordant effects for synthetic (moderate benefit, 5 RCTs, MD −1.20, 95% CI −2.21 to −0.47, I^2=58%) and purified products (no benefit, 3 trials, MD 0.10, 95% CI −1.08 to 1.02, I^2=48%; Appendix D, Figure D-9).

Three trials (including the new RCT) reported likelihood of pain response (≥30% improvement from baseline) for synthetic or purified high THC to CBD ratio products.[55,75,78] Although the overall estimate indicated no difference between high THC to CBD products versus placebo in likelihood of pain response (3 trials, N=143, RR 0.99, 95% CI 0.43 to 2.37; Appendix D, Figure D-10), the estimate was imprecise and statistical heterogeneity was present (I^2=72%). Two trials,[55,78] including the new RCT (n=59), found dronabinol for neuropathic pain associated with a nonstatistically significant decreased likelihood of experiencing a pain response versus placebo (43% vs. 57%, RR 0.76, 95% CI 0.45 to 1.28 and 29% vs. 57%, RR 0.64, 95% CI 0.31 to 1.31). However, a previously included, small RCT that was low risk of bias (n=26) of patients with diabetic neuropathy found nabilone associated with a large increase in likelihood of pain response (85% vs. 38%, RR 2.20, 95% CI 1.06 to 4.55).[75] In addition to inconsistency, pain response was only reported in three of seven RCTs evaluating this outcome, potentially introducing a form of selective reporting bias. Therefore, the evidence for this outcome remained insufficient.

Four RCTs reported on overall function (including pain interference) or disability.[75-78] A pooled analysis of three RCTs (N=98) found little difference between synthetic or purified high THC to CBD ratio products versus placebo for function, though the estimate was imprecise (0 to 10 scale, MD −0.18, 95% CI −1.25 to 0.77, I^2=51%; Appendix D, Figure D-11).[75,76,78] Two trials evaluated nabilone and one trial dronabinol. A fourth, small (n=13) RCT reported that neither high THC nor placebo was associated with change in disability, measured with the Bartell Index, but did not provide data.[77]

Few synthetic or purified THC studies reported secondary outcomes, and results were mixed. A small (n=26), low risk of bias RCT of patients with diabetic neuropathy reported no difference

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between nabilone versus placebo in depression using the Hospital Anxiety and Depression-D [HADS-D] scale at 5 weeks (0 to 10, MD −0.4, 95% CI −1.26 to 1.46), although there was a statistically significant improvement in anxiety (HADS-A, 0 to 10 scale, MD −2.9, 95% CI −3.80 to −2.0).[75] Quality of life findings were mixed, with a statistically nonsignificant difference in EQ-5D Utility scores (endpoint scores 72.6 vs. 61.4) and a statistically significant difference using the EQ-5D Index scores (endpoint scores 0.74 vs. 0.60, $p<0.05$ using analysis of covariance [ANCOVA]). A small, moderate risk of bias study (n=40) of patients with fibromyalgia evaluated secondary outcomes using the Fibromyalgia Impact Questionnaire (FIQ). The overall FIQ score improved more at 4 weeks with nabilone than with placebo (MD −12.07, $p<0.02$). Using the anxiety questions on the FIQ, nabilone was associated with a statistically significant improvement after 4 weeks (0 to 10 scale, MD −2.2, $p<0.01$).[74] FIQ depression scores were not significantly improved with nabilone. The three RCTs that permitted opioid use during the study period did not report on the effect of the study medications on opioid use.[70,73,74] One low risk of bias RCT (n=58) found no differences between purified 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).[78]

For adverse events, findings were similar with the addition of the new RCT.[55]. As in the prior update, the addition of the new RCT found synthetic or purified THC associated with a moderate increased risk of WAEs (6 RCTs, 14% vs. 7%, RR 1.92, 95% CI 1.10 to 4.80, $I^2=0\%$, Appendix D, Figure D-12). Although the updated estimate for WAE became statistically significant, imprecision was still present (the lower limit of the confidence interval crosses the threshold for a small effect) and the SOE remained low. Of six RCTs reporting WAEs, two evaluated nabilone[74,76] (7% vs. 4%, RR 1.54, 95% CI 0.14 to 17.71, $I^2=0\%$) and four evaluated synthetic or purified dronabinol[55,69,73,78] (15% vs. 7%, RR 1.95, 95% CI 1.08 to 6.55, $I^2=0\%$, Appendix D, Figure D-13), with no statistically significant differences between nabilone or dronabinol ($p=0.71$). A previously reported pooled analysis of two RCTs reporting any adverse event (1 nabilone, 1 dronabinol) found a small, nonstatistically significant increase with synthetic THC (2 RCTs, 86% vs. 71%, RR 1.20, 95% CI 0.96 to 1.48, $I^2=0\%$, Appendix D, Figure D-14).[73,75] The estimate for SAEs remained very imprecise with the addition of the new RCT (2 RCTs, N=312, 9% vs. 6%, RR 1.53, 95% CI 0.52 to 4.15).[55,73]

As in prior updates, synthetic or purified high THC to CBD ratio products were associated with statistically significant increased risk of dizziness (4 RCTs, 33% vs. 15%, RR 2.30, 95% CI 1.53 to 3.52, $I^2=22\%$, Appendix D, Figure D-15)[55,69,73,78] and sedation (5 RCTs, 24% vs. 16%, RR 1.57, 95% CI 1.11 to 2.29, $I^2=0\%$, Appendix D, Figure D-16).[55,69,73,74,78] As in the prior update, the updated meta-analysis found synthetic or purified THC associated with large increased risk of nausea versus placebo (4 RCTs, 12% vs. 6%, RR 2.12, 95% CI 1.09 to 3.96, $I^2=0\%$, Appendix D, Figure D-18).[55,69,73,78] Although the updated estimate for nausea became statistically significant, imprecision was still present and the SOE remained low. A sensitivity analysis using the Bartlett's correction resulted in a more imprecise pooled estimate for sedation that was no longer statistically significant and imprecise (sedation: 5 RCTs, RR 1.57, 95% CI 0.99 to 2.78, $I^2=0\%$, Figure D-17; Table D-7). In stratified analyses for sedation, one study of nabilone (n=33) reported a greater magnitude of effect (RR 8.40, 95% CI, 1.16 to 60.84, Figure D-16) than four trials of dronabinol (N=425, RR 1.49, 95% CI 1.04 to 2.12, $I^2=0\%$, Figure D-16) with no statistically significant subgroup difference ($p=0.09$).

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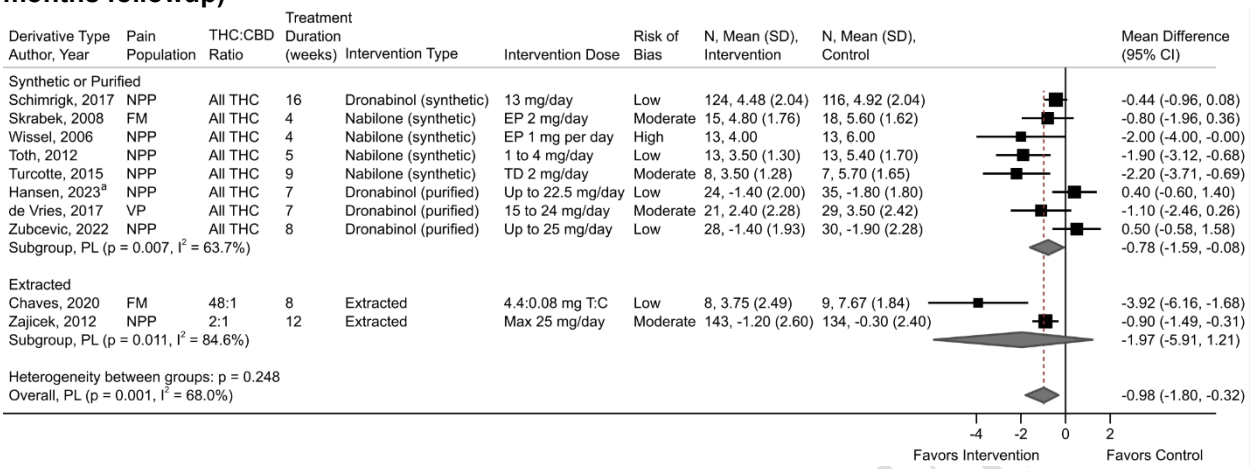
3.2 Results, Key Question 1 and Key Question 2. Benefits and harms of cannabinoids for treatment of chronic or subacute pain

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



Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; T:C = THC to CBD; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain; WP = whole plant.

[a] Study is new to the 2024 update.

Active-control studies of synthetic THC versus noncannabinoids. Three previously included crossover RCTs compared synthetic THC versus other (noncannabinoid) medications. One low risk of bias RCT (n=80) found no statistically significant difference between nabilone (0.5 mg daily) versus ibuprofen (400 mg daily) in pain severity at 8 weeks in patients with medication overuse headache.[71] There were also no statistically significant differences in depression, anxiety, quality of life, risk of adverse events, or risk of WAEs (SAEs were not reported). At 2 weeks post-study, nabilone was associated with lower daily analgesic intake than ibuprofen (0.89 analgesics daily vs. 1.34 analgesics daily; p=0.03). However, specific analgesic medications were not reported. Adverse events were infrequent and estimates were imprecise (dizziness 7.7% with nabilone vs. 0% with ibuprofen, cognitive deficits 3.8% vs. 0% nausea 3.8% vs. 7.7%, and sedation 0% vs. 3.8%). A moderate risk of bias RCT (n=73) found dihydrocodeine (30 to 240 mg daily) associated with greater reduction in pain severity versus nabilone (max dose of 2 mg daily) at 6 weeks (VAS 0 to 100 scale; MD −5.7, 95% CI −10.9 to −0.5, p=0.03).[70] There were no statistically significant differences in secondary outcomes (depression, anxiety, quality of life, or sleep). A very small (n=7), high risk of bias RCT found no difference between dronabinol versus diphenhydramine in pain intensity in patients with spinal cord injury.[72] Other efficacy outcomes were reported.

A moderate risk of bias, prospective observational study (n=101 for nabilone and gabapentin arms) found no difference between nabilone versus gabapentin in pain severity between groups at 3 months in patients with mixed neuropathic pain.[84] However, at 6 months nabilone was associated with a greater reduction in pain intensity (0 to 100 VAS, MD −5.8, 95% CI −10.18 to −1.42), and better sleep scores on the Medical Outcomes Study Sleep Scale (scale 0 to 60, MD −3.1, 95% CI −7.57 to 1.37) versus gabapentin, with no differences in pain interference, quality of life, depression, or anxiety. Nabilone was associated with decreased likelihood of any adverse event (38% vs. 48%, RR 0.72, 95% CI 0.49 to 1.07), WAEs (10% vs. 23%, RR 0.44, 95% CI 0.17 to 1.16), and sedation (35% vs. 60%, RR 0.58, 95% CI 0.37 to 0.91), although only the estimate was sedation was statistically significant. The likelihood of experiencing dizziness was similar (33% vs. 39%, RR 0.85, 95% CI 0.50 to 1.44).

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Head-to-head comparisons of cannabis-based products. Two low risk of bias RCTs, including a new RCT (n=94),[55] compared purified oral dronabinol versus two low-THC products (synthetic oral CBD alone or purified THC plus synthetic CBD in a 1:2 ratio).[55,78] Median daily doses were 22.5 to 25 mg for THC, 45 to 50 mg for CBD, and 15 to 17.5 mg THC/30 to 35 mg CBD for the combination. Estimates for each product versus placebo for pain intensity, function, and secondary outcomes (sleep, quality of life, anxiety, and depression) were imprecise and had overlapping confidence intervals, indicating no statistically significant differences between arms. There were no statistically significant differences between dronabinol and CBD or combined THC/CBD in likelihood of ≥30% improvement in pain score in either trial, though estimates were imprecise. Estimates for adverse events were also imprecise.

A previously included retrospective cohort study (n=774) compared extracted nabiximols oromucosal spray (comparable THC to CBD ratio) with oral synthetic dronabinol (high THC to CBD ratio) in patients with neuropathic pain and inadequate pain relief with recommended first- and second-line treatments (e.g., nonopioid analgesics, opioid analgesics, antiseizure medications, or antidepressants), in a propensity matched analysis.[85] Mean age was 46 years, 57 percent of patients were female, and mean pain intensity at baseline was 4.4 (SD 1.46) on a 0 to 10 scale. Mean daily doses were 16.6 mg THC/15.4 mg CBD for nabiximols, and 17.2 mg THC for dronabinol. At 24 weeks, nabiximols were associated with greater improvement in pain intensity than dronabinol, although the difference was below the threshold for a small effect (MD 3.5, 95% CI 1.6 to 5.4 on the Pain Intensity Index [0 to 100 scale]), and there was a small improvement in function (76.0% vs. 68.3% on the modified Pain Disability Index, p<0.001). Nabiximols were also associated with greater improvements in quality of life, anxiety, and depression, and higher likelihood of discontinuing all rescue analgesics than dronabinol (75.6% vs. 45.9%, RR 1.7, p<0.001), as well as decreased likelihood of nervous system adverse events (9.5% vs. 19.9%, RR 0.48, 95% CI 0.32 to 0.71) and psychiatric adverse events (4.2% vs. 14.8%, RR 0.28, 95% CI 0.16 to 0.50). The study was rated moderate risk of bias and methodological limitations included failure to report attrition or missing data and unclear blinding of data analysts to interventions.

3.2.4.2 Extracted THC

Two previously included placebo-controlled RCTs (N=294) studied extracted high THC to CBD ratio products with different ratios of THC to CBD.[67,68] A 12-week, moderate risk of bias RCT of patients with pain due to MS (n=277) studied a product described as an extract from *Cannabis sativa L.* containing 2.5 mg of THC and CBD in the range of 0.8 to 1.8 mg per capsule (twice daily, titrated to a maximum of 25 mg daily) versus placebo.[68] More than half of patients enrolled were using an analgesic at baseline, but the type of analgesic or whether they could continue use during the trial was not reported. Patients using cannabis within 30 days of study enrollment were excluded. An 8-week, low risk of bias RCT of 17 patients with fibromyalgia studied low-dose, sublingual THC oil.[67] The product contained 24.44 mg/mL of THC and 0.51 mg/mL of CBD (THC to CBD ratio ~48:1), and small quantities of other cannabinoids. The mean daily dose in the active treatment group was 4.4 mg THC/0.08 mg CBD in the active treatment group. The dose of CBD in this preparation was described as being so low as to not contribute meaningfully to outcomes. Twenty-five percent of patients had used an opioid prior to the study, but opioid use during the trial was not reported.

In pooled analysis, pain severity was improved with the extracted high THC products, but the difference was not statistically significant (2 RCTs, 0 to 10 scale, MD −1.97, 95% CI −5.91 to

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1.21, I^2=85%; Figure 4). There was a high degree of heterogeneity in this combined estimate, likely due to multiple differences between the studies, including sample size, dose, duration, and pain condition evaluated (fibromyalgia vs. multiple sclerosis), with a large difference in the magnitude of effect across the two studies. Individually, each study found a statistically significant reduction in pain severity. The 8-week, low-dose THC oil study of 17 women with fibromyalgia reported a larger effect (0 to 10 scale, MD −3.92, 95% CI −5.98 to −1.86)[67,68] on pain intensity than the larger (n=277) 12-week study of a much higher dose of a high-THC capsule product (MD −0.90, 95% CI −1.49 to −0.31).[67,68] Pain response was not reported.

In the RCT of patients with fibromyalgia, cannabis was not associated with improvement in physical functioning (1 RCT, FIQ subscale 0 to 10, MD 1.75, 95% CI −0.46 to 3.98) versus placebo, although the extracted product was associated with improved quality of life (1 RCT, FIQ scale 0 to 100 scale, MD 36.0, p=0.005).[67] However, these analyses did not adjust for potentially important differences in baseline scores between groups. There were no differences between groups in measures of depression and anxiety.

In the RCT of patients with MS, the extracted high THC product was associated with higher risk of WAEs (13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33) and dizziness (62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34) versus placebo.[68] The estimate for SAEs was imprecise (4.9% vs. 2.2%, RR 2.19, 95% CI 0.58 to 8.28). In the RCT of patients with fibromyalgia, the extracted high THC product was associated with large increased risk of somnolence versus placebo (1 RCT, 88% vs 11%, RR 7.9, 95% CI 1.2 to 50.9).[67] Other adverse events of interest were not reported by either study.

3.2.4.3 Combined Analysis of Synthetic THC and Plant-Derived THC Products

To evaluate whether there was an effect for any form of high-THC product (synthetic, purified, or extracted), we combined results from all studies of high THC to CBD ratio interventions (Figure 4). The updated (1 new RCT) overall combined mean difference was −0.98 (95% CI −1.80 to −0.32, I^2= 68%), or similar to the prior pooled estimate (−1.12, 95% CI −1.97 to −0.48, I^2=65%). Although substantial statistical heterogeneity was present, a subgroup analysis of synthetic or purified versus extracted forms of high THC (Appendix D, Table D-8) did not indicate a statistically significant subgroup difference (p=0.318). The number of RCTs included in the combined analysis (≥8 studies) allowed evaluation for publication bias using graphical and statistical methods. Both the funnel plot and the Egger test (p=0.131) suggested potential small sample effects, a marker for publication bias, though the Egger test was above the threshold for statistical significance (Appendix I, Figure I-1).

3.2.5 Key Points for Low THC to CBD Ratio

- Two new trials enabled new meta-analyses of oral CBD alone versus placebo and combined THC plus CBD (low THC to CBD ratio) versus placebo.
- Synthetic or purified oral CBD alone was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale, MD 0.40, 95% CI −0.14 to 1.00, I^2=20%) (SOE: moderate), greater likelihood of pain response (4 RCTs, N=334, 37.0% vs. 44.4%, RR 0.84, 95% CI 0.62 to 1.10; I^2=0%) (SOE: moderate), or improved function (3 RCTs, N=272, SMD 0.11, 95% CI −0.14 to 0.41, I^2=0%) (SOE: moderate) versus placebo. CBD was not associated with increased likelihood of any adverse event (2 RCTs, N=205, 71.3% vs. 59.6%, RR 1.12, 95% CI 0.93 to 1.49, I^2=0%) (SOE: moderate), dizziness (3 RCTs,

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N=206, 13.3% vs. 18.5%, RR 0.75, 95% CI 0.28 to 1.81, I^2=12%) (SOE: low), or sedation (3 RCTs, N=206, 16.3% vs. 19.4%, RR 1.07, 95% CI 0.21 to 1.93, I^2=34%) versus placebo (SOE: low).

- Combined oral purified THC (dronabinol) and synthetic CBD in ~1:2 ratio was not associated with decreased pain intensity (2 RCTs, N=113, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I^2=0%) (SOE: low), greater likelihood of experiencing ≥30% improvement in pain (2 RCTs, N=123, 55.2% vs. 50.8%, RR 1.07, 95% CI 0.73 to 1.57, I^2=0%) (SOE: low), or improved function (1 RCT, N=60, SMD 0.29, 95% CI −0.21 to 0.80, I^2=0%) (SOE: low) versus placebo, but estimates were imprecise. The low THC to CBD ratio combination was associated with increased risk of nausea versus placebo (2 RCTs, N=123, 24.1% vs. 6.2%, RR 3.80, 95% CI 1.08 to 17.05, I^2=0%) (SOE: moderate); combined low THC to CBD was also associated with a nonstatistically significant increase in risk of dizziness (2 RCTs, N=122, 35.1% vs. 23.1%, RR 1.74, 95% CI 0.47 to 3.46, I^2=32%) (SOE: low) and sedation (2 RCTs, N=123, 43.1% vs. 29.2%, RR 1.55, 95% CI 0.86 to 2.72, I^2=0%) (SOE: low).
- One new RCT (n=60) evaluated intraoral CBD for temporomandibular disorders, but had serious methodological limitations. In addition, the origin of the CBD (synthetic or plant-derived) was not reported, and it was unclear whether the CBD was intended to have systemic or only topical effects (SOE: insufficient).

3.2.6 Summary of Findings for Low THC to CBD Ratio

Three new RCTs[55,57,58] and four previously included RCTs[78,80-82] evaluated short-term outcomes of low THC to CBD ratio products versus placebo. Four RCTs[55,57,78,81] evaluated oral products and two RCTs evaluated nonoral products.[80,82] One RCT evaluated two intraoral products (unclear if effects intended to be systemic or only topical).[58] Regarding oral low-THC products, two RCTs (N=177), including one new RCT[55] (also included in the high-THC section), evaluated synthetic oral CBD (median 45 or 50 mg daily) or the combination of purified oral THC (dronabinol, median 17.3 or 15 mg daily) plus synthetic CBD (median 35 or 30 mg daily) in a ~1:2 ratio in patients with neuropathic pain (due to multiple sclerosis or spinal cord injury in the new RCT, and peripheral neuropathic pain in the prior RCT). A prior RCT (n=158) evaluated synthetic oral CBD as add-on to usual analgesic regimen (not specified) in patients with hand osteoarthritis or psoriatic arthritis[81] and a new RCT (n=86) evaluated purified oral CBD as add-on to acetaminophen in patients with knee osteoarthritis.[57] Another new RCT (n=60) evaluated intraoral CBD (20 or 40 mg daily) for temporomandibular pain. The origin of the CBD products (synthetic or plant-derived) was not reported, and it was unclear if effects were intended to be systemic or only topical.[58] Both RCTs of nonoral low-THC products were previously included. A small (n=15) RCT[80] evaluated extracted sublingual THC to CBD oil (1 to 6 ratio, median dose 15 mg THC to 90 mg CBD) or a more purified version of the same product (≥97% pure CBD and THC) in patients with chronic pain undergoing hemodialysis and another small (n=29) RCT evaluated topical CBD cream (250 mg/3 oz) applied to symptomatic areas up to 4 times daily or placebo in patients with neuropathic pain.[82] Across trials, the median age ranged from 24 to 68 and the proportion of patients female ranged from 13 to 74 percent. Two trials excluded patients currently undergoing opioid treatment,[55,78] three trials allowed concomitant opioids or opioids as rescue medications,[57,80,81] and two trials did not report either way.[58,82] Three studies required that patients abstain from cannabis for at least 3 months in order to be eligible,[55,58,80] three studies

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allowed previous use of cannabinoids,[78,81,82] and one study did not report either way.[57] The availability in the United States of the low-THC products used in the RCTs is unknown.

Among the RCTs that evaluated oral products, two were rated low risk of bias[55,78] and two were rated moderate risk of bias.[57,81] Two RCTs of nonoral products were rated high risk of bias, and one RCT on intraoral products was rated moderate risk of bias.[58,80,82] Methodological limitations in the high and moderate risk of bias RCTs included unclear randomization and allocation concealment methods, high or differential attrition, and unclear blinding of outcome assessors. In addition, a high risk of bias crossover RCT of sublingual CBD did not report outcomes for the initial (prior to crossover) period.[80] A high risk of bias RCT of topical CBD oil did not report all planned analysis, did not preregister its protocol, and raised important ethical concerns, as the study authors reported that they were unable to obtain institutional review board approval yet still carried out the trial.[82] Study details and results can be found in **Appendix E**, Tables E-1 to E-4, and risk of bias assessments are shown in **Appendix F**, Table F-1.

Placebo-controlled trials of synthetic or purified oral low-THC products. The addition of two new RCTs of synthetic or purified oral CBD enabled a new meta-analysis for this update.[55,57] We analyzed trials of CBD alone separately from trials of combined THC plus CBD (ratio ~1:2).

Oral synthetic or purified CBD was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale MD 0.40, 95% CI −0.14 to 1.00, I^2=20%; Figure 5), greater likelihood of experiencing ≥30% improvement in pain (4 RCTs, N=334, 37.0% vs. 44.4%, RR 0.84, 95% CI 0.62 to 1.10; I^2=0%; Appendix D, Figure D-19),[55,57,78,81] or improved function (3 RCTs, N=272, SMD 0.11, 95% CI −0.15 to 0.41, I^2=0%; Appendix D, Figure D-20) versus placebo, with point estimates favoring placebo.[57,78,81] CBD was also not associated with increased likelihood of any adverse event (2 RCTs, N=205, 71.3% vs. 59.6%, RR 1.12, 95% CI 0.93 to 1.49, I^2=0%; Appendix D, Figure D-21),[57,81] dizziness (3 RCTs, N=206, 13.3% vs. 18.5%, RR 0.75, 95% CI 0.28 to 1.81, I^2=12%; Appendix D, Figure D-22),[55,57,78] or sedation (3 RCTs, N=206, 16.3% vs. 19.4%, RR 1.07, 95% CI 0.21 to 1.93, I^2=34%; Appendix D, Figure D-23),[55,57,78] though estimates were imprecise. Estimates for SAEs (Appendix D, Figure D-24),[55,57,78] WAEs (Appendix D, Figure D-25),[55,57,78,81] and nausea (Appendix D, Figure D-26)[55,57,78] were too imprecise to inform reliable conclusions. Three of the RCTs evaluated synthetic CBD and one RCT[57] evaluated purified synthetic equivalent CBD. Restricting the analysis to trials of synthetic CBD resulted in similar findings (for pain intensity, 3 RCTs, N=248, MD 0.51, 95% CI −0.23 to 1.34, I^2=36%; Appendix D, Figure D-27).

The combination of plant-derived, synthetic equivalent THC (dronabinol) and synthetic CBD (~1:2 ratio) was also not associated decreased pain intensity (2 RCTs, N=113, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I^2=0%; Figure 5),[55,78] greater likelihood of experiencing ≥30% improvement in pain (2 RCTs, N=123, 55.2% vs. 50.8%, RR 1.07, 95% CI 0.73 to 1.57, I^2=0%; Appendix D, Figure D-28),[55,78] or improved function (1 RCT, n=60, SMD 0.29, 95% CI −0.21 to 0.80, I^2=0%; Appendix D, Figure D-29).[78] However, estimates were based on only one or two RCTs each and were imprecise. Estimates for SAEs (Appendix D, Figure D-24) and WAEs (Appendix D, Figure D-30) were extremely imprecise. The combined low THC to CBD ratio intervention was associated with increased risk of nausea versus placebo (2 RCTs, N=123, 24.1% vs. 6.2%, RR 3.80, 95% CI 1.08 to 17.05, I^2=0%; Appendix D, Figure D-26);[55,78] low THC to CBD was also associated with a nonstatistically significant increase in risk of dizziness (2 RCTs, N=122, 35.1% vs. 23.1%, RR 1.74, 95% CI 0.47 to 3.46, I^2=32%; Appendix D, Figure

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D-31) and sedation (2 RCTs, N=123, 43.1% vs. 29.2%, RR 1.55, 95% CI 0.86 to 2.72, I^2=0%; Appendix D, Figure D-32).[55,78]

Evidence on secondary outcomes was limited. One new RCT (n=86) found no difference between purified CBD versus placebo in SF-36 physical (0 to 100 scale, MD 0.65, 95% CI −3.6 to 4.9) or mental (0 to 100 scale, MD 1.85, 95% CI −1.2 to 4.9) component summary scores.[57] One previously included RCT (n=87) found no difference between either synthetic CBD alone or the combination of purified THC plus CBD versus placebo in mood or quality of life.[78] CBD alone, but not the combination, was associated with improved sleep versus placebo (0 to 10 scale; CBD: MD 2.03, 95% CI 0.35 to 3.71; THC/CBD: MD 0.89, 95% CI −0.64 to 2.42). Another previously included RCT (n=129) found no differences between synthetic CBD versus placebo in sleep quality, depression or anxiety.[81]

Placebo-controlled trials of extracted low-THC products. A previously included, small (n=15) high risk of bias crossover RCT (n=15) evaluated two low THC to CBD ratio products versus placebo.[80] The products were extracted sublingual THC to CBD oil [1:6 ratio] or the same product with further purification (≥97% pure CBD and THC). Maximum daily doses were 18 drops per day (15 mg THC/90 mg CBD). The study used a crossover design consisting of two 16-week treatment periods with a 2-week washout. Estimates for pain severity at the end of treatment were imprecise and indicated no statistically significant between-group differences; pain response and function were not reported. There were too few cases of SAEs or WAEs to evaluate these outcomes and specific harms were not reported.

A previously included, small (n=29), high risk of bias RCT evaluated extracted topical CBD cream in patients with neuropathic pain (mean age 68 years, 38% female).[82] Patients were randomized to 4 weeks of CBD cream (250 mg/3 oz) applied to symptomatic areas up to 4 times daily or placebo (total daily dose received not reported). CBD was associated with significantly greater improvement in pain intensity versus placebo (−1.34 vs. −0.59, p=0.009 by ANCOVA). However, this trial is difficult to interpret because it was unclear if the topical CBD oil was intended to have local or systemic effects, and details regarding the extraction process and extent of purification was not reported. It was also unclear if the analysis included a crossover extension phase in which patients initially randomized to placebo were given CBD. This RCT did not report pain response, pain interference, overall function/disability, or secondary outcomes, and no adverse events were reported.

Placebo-controlled trials of low-THC products of unknown origin. One new moderate risk of bias RCT (n=60) evaluated two low THC to CBD ratio products versus placebo in patients with temporomandibular pain (mean age 24 years, 60% female).[58] The products were an intraoral gel with CBD concentrations of 5 or 10 percent.[58] It was unclear whether the CBD gel was intended to have local or systemic effects, and details regarding the source of the CBD (synthetic or plant-derived) were not reported. Patients receiving the 10 percent CBD gel used 20 mg per masseter muscle intraorally, for a total of 40 mg of CBD per day. Patients receiving the 5 percent CBD gel used a total of 20 mg of CBD per day. CBD was associated with significantly greater

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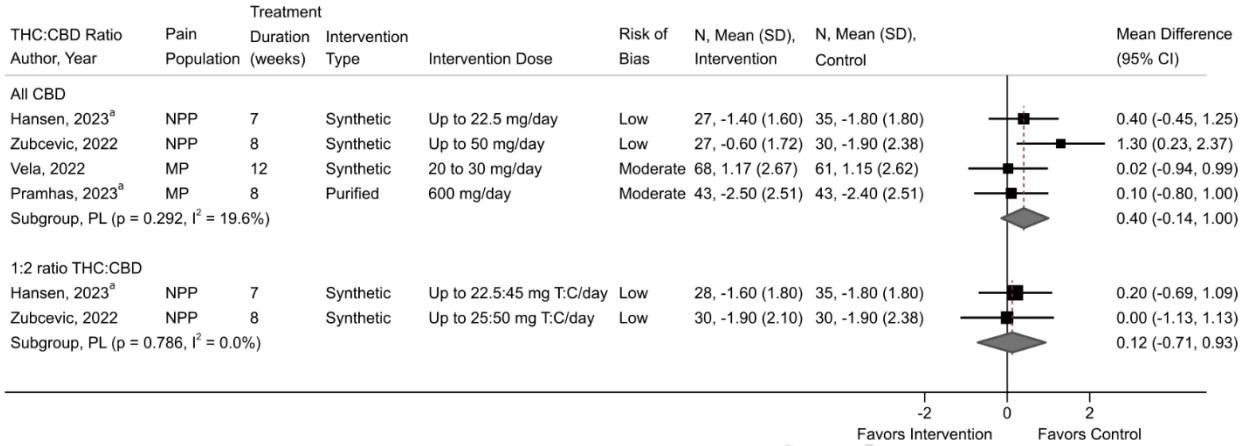
improvement in pain severity versus placebo after 30 days (median 6.0 vs. 2.0 for 10% CBD, 6.0 vs. 3.5 for 5% CBD, 6.0 vs. 5.5 for placebo).[58]

Figure 5. Change in pain severity with oral low-THC ratio products versus placebo (short term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; T:C = THC to CBD; THC = tetrahydrocannabinol.
[a] Study is new to the 2024 update.

3.2.7 Key Points for Other or Mixed Cannabinoids

- Three cohort studies (n=296, 761, and 32,332), including two new studies, of various or mixed cannabinoids had methodological limitations and provided insufficient evidence to draw conclusions regarding effects on pain, function, and adverse events (including cardiovascular events).
- One short-term RCT (n=31) of cannabinoids other than THC and CBD provided insufficient evidence to draw conclusions.

3.2.8 Summary of Findings for Other or Mixed Cannabinoids

One large (n=32,332) new cohort study evaluated the association between medical cannabis use and arrhythmia or ischemic coronary disease in Danish patients with chronic pain (Appendix E, Table E-5).[59] Median age was 59 years and women comprised 63 percent of the study population. The pain conditions varied (39% musculoskeletal, cancer 17%, neurological 13%, and unspecified 31%). Patients who newly used medical cannabis were matched to controls not using patients on age, sex, chronic pain diagnosis, and use of other pain medications. Use of any medical cannabis was associated with increased 180-day risk of new-onset arrythmia versus no medical cannabis (0.8% vs. 0.4%, adjusted RR 2.07, 95% CI 1.34 to 2.80), after adjusting for comorbidities, educational level, and age, but there was no statistically significant association with 180-day risk of acute coronary syndrome (adjusted RR 1.20, 95% CI 0.35 to 2.04). However, the estimate for acute coronary syndrome was imprecise. Rates of new-onset arrhythmia were similar when patients were stratified according to cannabinoid type (CBD alone, THC alone, or mixed THC/CBD). The study was rated moderate risk of bias; methodological limitations included unclear blinding of outcomes assessors or data analysis and failure to report attrition or missing data (Appendix F, Table F-2).

Another new cohort study (n=296 for primary analysis) compared outcomes of various oral and inhaled cannabis products (ranging from low to high THC to CBD ratio) in an Australian

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cohort of patients with various types of chronic pain.[86] Although outcomes for pain intensity, pain interference, and physical function were somewhat better in the comparable THC to CBD and low THC to CBD ratio groups compared to the high THC to CBD ratio group, the study was rated high risk of bias due to serious methodological limitations, including failure to control for confounders (Appendix F, Table F-2).

A previously included, moderate risk of bias prospective cohort study (n=761) evaluated different cannabis products for patients with chronic pain (mixed conditions) in the UK Medical Cannabis Registry.[87] It compared an inhaled dry flower, sublingual cannabis oils, or both. The oils varied in composition, with some only containing THC or CBD, and some with THC to CBD ratios that ranged from 1:1 to 1:20. The mean age was 47, and 47 percent of participants were female. Race was not reported. In multivariate analysis, there were no differences between arms in likelihood of experiencing improvement in Brief Pain Inventory [BPI] pain severity (adjusted odds ratio [OR] 1.36, 95% CI 0.51 to 3.65 for combination versus oils and 2.12, 95% CI 0.28 to 16.11 for dried flower versus oils) or interference (adjusted OR 1.90, 95% CI 0.68 to 5.29 for combination versus oils and 1.61, 95% CI 0.21 to 12.18 for dried flower versus oils), though estimates were imprecise and favored the combination and dried flower over oils alone. There was no difference between the combination versus oils alone in likelihood of experiencing an adverse event, though this estimate was also imprecise (adjusted OR 1.00, 95% CI 0.64 to 1.58).

A previously included small (n=31), moderate risk of bias trial evaluated oral CBDV (described as "a novel phytocannabinoid derived from the *Cannabis sativa* L. plant").[79] Patients with HIV-related chronic pain (mean age 50 years, 3% female) were randomized to oral CBDV oil (50 mg/ml) dosed at 8 ml daily (400 mg CBDV) or placebo oil for 4 weeks, then crossed over after a 21-day washout. Using the numerical rating scale (NRS) pain scale (10-point scale), statistically significantly fewer patients achieved response (≥30% pain reduction) with CBDV compared with placebo (38% vs. 81%, RR 0.46, 95% CI 0.24 to 0.91). There was no difference between CBDV and placebo in the change in pain severity from baseline (MD 0.62, 95% CI −0.05 to 1.32). Secondary outcomes of anxiety, depression, and insomnia also did not differ statistically between the groups. Although more patients reported any adverse event while using CBDV than placebo (91% vs. 79%), the difference was not statistically significant (p=0.28). Other adverse event outcomes occurred slightly more often in the CBDV groups than placebo (WAEs, 1 vs. 0; SAEs, 1 vs. 0; diarrhea, 3 vs. 0; dry mouth, 3 vs. 0).

3.2.9 Key Point for Whole-Plant and Unspecified (Patient-Choice) Cannabis Products

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

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

No new studies evaluated whole-plant or unspecified (patient-choice) cannabis products. Six previously included observational studies (N=12,939) reported on the effects of cannabis, with five (3 high, 2 moderate risk of bias) studies evaluating medical cannabis programs (cannabis product unspecified),[88-90] or self-reported use of cannabis (product unspecified),[91,92] and one

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moderate risk of bias study evaluating a specific whole-plant cannabis product.[93] Patient characteristics are summarized across studies in Table 5. The type of pain was not well reported. Mean age was 53 years, and 55 percent were female. Baseline pain was 5.35 (95% CI 4.56 to 8.00) on a 0 to 10 scale. One study evaluated outcomes at 3 months (short duration),[90] and the other five were long duration (1 to 4 years observation).[88,89,91-93] The three studies of medical cannabis programs allowed patients to self-select the cannabis products they used and compared them with patients who chose not to enroll in the programs (assumed to be no cannabis use).[88,89,93] Two of the studies were retrospective analyses of larger prospective cohort studies of patients with chronic pain taking opioids,[91,92] based on patient self-report of cannabis use, but specific products used were not reported. In the study of a whole-plant cannabis product, the cannabis group received herbal cannabis containing 12.5 percent (+/- 1.5%) THC.[93] Total daily doses received were reported in two studies with one reporting 93 mg of THC per week (mean) in a medical cannabis program,[90] and the other reporting 2.5 grams per day of a whole-pant cannabis product (dose confirmed with study authors).[93]

Two studies reported on primary pain or function outcomes. A high risk of bias study assessing a medical cannabis program study (n=46) found nonstatistically significant differences between groups on measures of pain severity, pain-related disability, quality of life, depression, anxiety, and sleep.[90] A moderate risk of bias study of individuals using opioids also reported no statistically significant differences on pain or pain interference outcomes between frequent cannabis users (daily or near-daily)[91] and nonusers over 4 years of followup. Because the number of patients enrolled changed from year to year along with their cannabis use status, these analyses were conducted based on use in the prior 12 months.

A high risk of bias cohort study (n=431) of a whole-plant cannabis product with 12.5 percent THC (amount of CBD not reported) with 52 weeks of followup reported on adverse events.[93] Patients for whom standard treatments were not effective were enrolled, with patients already using cannabis for pain preferentially enrolled in the treatment group. The median dose was 2.5 gm of herbal cannabis per day (confirmed with study authors as amount dispensed). While the overall percentage of patients reporting any adverse event or SAEs was greater than in other studies, differences were not statistically different between groups. Dizziness was also not reported more often in the cannabis group. Both nausea (16.7% vs. 9.7%, RR 1.72, 95% CI 1.04 to 2.85) and sedation (13.5% vs. 4.6%, RR 2.91, 95% CI 1.46 to 5.83) were reported significantly more frequently in the cannabis group. Study WAEs were poorly reported for the usual care group and occurred in 4.7 percent of those using cannabis.

Four observational studies reported on the association between cannabis use (product unspecified) and opioid use for chronic pain.[88,89,91,92] The studies used different methods and reported outcomes differently, with no consistent direction of effect across the studies. A large, moderate risk of bias, retrospective cohort study (n=10,746) with propensity matching found a nonstatistically significant decrease in weekly oral morphine equivalent (OME) doses in the cannabis group (−183.2 OME, 95% CI −449.8 to 83.3). Preplanned subgroup analyses found that patients taking lower initial doses of opioids (<50 OME weekly) increased opioid use after medical cannabis authorization, while those using higher doses at baseline (>100 OME weekly) had a decrease (−435.5, 95% CI −596.8 to −274.2). Discontinuation of prescription opioids was found to be less likely in the cannabis group versus the control group (49.3% vs. 72.3%, adjusted OR 0.38, 95% CI 0.34 to 0.41).

In a moderate risk of bias study (n=1,514 at baseline, 1,217 at year 4) of individuals with chronic pain using opioids, a statistically nonsignificant difference in OME use at 1 year was

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found between patients reporting daily or near daily cannabis use (type and dose reported) and those reporting no use.[91] The analysis used a lagged mixed-effects linear regression model, identifying cannabis use in the prior year and opioid use in the current year across four possible years of study enrollment. The adjusted mean daily OMEs were 97.1 in frequent cannabis users and 85.5 in nonusers (difference 32.76 mg daily, 95% CI, −25.04 to 90.57).

A high risk of bias, 52-week, prospective cohort study of patients with HIV-related chronic pain (n=433) evaluated the effect of cannabis use.[92] At baseline 47 percent were using an opioid for chronic pain. Among daily or near daily cannabis users also using opioids, the adjusted OR for discontinuing opioids was 1.67 (95% CI 0.52 to 5.37). Among daily or near daily cannabis users not using opioids at baseline, the adjusted OR for initiating an opioid was 2.29 (95% CI 0.86 to 6.16). Impact on morphine equivalents were not reported.

In a small (n=66), high risk of bias, retrospective cohort of patients in a medical cannabis program for low back pain, compared with a group who declined to participate, those in the cannabis program were more likely to reduce their daily opioid dose than the control group (83.8% vs. 44.8%, OR 5.12, 95% CI 1.56 to 16.88).[89] The reduction in dose was small, but statistically significant (MD −0.64 mg intravenous morphine equivalent, 95% CI −1.10 to −0.18 from starting mean doses in the two groups of 24.4 mg vs. 16.2 mg).

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

3.3.1 Key Point

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

3.3.2 Summary of Findings

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

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4. Discussion

4.1 Findings in Relation to the Decisional Dilemma(s)

The key decisional dilemmas for treating chronic and subacute pain with plant-based compounds include their effectiveness and safety and the effect of route of administration, formulation, dose or potency of products, types of pain, and other patient characteristics on outcomes, including harms. Important harms include typical adverse effects such as dizziness, sedation and nausea, but may also include more serious risks, such as cannabis use disorder (CUD), psychosis, and cognitive impairment. Potential benefits and harms must be considered in the context of frequent, possibly daily, long-term use. This update did not identify studies of plant-based compounds other than cannabis. Four new studies were added for this update (1 placebo-controlled randomized controlled trial [RCT] of oral purified THC [dronabinol], synthetic CBD, and combined THC/CBD [low THC to CBD ratio],[55] 1 placebo-controlled RCT of purified oral CBD,[57] 1 observational study on the association between use of various cannabinoid products [not specified as synthetic or plant-derived] versus nonuse and risk of cardiovascular events,[59] and 1 observational study comparing different types of cannabis [not specified as synthetic or plant-derived]).[86] For synthetic or purified high THC to CBD products, updated pooled estimates that included one new RCT resulted in findings versus placebo that were similar to the prior update, including small effect on pain intensity, no effect on function or disability, and insufficient evidence for pain response, due to highly inconsistent results (Table 6). Additional RCTs of low THC to CBD products enabled new meta-analyses which did not find synthetic oral CBD alone or combined oral purified THC plus synthetic CBD (ratio ~1:2) to be associated with improved pain intensity, improved function, or likelihood of pain response versus placebo, although there was imprecision in estimates.

Overall, our findings are most applicable to short-term treatment (1 to <6 months), in adults with chronic pain (mainly neuropathic pain) compared with placebo. Although the scope of this living review was expanded in 2023 to include subacute pain and adolescents, no studies addressing these populations have been identified. Change in pain severity was reported across all studies, but other pain-related and overall functional outcomes (including pain interference) were reported sporadically.

Based on previously reviewed evidence, extracted comparable THC to CBD ratio oromucosal spray is probably associated with small improvements in pain severity (SOE: moderate) (SOE: moderate) versus placebo in the short-term. Although results for overall functioning also favored the comparable ratio oromucosal spray, the effect was slightly below the threshold for a small effect (SOE: moderate). Extracted comparable THC/CBD ratio oromucosal spray may also be associated with a moderate to large increased risk of dizziness (SOE: low), sedation (SOE: low), and nausea (SOE: low) versus placebo, with no effect on serious adverse events (SAEs) or study withdrawal due to adverse events (WAEs). There was a small increase in the proportion of patients with at least 30 percent improvement in pain (pain response) versus placebo; however, the finding was not statistically significant due to imprecision., and the SOE was low.

As noted above, updated findings with one new RCT was consistent with prior conclusions that synthetic or purified oral THC (high THC to CBD ratios) products may be associated with small improvement in pain severity and no effect on overall function (SOE: low). Stratified analyses of placebo-controlled synthetic and purified THC trials indicated that synthetic THC (primarily nabilone) was associated with reduced pain intensity, while there was no clear effect

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on pain intensity for purified dronabinol. This finding is not based on head-to-head comparisons and should be interpreted with caution. There were inconsistent findings from three RCTs of high THC to CBD ratio products and likelihood of pain response, resulting in insufficient evidence to determine effects. As in prior updates, synthetic or purified oral THC products are probably associated with a large increase in risk of dizziness (SOE: moderate) and moderate increased risk of sedation (SOE: low). Although updated meta-analyses for increased risk of WAEs and nausea became statistically significant, the magnitude of effect was unchanged from the prior update (moderate for WAEs and large for nausea) and imprecision remains present because the lower limit of the confidence interval (CI) for these outcomes crossed the threshold for a small effect. Therefore, the SOE for these outcomes remained low. For secondary outcomes, evidence with the addition of the new RCT remained very limited with no clear effect on quality of life, sleep, depression, or anxiety.

Based on previously reviewed evidence, extracted high THC to CBD ratio products may be associated with large increases versus placebo in risk of study WAEs and dizziness (SOE: low). There was insufficient evidence to determine effects on pain. Combining the evidence for all high THC to CBD ratio products resulted in a moderate improvement in pain severity, with a low SOE.

New meta-analyses for low THC to CBD ratio products that included two new trials[55,57] found that neither oral synthetic or purified CBD alone nor oral purified THC (dronabinol) in combination with CBD (ratio ~1:2) was associated with decreased pain intensity, greater likelihood of pain response, or improved function versus placebo (SOE: moderate for oral CBD alone, low for combined THC/CBD). THC/CBD, but not CBD, was associated with increased risk of nausea (SOE: moderate), dizziness (SOE: low), and sedation (SOE: low). Although one new RCT evaluated topical (intraoral) CBD for temporomandibular disorders, the sample size was relatively small, the trial had serious methodological limitations, the origin of CBD (synthetic or plant-derived) was not reported, and it was unclear if effects were intended to be systemic or only topical.[58]

Evidence on whole-plant cannabis, unspecified cannabis products (e.g., patient-choice), extracted and topical low THC to CBD ratio products, other cannabinoids (cannabidivarin [CBDV]), and comparisons with other active interventions or between cannabis-based products remained insufficient to draw conclusions. Evidence for other outcomes reported for comparable THC to CBD and high THC to CBD ratio products was also insufficient (see Appendix G for details).

Other adverse events (psychosis, CUD, cognitive deficits) and secondary outcomes were not reported for specific products. One new cohort study found medical cannabis use (various THC to CBD ratio categories) associated with increased 180-day risk of arrhythmia versus nonuse, but not acute coronary disease.[59]

The 2022 updated Centers for Disease Control and Prevention guideline on opioids for pain does not make recommendations on cannabis for pain. However, the 2019 U.K. National Institute for Health Care and Excellence clinical practice guideline[94] included a strong recommendations against use of cannabis for pain outside of clinical trials, though the guideline has been challenged as overly restrictive.[95] More recently, an international guideline funded by a cannabis research center issued a weak recommendation for use of noninhaled medical cannabis for chronic pain when standard care is not sufficient.[96] Additionally, there have been multiple systematic reviews conducted on the use of cannabinoids to treat chronic pain, including a 2015 publication in the Journal of the American Medical Association, a 2018 Cochrane review, and a

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2017 Veteran's Affairs Evidence Synthesis Program review.[20,97-99] These high-quality reviews found generally similar results as this review indicating some benefit in pain outcomes, primarily for short-term treatment in patients with neuropathic pain. However, the prior reviews combined all forms of cannabinoids in meta-analyses. Our review has more stratified results based on prespecified THC to CBD ratio categories, leading to a higher strength of evidence rating in some cases.[20] In addition, some higher-quality reviews are not current and may be missing newer evidence. Four other systematic reviews examining utility of cannabis for chronic pain were published in 2020; overall, these findings are also consistent with our findings.[100-103] One of the reviews conducted meta-regression, finding that the impact on pain was similar between neuropathic and nonneuropathic pain populations[102] and that pain reduction was of a small magnitude and similar across formulations (inhaled, oral, oromucosal spray).

Our review did not identify eligible evidence on kratom to treat chronic pain. Two recent reviews of kratom provided limited information, and are based on noncomparative data or pharmacological data. One evaluated surveys, cross-sectional studies, and poison-control center studies on the use of kratom; the other is a nonsystematic review addressing pharmacology, pharmacokinetics, prevalence and type of usage, and harms evidence.[27,28] Both found that patients report using kratom as a substitute for opioids apparently as a treatment for self-diagnosed opioid addiction or dependence in Thailand and Malaysia. They reported growing use in the United States for chronic pain and for recreational purposes. They also suggested that kratom may have addictive properties itself with symptoms of physiological withdrawal being common. Nonserious adverse effects include hyperpigmentation of the skin, constipation, weight loss, insomnia, xerostomia, and loss of libido. Poison control center data indicated an increase in calls involving kratom over the past 5 years with multi-substance exposures involving kratom associated with a statistically significant increase in a serious medical event. In cases where kratom was the only substance involved (N=1,174), symptoms included agitation or irritability (23%), tachycardia (21%), nausea (15%), drowsiness/lethargy (14%), vomiting (13.2%), confusion (11%), hypertension (10%), and seizures (10%).[28]

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

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

Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD - Extracted, Oromucosal Spray	Potential effect (4)[b] [✓]	Small effect (7) [✓✓]	No effect[c] (6) [✓✓]
High THC – Synthetic or Purified, Oral	Insufficient (3, 1 new)	Small effect (8, 1 new) [✓]	No effect (3) [✓]
High THC – Extracted, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Extracted CBD, Topical	No evidence	Insufficient (1)	No evidence
Low THC – Synthetic or Purified, Oral[d]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (3, 1 new)[e]** [✓✓]
Low THC – Synthetic CBD Plus Purified THC, Oral[f]	**No effect (2, 1 new)[e]** [✓]	**No effect (2, 1 new)[e]** [✓]	**No effect (1)** [✓]
Low THC – Sublingual CBD/THC, Extracted	No evidence	Insufficient (1)	No evidence

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Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	**Insufficient (1 new)**	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[g]	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] ≥30% improvement from baseline
[b] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[c] The pooled difference of -0.42 (95% CI -0.73 to -0.16) was just below the threshold for a small effect.
[d] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.
[e] Text is bolded to indicate that the strength of evidence has changed.
[f] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.
[g] Comparison was "usual care."
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 7. 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, Oromucosal Spray	No effect (5) [✓]	No effect (3) [✓]	Large effect (6) [✓]	Moderate effect (6) [✓]	Large effect (6) [✓]
High THC – Synthetic or Purified, Oral	Moderate effect[a] (6, 1 new) [✓]	Insufficient (2, 1 new)	Large effect (4, 1 new) [✓✓]	Large effect[a] (4, 1 new) [✓]	Moderate effect (5, 1 new) [✓]
High THC – Extracted, Oral	Large effect (1) [✓]	Insufficient (1)	Large effect (1) [✓]	No evidence	No evidence
Low THC – Extracted CBD, Topical	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Synthetic or Purified CBD, Oral[b]	Insufficient (4, 2 new)	Insufficient (2, 1 new)	**No effect (3, 2 new)[c]** [✓]	**Insufficient (2 new)[c]**	**No effect (3, 2 new)[c]** [✓]
Low THC – Synthetic CBD plus Purified THC, Oral[d]	**Insufficient (2, 1 new)**	**Insufficient (2, 1 new)**	**Potential effect (2, 1 new)[c]** [✓]	**Large effect (2, 1 new)** [✓✓]	**Potential effect (2, 1 new)[c]** [✓]
Low THC – Sublingual CBD/THC, Extracted	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence

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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]
Whole-Plant Cannabis (12% THC)[e]	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] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.
[c] Text is bolded to indicate that the strength of evidence has changed.
[d] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.
[e] Comparison was "usual care."
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.

4.2 Strengths and Limitations

The evidence base on cannabis and other plant-based treatments for chronic and subacute pain has multiple important limitations. Fifty-four percent of trials enrolled patients with chronic pain due to a neuropathic cause (7 in patients with multiple sclerosis, 7 with a mix of conditions or not specified, 2 with diabetic neuropathy, and 1 each with chemotherapy, HIV, back pain, or spinal cord injury). There is little or no evidence on other types of chronic pain, including low back pain, osteoarthritis, fibromyalgia, and inflammatory arthritis. Although inclusion criteria were revised to also address subacute pain, no eligible studies were identified. In terms of age, there is limited evidence on younger and older populations, with most patients being middle-aged (mean age 54 years). Inclusion criteria were expanded in 2023 to include adolescents; however, no eligible studies have identified. Studies generally excluded patients with a history of psychiatric disorders other than prior history of depression or anxiety. Importantly, there was either no evidence or inadequate evidence to evaluate important patient populations based on sex/gender, race/ethnicity, age, or pregnancy/lactating status.

Another limitation is the lack of consistent nomenclature and details regarding the interventions and products studied. For example, products are described as plant-derived in some studies, but without a consistent way of describing the process or the resulting purity of the products. Other studies used words such as "standardized" to describe the amount of THC in a whole-plant cannabis product, again with lack of description of how this was defined or determined. Studies that evaluated products that contained THC and CBD did not consistently report the ratio of THC to CBD, other than for Sativex oromucosal spray (close to a 1 to 1 ratio). Two trials that evaluated topical product did not describe details regarding extraction methods or product purity, and it was unclear if the products were intended to provide local or systemic effects.[58,82] When necessary, we attempted to obtain additional details regarding products from study authors, not all authors responded to queries. Although we attempted to categorize products accurately, some misclassification is possible. Other limitations include the absence of evidence on other plant-based compounds such as kratom, no RCT evidence on whole-plant cannabis products, and insufficient evidence for topical or sublingual CBD and cannabinoids other than THC or CBD due to small numbers of studies and methodological limitations.

Change in pain severity was the most commonly reported outcome. Other important outcomes were mainly not reported or inconsistently reported or defined. Pain response, defined

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as a 30 percent or greater improvement in pain, was reported in 10 of 37 studies (27%); 24 of 37 studies (65%) reported on overall function (including pain interference) or disability. The studies poorly reported baseline use of opioids for pain, and only observational studies (7 studies) reported the impact of cannabis interventions on changes to prescription opioid use. While almost all studies reported the number of patients who withdrew from studies due to adverse events, 49 percent did not report SAEs, and 59 percent did not report the overall adverse events, particularly by group. When SAEs were reported, studies either used a unique definition, or did not provide one. In reporting on specific adverse events, not all studies were clear about whether the events were the number of individuals with at least one event, or if a single patient could contribute to an event more than once. Other adverse events that have been reported in noncomparative observational studies and were prioritized for this review (development or exacerbation of psychosis, CUD, and cognitive deficits) were not reported.

Trials were limited by study design and small sample sizes (range 5 to 339; mean 88), particularly for assessing harms. The SOE of the findings was very commonly downgraded due to imprecise estimates (see Appendix G). There were also differences in some key baseline characteristics, including baseline pain scores, which were frequently not adjusted for in study analyses. Another methodologic concern is that many conclusions in the included studies were drawn from post-hoc analyses. Study durations of included RCTs were primarily short-term and included less than 6 months followup (1 RCT reported intermediate followup durations of 47 weeks); 40 percent of trials were 4 to 6 weeks long. This is a key limitation, as pain severity in patients with chronic pain may vary substantially in the short-term and may be influenced temporarily by an intervention or treatment; it is most useful to understand the enduring impact of a treatment on pain severity. Similarly, adverse events such as CUD, cognitive deficits, and SAEs may take time to develop and longer studies are required to capture such events. Two RCTs[61,75] utilized an enriched enrollment randomized withdrawal design in which all patients receive cannabis in a run-in phase; only patients who respond to cannabis and tolerate it are randomized, to continuation or withdrawal. Such trials are intentionally designed to select for patients who respond to and tolerate cannabis, potentially exaggerating treatment effects and underestimating harms compared to patients not selected based on these features.[104,105] However, our findings were similar when the enriched enrollment randomized withdrawal trials were excluded from analyses. Well-designed head to head studies comparing a plant-based product with a standard of care treatment for chronic pain are lacking. The current evidence consists only of small, poorly designed, crossover or observational studies.

Despite limitations in the evidence base, our review has several strengths. First, the living systematic review approach allows us to add new studies soon after they are published, thereby providing an opportunity to update conclusions in a timely fashion. This may be important as cannabis and other plant-based treatments become more readily available to patients, clinicians, and researchers. For this update, new evidence on high THC to CBD ratio products resulted in reduced effect size for improvement in pain intensity and downgrading of the SOE from low to insufficient for pain response SOE, underscoring the importance of incorporating new evidence. Another strength of our approach is using a framework that categorizes cannabis-related products by both their THC and CBD ratios and type (synthetic or purified and extracted), providing a way to conceptualize the evidence on these two prominent cannabinoids that is consistent with how they are available to consumers. These categories were determined *a priori,* with the input of a Technical Expert Panel convened for this review. A final strength that separates this review

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from others is the exclusion of very short-term studies (e.g., a small number of dosing sessions), improving the applicability of findings to chronic pain, where use is likely to be longer term.

There are also some limitations to our review process. We excluded non-English language publications and study results published only as abstracts.

For almost all analyses, there were too few trials to apply graphical or statistical methods to detect small sample effects,[106] a potential marker of publication bias. Although there were sufficient trials when combining synthetic or purified and extracted high THC to CBD ratio products versus placebo to apply such methods, which indicated potential small sample effects, results are difficult to interpret because a statistical test for small sample effects was above the threshold for statistical significance, and there was potential heterogeneity introduced by combining synthetic and extracted products. We did not identify unpublished trials of high THC to CBD products; one unpublished trial[107] of patients with diabetic neuropathy (n=294) found no difference between nabiximols (comparable THC to CBD ratio oromucosal spray) for diabetic neuropathy (0 to 10 scale, mean difference -0.12, 95% CI -0.60 to 0.36), suggesting that additional unpublished trials could attenuate estimates of effect.

Another potential limitation is that we categorized nabilone as a synthetic high-THC product, although it may be more accurately described as a synthetic cannabinoid – a chemical analog to THC, which could have differing effects than THC/dronabinol. To address this possibility, we performed stratified analyses among outcomes that were pooled for synthetic high-THC interventions. The effect size for change in pain severity was larger with nabilone than with dronabinol, but the difference between the effect sizes was not statistically significant. We also grouped purified THC (dronabinol) or CBD with synthetic dronabinol and CBD, because they are chemically identical to the synthetic product. As noted above, when synthetic THC was analyzed separately from purified THC, benefits were present with synthetic THC but not with purified THC. However, results should be interpreted with caution because they are not based on head-to-head comparisons, and there were potential sources of heterogeneity that could invalidate indirect comparisons. For example, all trials of purified THC evaluated dronabinol, but almost all trials of synthetic THC evaluated nabilone.

Our meta-analyses were based on relatively small numbers of trials (less than 20), which can result in overly narrow estimates using standard random effects approaches, including the profile likelihood model.[108,109] Therefore, we conducted sensitivity analyses using the Bartlett's correction. Although the Bartlett's correction resulted in wider CIs for pooled estimates, it did not change overall conclusions regarding the statistical significance of findings. The exception was high-THC products and increased risk of sedation, which was imprecise and no longer statistically significant using the Bartlett's correction. We did not apply the Bartlett's correction when there were fewer than five studies, because it may result in overly conservative (wide) CIs in this situation.[47] Meta-analyses based on fewer than five studies should be interpreted with caution, as CIs based on the profile likelihood method may be overly precise.

Our inclusion criteria required that the study population have chronic or subacute pain, or have subgroup analyses for this group, which may be why we did not find evidence related to kratom. As in other recent systematic reviews of interventions to treat chronic pain, we grouped the magnitude of effects into small, moderate and large effects, rather than according to published minimal clinically important difference (MCID) thresholds. Defining clinical significance in chronic pain is difficult because it is subjective and difficult to correlate with real-life experiences of patients. For example, the MCID for improvement in pain is 15 points on a 0 to 100 scale.[110] However, interventions commonly used for chronic pain, including opioids and

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nonsteroidal anti-inflammatory drugs do not achieve this level of reduction.[13,15] The typical reduction with opioids, nonopioid medications, nonpharmacological interventions, and cannabinoids is small, 5 to 10 points and may be considered a clinically important effect by patients and clinicians. In addition, when the pooled estimate is close to a predefined effect size threshold, a relatively small change in pooled estimates can result in recategorization. In this update, for synthetic high THC to CBD ratio products versus placebo, the effect size for pain intensity was reclassified from moderate to small, based on the addition of one new trial that decreased the pooled estimate from −1.10 to −0.95, which could suggest a more substantial change in the estimate than actually observed. On the other hand, using predefined thresholds provides consistency in classifying effect size. With more evidence, pooled estimates should become more stable and less likely to require recategorization. Since this is a living systematic review, new evidence will be incorporated into the review and findings updated on a regular basis.

4.3 Applicability

A number of factors could impact the applicability of our findings. The evidence currently is most applicable to patients with neuropathic pain with mostly moderate to severe pain (mean baseline score in RCTs was 6.6 on a 0 to 10 scale, with a range of 4.0 to 8.67). There is also considerable variability within the included studies among the types of neuropathic pain patients experience, and treatment effects might be different depending on the specific neuropathic pain condition. As described above, two RCTs[61,75] utilized an enriched enrollment randomized trial design, which is purposefully designed to selectively randomized patients who respond to cannabis and tolerate it.

The evidence applies to adults with chronic pain. The evidence base addressed similar proportion of men and women, with around 58 percent of enrolled participants across all studies being female. While the age range across studies was broad, with mean study ranges of 24 to 68 years, the evidence is mainly applicable to middle-aged patients (overall mean age 54 years). Therefore, the applicability of findings to older patients, in whom the balance of benefits to harms may be very different, with potentially more harms, is uncertain. No study evaluated adolescents and no study enrolled patients with subacute pain. Non-White individuals were not well-represented in the studies. It is also unclear how the evidence applies to patients currently taking prescription opioids to treat chronic pain or patients with serious mental illness or other comorbidities who are often excluded from trials. There was also insufficient information to determine how findings apply to patients with or without prior cannabis use, as no study stratified findings by prior cannabis use history and reporting of prior use was inconsistent. In terms of interventions, this evidence is most applicable to extracted comparable THC to CBD ratio oromucosal spray, high-THC (THC or THC analogue only) synthetic and purified (dronabinol) oral products, and low-THC (CBD only) synthetic oral products. The evidence for comparable THC to CBD oral spray is applicable to mean dosing of 8.4 sprays per day (23 mg THC/21 mg CBD). The evidence for high THC to CBD ratio synthetic and plant-derived, synthetic equivalent products applies to dosing that was titrated upward, with a maximum dose of 13 to 25 mg per day of dronabinol and 0.25 to 4 mg per day of nabilone (mean doses not reported). For extracted high THC to CBD products, the evidence was too heterogeneous and limited (2 RCTs) to describe a generally applicable dose. For low THC to CBD products, findings are most applicable to oral synthetic CBD at a dose of up to 20 to 50 mg daily and combined oral purified THC and synthetic CBD (synthetic) at a dose of 22.5 to 25 mg THC and

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45 to 50 mg CBD daily. The applicability of evidence to other products including topical or sublingual low THC to CBD ratio products and whole plant cannabis is very low or nonexistent.

Another factor impacting applicability is that availability of the studied cannabis products varies depending on regulatory and other factors. For example, purified THC (dronabinol) was manufactured in the Netherlands and Denmark and may be available in some European countries, but is not approved by the U.S. Food and Drug Administration (FDA) at this time. Nabiximols are manufactured and available in Canada and some European countries, but are not approved by the FDA. In the United States, multiple whole-plant CBD products are available, but their composition varies, none are FDA approved, and availability varies from state to state depending on laws regarding cannabis use. Although our intervention categories were based on THC to CBD ratio and intended to group together interventions more likely to have similar effect, the generalizability of one cannabis product within a particular category to others is uncertain.

This evidence applies to short-term treatment and mainly informs the impact on mean changes in pain severity and common adverse events. The outcomes after longer term treatment may be different and could influence other outcomes not considered in short-term studies included here (e.g. psychosis, CUD, cognitive deficits). Other information for assessing applicability, such as settings for recruiting participants or the number randomized relative to the number eligible, was lacking.

Only 13 percent of studies were conducted in the United States, with the majority being from Europe (58%). We were unable to assess the impact of country of study or other geographic location characteristics (e.g., rural, metropolitan) on the applicability of specific results.

A number of evidence gaps or limitations in the evidence potentially impacted the applicability of our findings including lack of evidence on extracted whole-plant or purified products, whole-plant cannabis, low THC to CBD ratio nonoral products, and kratom.

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

The implications of the present findings for clinical practice and policy are mixed. Our results suggest that select individuals with chronic neuropathic pain may experience small short-term improvements in pain when using high THC to CBD cannabis products (synthetic or plant-derived, synthetic equivalent THC). The impact of this intervention on moderate or long-term outcomes is unknown. Extracted cannabis products with a comparable THC to CBD ratio may also result in small improvements in pain severity. On the rother hand, cannabis products with a low THC to CBD ratio (oral synthetic or purified CBD alone or combined purified THC and synthetic CBD in a ratio of ~1:2) may not result in improvements in pain or function. Those who take products containing comparable or high ratios of THC or combined THC plus CBD in a ~1:2 ratio are also at increased risk for adverse events, including dizziness, sedation and nausea. The expected benefit of cannabis products compared to placebo appears comparable to those observed with prescription opioids, several nonopioid medications, and nonpharmacological interventions.[13,15,16] However, comparing effects of different interventions based on cross-trial comparisons must be done with extreme caution, due to potential differences across studies in the populations studied, interventions evaluated, and outcomes assessed; head-to-head trials are needed to understand the comparative effectiveness of cannabis products versus other interventions. The evidence on adverse events with cannabis-related products is much less robust than the evidence on similar outcomes with opioids or nonopioid medications. The risk of

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sedation and dizziness appears similar with cannabis-related products, opioids, and the anticonvulsants pregabalin and gabapentin, while the risk for nausea may be larger with opioids and the antidepressant duloxetine than with cannabis-related products. However, these comparisons are qualitative and indirect and based on limited evidence on cannabis products relative to the other drugs and require confirmation. Evidence is too limited to compare effects on serious and long-term harms, even indirectly, though respiratory depressant effects of opioids potentially resulting in death are well-known. Understanding how cannabis products' adverse event profiles compare with other available treatments for chronic pain, particularly opioid and nonopioid medications, is essential to determine the benefit to harm ratio. At this time, the strength of this evidence is mostly low, and more data are needed to confidently recommend this as a treatment for various chronic pain-related conditions or for patients with diverse demographic or clinical characteristics. No studies are available to inform decisions regarding use of cannabis for subacute pain or in adolescents.

As noted in the limitations above, baseline use of opioids for pain and the impact of cannabinoids on the use of opioids for pain were very poorly reported. In an effort to more effectively and safely manage chronic pain, a prominent goal of current research is to identify alternative treatments with equal or better benefits for pain while avoiding potential unintended consequences that could result in harms. Unfortunately, much of the findings to date are low SOE or insufficient evidence, and more high-quality studies are needed. Furthermore, the unavailability or unclear availability of studied cannabis products in specific settings may reduce the generalizability of findings.

Our synthesis of the evidence also suggests several important additional questions that might be suitable to be addressed in a clinical practice guideline, based on an assessment of potential benefits and harms, as well as uncertainties in the evidence. Examples of questions that could be addressed through a guideline process include: At what point in the treatment decision tree should cannabis-based medicines be considered? How should patient preferences be taken into account? What are pragmatic dosing guidelines? To further inform guidelines, additional studies on the comparative effects on costs of care would be useful.

4.5 Implications for Future Research

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

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

PICOTS Element	Gap in Evidence	Suggested Future Research
Populations	• Non-White populations, older adults • Pain conditions other than neuropathic pain • Subacute pain • Adolescents	• Studies to specifically recruit non-White participants to ensure appropriate representation and diversity in studied populations • Stratified analyses according to sex, including effects in pregnant and lactating individuals • Studies of patients with subacute pain • Studies of adolescents • Studies to assess effects based on age differences • Pain populations expanded to include patients with nonneuropathic chronic pain, specifically back pain, other musculoskeletal pain, and fibromyalgia

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4 Discussion

PICOTS Element	Gap in Evidence	Suggested Future Research
Interventions	• Extracted high THC to CBD ratio • Comparable THC to CBD ratio formulations other than extracted oromucosal spray • Extracted and nonoral low THC to CBD ratio products, whole-plant cannabis, and other cannabinoids • Kratom	• Studies of extracted high- THC to CBD ratio products, with clear description of extraction or purification process and consistent nomenclature regarding the final product • Studies of extracted low THC to CBD ratio products, with clear description or extraction or purification processes and consistent nomenclature regarding the final product • Studies to compare different routes of administration (e.g., oromucosal spray, oral oil, oral capsule, smoked, etc.) • Studies should include and compare standardized treatment plans • Head-to-head studies on effects of different cannabinoids, including cannabinoids within a THC to CBD ratio category (e.g., synthetic vs. purified THC) • Studies to asses kratom and/or other plant-based treatments
Comparators	• Head-to-head comparisons	• Studies comparing plant-based interventions with other plant-based treatments (including head-to-head comparisons of different cannabis-related products), opioids, nonopioid medications, or nonpharmacological interventions to evaluate active-control comparisons to provide direct evidence on comparative effectiveness
Outcomes	• Pain response (≥30% improvement in pain severity) • Overall function, quality of life • Depression, anxiety, sleep, opioid use • Adverse event outcomes	• Outcomes should be consistently defined and reported across studies; ideally utilizing core outcome sets developed for studies of treatments for chronic pain. • Future studies should include pain response, measures of overall function, and adverse events (overall, serious, and withdrawals due to adverse events at a minimum), in addition to changes in pain severity. • Patient-centered and patient-reported outcomes (e.g., quality of life, depression, anxiety, and sleep) should be measured using validated tools for diagnosis and measurement of change. • In addition to reporting on opioid use prior to study enrollment, future studies should report on use of opioids, and other pain medications, during the trial. In particular, there is a need for more information on possible opioid sparing effects of plant-based treatments. • Studies need to assess serious harms such as development of cannabis use disorder, psychosis, and cognitive deficits. Other adverse events (e.g. sexual dysfunction and oral, dental-related, or pulmonary adverse events from inhaled, buccal, or smoked products) may need to be studied as new data emerge.
Timing	• Limited evidence on studies >6 weeks in duration	• Considering the chronic nature of the conditions, studies should provide followup assessments at longer timepoints, e.g., ≥3, 6 or 12 months

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PICOTS Element	Gap in Evidence	Suggested Future Research
Study Design	• RCTs and cohort studies with adequate sample sizes to evaluate all important outcomes • Cohort studies with adequate control for confounding, ascertainment of exposures and outcomes • RCT and cohort studies with low risk of bias	• All Designs: o Studies with larger sample sizes to adequately power statistical analyses for key outcomes are needed across all interventions except the synthetic medications o Should be designed and powered *a priori* to conduct subgroup analyses on important factors such as race, age, sex, and type of product or dose where these are variable • Cohort studies: o Should be conducted prospectively where possible, and conduct and report on ascertainment and validation of exposure and outcomes following best-practice guidance[102] o Should use appropriate methods to control for confounding on prognostic factors (e.g., baseline pain, prior and continued use of other interventions for pain, psychiatric illnesses) • RCTs: o Should not use run-in periods, or enriched enrollment randomized withdrawal designs that may overestimate effects and limit the generalizability of the findings[111,3] o Should be conducted using the parallel design (not crossover) • Systematic Reviews o As more evidence emerges, analyses should stratify and conduct subgroup analyses based on product specifics, pain conditions, and population characteristics.

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

4.6 Conclusions

Low to moderate strength evidence suggests small improvements in pain (mostly neuropathic), and moderate to large increases in common adverse events (dizziness, sedation, nausea) with extracted comparable THC to CBD ratio and synthetic or purified high THC to CBD ratio products versus placebo during short-term treatment (1 to 6 months). Low to moderate strength evidence suggests that low THC to CBD ratio products (synthetic or purified CBD alone, or purified THC in combination with synthetic CBD) may not be associated with improved outcomes versus placebo. Evidence for whole-plant cannabis, other comparisons, other outcomes, and plant-based compounds was unavailable or insufficient to draw conclusions. No studies evaluated adolescents or cannabis for subacute pain. Imprecision, lack of evidence for moderate and long-term outcomes and other key outcomes, such as SAEs and impact on opioid use during treatment, highlight the need for more research.

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References

1. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain– United States, 2016. JAMA. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464. PMID: 26977696.
2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. MMWR Recomm Rep. 2016 Mar 18;65(1):1-49. doi: 10.15585/mmwr.rr6501e1. PMID: 26987082.
3. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. . MMWR Morb Mortal Wkly Rep. 2018;67(36):1001-6. doi: 10.15585/mmwr.mm6736a2. PMID: 30212442.
4. Institute of Medicine (US) Committee on Advancing Pain Research C, and Education. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: National Academies Press; National Academy of Sciences; 2011.
5. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. The Clinical Journal of Pain. 2008 Jul-Aug;24(6):469-78. doi: 10.1097/AJP.0b013e31816b2f26. PMID: 18574357.
6. Eriksen J, Sjogren P, Bruera E, et al. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain. 2006 Nov;125(1):172-9. doi: 10.1016/j.pain.2006.06.009. PMID: 16842922.
7. U.S. Centers for Disease Control and Prevention. Annual surveillance report of drug-related risks and outcomes--United States, 2017. Atlanta, GA: 2017. https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf.
8. 2019 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. . Published November 1, 2019. https://www.cdc.gov/overdose-prevention/media/pdfs/pubs/2019-cdc-drug-surveillance-report.pdf. Accessed May 7 2024.
9. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers--United States, 1999-2008. MMWR. Morbidity and mortality weekly report. 2011 Nov 04;60(43):1487-92. PMID: 22048730.
10. Drug Abuse Warning Network. The DAWN Report: highlights of the 2010 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. Rockville, MD: Substance Abuse and Mental Health Services Administration; Center for Behavioral Health Statistics and Quality; 2012. https://www.samhsa.gov/data/sites/default/files/DAWN096/DAWN096/SR096EDHighlights2010.htm.
11. National Institute on Drug Abuse. Drug Overdose Death Rates. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates. Accessed May 7 2024.
12. U.S. Department of Health and Human Services. HHS acting secretary declares public health emergency to address national opioid crisis. HHS Press Office; 2017. https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html. Accessed Jul 30 2020.
13. Chou R, Hartung D, Turner J, Blazina I, Chan B, Levander X, McDonagh M, Selph S, Fu R, Pappas M. Opioid Treatments for Chronic Pain [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Apr. Report No.: 20-EHC011. PMID: 32338848.

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14. Dowell D, Ragan KR, Jones CM, et al. CDC guideline for prescribing opioids for chronic pain– United States, 2022. MMWR Recomm Rep 2022. 2022;71((No. RR-3)):1-95. doi: 10.15585/mmwr.rr7103a1.

15. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid pharmacologic treatments for chronic pain. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER228. PMID: 32338847.

16. Skelly AC, Chou R, Dettori JR, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review update. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER227. PMID: 32338846.

17. Stockings E, Campbell G, Hall WD, et al. Cannabis and Cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018 Oct;159(10):1932-54. doi: 10.1097/j.pain.0000000000001293. PMID: 29847469.

18. Sampson PB. Phytocannabinoid Pharmacology: Medicinal Properties of Cannabis sativa Constituents Aside from the "Big Two". J Nat Prod. 2021 Jan 22;84(1):142-60. doi: 10.1021/acs.jnatprod.0c00965. PMID: 33356248.

19. Elikkottil J, Gupta P, Gupta K. The analgesic potential of cannabinoids. J Opioid Manag. 2009 Nov-Dec;5(6):341-57. doi: 10.5055/jom.2009.0034. PMID: 20073408.

20. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73. doi: 10.1001/jama.2015.6358. PMID: 26103030.

21. Vučković S, Srebro D, Vujović KS, et al. Cannabinoids and pain: new insights from old molecules. Front Pharmacol. 2018 Nov 13;9:1259. doi: 10.3389/fphar.2018.01259. PMID: 30542280.

22. Morales P, Hurst DP, Reggio PH. Molecular targets of the phytocannabinoids: a complex picture. Phytocannabinoids. 2017:103-31.

23. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016 06;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002. PMID: 27001005.

24. Boehnke KF, Scott JR, Litinas E, et al. Pills to Pot: Observational Analyses of Cannabis Substitution Among Medical Cannabis Users With Chronic Pain. J Pain. 2019 07;20(7):830-41. doi: 10.1016/j.jpain.2019.01.010. PMID: 30690169.

25. Piper BJ, DeKeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. J Psychopharmacol. 2017 May;31(5):569-75. doi: 10.1177/0269881117699616. PMID: 28372506.

26. Corroon JM, Jr., Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. J Pain Res. 2017;10:989-98. doi: 10.2147/jpr.S134330. PMID: 28496355.

27. Swogger MT, Walsh Z. Kratom use and mental health: a systematic review. Drug Alcohol Depend. 2018 Feb 1;183:134-40. doi: 10.1016/j.drugalcdep.2017.10.012. PMID: 29248691.

28. White CM. Pharmacologic and clinical assessment of Kratom: an update. Am J Health-Syst Pharm. 2019 Nov 13;76(23):1915-25. doi: 10.1093/ajhp/zxz221. PMID: 31626272.

29. Risks of adolescent marijuana use. U.S. Department of Health & Human Services; Office of Population Affairs. https://www.hhs.gov/ash/oah/adolescent-development/substance-use/marijuana/risks/index.html. Accessed May 25, 2020.

30. Swetlitz I. HHS recommended that the DEA make kratom a Schedule I drug, like LSD or heroin. PBS; 2018. https://www.pbs.org/newshour/nation/hhs-recommended-that-the-dea-make-kratom-a-schedule-i-drug-like-lsd-or-heroin. Accessed Jul 14 2021.

PRE-PUBLICATION FINAL

31. Boehnke KF, Gangopadhyay S, Clauw DJ, et al. Qualifying Conditions Of Medical Cannabis License Holders In The United States. Health Aff (Millwood). 2019 02;38(2):295-302. doi: 10.1377/hlthaff.2018.05266. PMID: 30715980.

32. Jaeger K. Congressional committee slams schedule I and calls for marijuana and kratom research. Marijuana Moment; 2019. https://www.marijuanamoment.net/congressional-committee-slams-schedule-i-and-calls-for-marijuana-and-kratom-research/. Accessed Jul 14 2021.

33. NIDA. Hearing on cannabis policies for the new decade. 2020. https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2020/hearing-on-cannabis-policies-for-the-new-decade. Accessed Jul 14 2021.

34. Marin TJ, Van Eerd D, Irvin E, et al. Multidisciplinary biopsychosocial rehabilitation for subacute low back pain. Cochrane Database Syst Rev. 2017 Jun 28;6(6):Cd002193. doi: 10.1002/14651858.CD002193.pub2. PMID: 28656659.

35. Feldman DE, Nahin RL. National Estimates of Chronic Musculoskeletal Pain and Its Treatment in Children, Adolescents, and Young Adults in the United States: Data From the 2007-2015 National Ambulatory Medical Care Survey. J Pediatr. 2021 Jun;233:212-9.e1. doi: 10.1016/j.jpeds.2021.01.055. PMID: 33524388.

36. Zuckermann AME, Battista KV, Bélanger RE, et al. Trends in youth cannabis use across cannabis legalization: Data from the COMPASS prospective cohort study. Prev Med Rep. 2021 Jun;22:101351. doi: 10.1016/j.pmedr.2021.101351. PMID: 33816088.

37. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2018. https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide. Accessed June 1, 2019.

38. Chou R, Ahmed AY, Iyer S, et al. Living Systematic Reviews: Practical Considerations for the Agency for Healthcare Research and Quality Evidence-based Practice Center Program from Year 2 of an Ongoing Review [White Paper]. Agency for Healthcare Research and Quality: Pacific Northwest Evidence-based Practice Center; 2023.

39. Chou R, Ahmed AY, Morasco BJ, et al. Living Systematic Review on Cannabis and Other Plant-based Treatments for Chronic and Subacute Pain. PROSPERO 2021 CRD42021229579 Available from: . https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021229579.

40. Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, Fu R, Dana T, Kraegel P, Griffin J, Grusing S, Brodt E. Noninvasive Treatments for Low Back Pain [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Feb. Report No.: 16-EHC004-EF. PMID: 26985522.

41. Skelly AC, Chou R, Dettori JR, Turner JA, Friedly JL, Rundell SD, Fu R, Brodt ED, Wasson N, Winter C, Ferguson AJR. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Jun. Report No.: 18-EHC013-EF. PMID: 30179389.

42. Klumpers LE, Beumer TL, van Hasselt JG, et al. Novel Δ(9) -tetrahydrocannabinol formulation Namisol® has beneficial pharmacokinetics and promising pharmacodynamic effects. Br J Clin Pharmacol. 2012 Jul;74(1):42-53. doi: 10.1111/j.1365-2125.2012.04164.x. PMID: 22680341.

43. Morton SC, Murad MH, O'Connor E, et al. Quantitative synthesis—an update: Agency for Healthcare Research and Quality (US), Rockville (MD); 2018.

44. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120.

PRE-PUBLICATION COPY

45. Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. Statistics in medicine. 1996 Mar 30;15(6):619-29. doi: 10.1002/(SICI)1097-0258(19960330)15:6<619::AID-SIM188>3.0.CO;2-A. PMID: 8731004.

46. Huizenga HM, Visser I, Dolan CV. Testing overall and moderator effects in random effects meta-regression. The British journal of Mathematical and Statistical Psychology. 2011 Feb;64(Pt 1):1-19. doi: 10.1348/000711010x522687. PMID: 21506942.

47. Noma H. Confidence intervals for a random-effects meta-analysis based on Bartlett-type corrections. Stat Med. 2011 Dec 10;30(28):3304-12. doi: 10.1002/sim.4350. PMID: 21964669.

48. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015 Nov;68(11):1312-24. doi: 10.1016/j.jclinepi.2014.11.023. PMID: 25721570.

49. Gerrity M, Fiordalisi C, Pillay J, et al. Roadmap for narratively describing effects of interventions in systematic reviews. AHRQ Methods for Effective Health Care. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.

50. Murad MH, Fiordalisi C, Pillay J, et al. Making narrative statements to describe treatment effects. J Gen Intern Med. 2021 Jan;36(1):196-9. doi: 10.1007/s11606-020-06330-y. PMID: 33111244.

51. Gerrity M, Fiordalisi C, Pillay J, et al. AHRQ methods for effective health care. Roadmap for Narratively Describing Effects of Interventions in Systematic Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.

52. McDonagh MS, Wagner J, Ahmed AY, Fu R, Morasco B, Kansagara D, Chou R. Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021 Oct. Report No.: 21(22)-EHC036. PMID: 34882379.

53. Chou R, Wagner J, Ahmed AY, et al. Living systematic review on cannabis and other plant-based treatments for chronic pain: 2022 update. AHRQ Comparative Effectiveness Reviews. 2022. doi: 10.23970/AHRQEPCCER250UPDATE2022. PMID: 36351096.

54. Chou R, Ahmed AY, Morasco BJ, et al. Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2023 Update. 2023. doi: 10.23970/AHRQEPCCER250UPDATE2023. PMID: 37847805.

55. Hansen JS, Gustavsen S, Roshanisefat H, et al. Cannabis-based medicine for neuropathic pain and spasticity—A multicenter, randomized, double-blinded, placebo-controlled trial. Pharmaceuticals (Basel). 2023a;16(8):1079. doi: 10.3390/ph16081079. PMID: 37630995.

56. Hansen JS, Boix F, Hasselstrom JB, et al. Pharmacokinetics and pharmacodynamics of cannabis-based medicine in a patient population included in a randomized, placebo-controlled, clinical trial. Clin Transl Sci. 2023b;06:06. doi: 10.1111/cts.13685. PMID: 38054364.

57. Pramhas S, Thalhammer T, Terner S, et al. Oral cannabidiol (CBD) as add-on to paracetamol for painful chronic osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Lancet Reg Health Eur. 2023;35doi: 10.1016/j.lanepe.2023.100777. PMID: 38033459.

58. Walczyńska-Dragon K, Kurek-Górecka A, Niemczyk W, et al. Cannabidiol Intervention for Muscular Tension, Pain, and Sleep Bruxism Intensity—A Randomized, Double-Blind Clinical Trial. J Clin Med. 2024;13(5)doi: 10.3390/jcm13051417.

59. Holt A, Nouhravesh N, Strange JE, et al. Cannabis for chronic pain: cardiovascular safety in a nationwide Danish study. European Heart Journal. 2024doi: 10.1093/eurheartj/ehad834. PMID: 38200679.

PRE-PUBLICATION FINAL

60. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006 Jan;45(1):50-2. PMID: 16282192.

61. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.

62. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014 Jan;47(1):166-73. doi: 10.1016/j.jpainsymman.2013.02.018. PMID: 23742737.

63. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007 Dec 15;133(1-3):210-20. PMID: 17997224.

64. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9. PMID: 16186518.

65. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.

66. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.

67. Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Pain Med. 2020;21(10):2212-8. doi: 10.1093/pm/pnaa303. PMID: 33118602.

68. Zajicek JP, Hobart JC, Slade A, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32. doi: 10.1136/jnnp-2012-302468. PMID: 22791906.

69. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. Clin Gastroenterol Hepatol. 2017 Jul;15(7):1079-86.e4. doi: 10.1016/j.cgh.2016.09.147. PMID: 27720917.

70. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ. 2008 Jan 26;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80. PMID: 18182416.

71. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012 Nov;13(8):677-84. doi: 10.1007/s10194-012-0490-1. PMID: 23070400.

72. Rintala DH, Fiess RN, Tan G, et al. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil. 2010 Oct;89(10):840-8. doi: 10.1097/PHM.0b013e3181f1c4ec. PMID: 20855984.

73. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78(5-6):320-9. doi: 10.1159/000481089. PMID: 29073592.

74. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008 Feb;9(2):164-73. PMID: 17974490.

PRE-PUBLICATION FINAL

75. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024. PMID: 22921260.

76. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59. doi: 10.1111/pme.12569. PMID: 25288189.

77. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. J Neurol. 2006 Oct;253(10):1337-41. PMID: 16988792.

78. Zubcevic K, Petersen M, Bach FW, et al. Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment. Eur J Pain. 2022doi: 10.1002/ejp.2072. PMID: 36571471.

79. Eibach L, Scheffel S, Cardebring M, et al. Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial. Clin Pharmacol Ther. 2020 Aug 08;109(4):1055-62. doi: 10.1002/cpt.2016. PMID: 32770831.

80. Kliuk-Ben Bassat O, Schechter M, Ashtamker N, et al. Medical cannabis for pain management in patients undergoing chronic hemodialysis: randomized, double-blind, cross-over, feasibility study. Clin Kidney J. 2023;16(4):701-10. doi: 10.1093/ckj/sfac275. PMID: 37007688.

81. Vela J, Dreyer L, Petersen KK, et al. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. Pain. 2021 Jun 1;163(6):1206-14. PMID: 34510141.

82. Xu DH, Cullen BD, Tang M, et al. The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. Curr Pharm Biotechnol. 2020;21(5):390-402. doi: 10.2174/1389201020666191202111534. PMID: 31793418.

83. Ueberall MA, Vila Silvan C, Essner U, et al. Effectiveness, safety, and tolerability of nabiximols oromucosal spray vs typical oral long-acting opioid analgesics in patients with severe neuropathic back pain: analysis of 6-month real-world data from the German pain e-registry. Pain Med. 2022b;23(4):745-60. doi: 10.1093/pm/pnab263. PMID: 34480564.

84. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011 Jul-Aug;11(4):353-68. doi: 10.1111/j.1533-2500.2010.00427.x. PMID: 21087411.

85. Ueberall MA, Essner U, Silván CV, et al. Comparison of the effectiveness and tolerability of nabiximols (THC:CBD) oromucosal spray versus oral dronabinol (THC) as add-on treatment for severe neuropathic pain in real-world clinical practice: retrospective analysis of the German pain e-registry. J Pain Res. 2022a;15:267-86. doi: 10.2147/JPR.S340968. PMID: 35140513.

86. Schubert EA, Johnstone MT, Benson MJ, et al. Medicinal cannabis for Australian patients with chronic refractory pain including arthritis. Br J Pain. 2023;17(2):206-17. doi: https://dx.doi.org/10.1177/20494637221147115. PMID: 37057257.

87. Tait J, Erridge S, Holvey C, et al. Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK Medical Cannabis Registry. Expert Rev Neurother. 2023:1-11. doi: 10.1080/14737175.2023.2195551. PMID: 37021592.

88. Lee C, Lin M, Martins KJB, et al. Opioid use in medical cannabis authorization adult patients from 2013 to 2018: Alberta, Canada. BMC Public Health. 2021;21(1):843. doi: 10.1186/s12889-021-10867-w. PMID: 33933061.

89. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS ONE. 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795. PMID: 29145417.

PRE-PUBLICATION FINAL

90. Gruber SA, Smith RT, Dahlgren MK, et al. No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. Exp Clin Psychopharmacol. 2021;29(2):147-56. doi: 10.1037/pha0000435. PMID: 33764103.

91. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Health. 2018 Jul;3(7):e341-e50. doi: 10.1016/s2468-2667(18)30110-5. PMID: 29976328.

92. Merlin JS, Long D, Becker WC, et al. Marijuana use is not associated with changes in opioid prescriptions or pain severity among people living with HIV and chronic pain. J Acquir Immune Defic Syndr. 2019 06 01;81(2):231-7. doi: 10.1097/QAI.0000000000001998. PMID: 30865181.

93. Ware MA, Wang T, Shapiro S, et al. Cannabis for the management of pain: assessment of safety study (COMPASS). J Pain. 2015 Dec;16(12):1233-42. doi: 10.1016/j.jpain.2015.07.014. PMID: 26385201.

94. National Institute for Health and Care Excellence. Cannabis-based Medicinal Products: NICE Guideline [NG144]. 2019. https://www.nice.org.uk/guidance/ng144. Accessed Jul 12 2022.

95. Dyer C. Parents can challenge NICE guidance on medicinal cannabis in court. BMJ. 2020 Aug 20;370:m3304. doi: 10.1136/bmj.m3304. PMID: 32819963.

96. Busse JW, Vankrunkelsven P, Zeng L, et al. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. BMJ. 2021 Sep 8;374:n2040. doi: 10.1136/bmj.n2040. PMID: 34497062.

97. Kansagara D, O'Neil M, Nugent S, et al. Benefits and harms of cannabis in chronic pain or post-traumatic stress disorder: a systematic review. Department of Veterans Affairs (US), Washington (DC); 2017.

98. Mucke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018 Mar 07;3(3):CD012182. doi: 10.1002/14651858.CD012182.pub2. PMID: 29513392.

99. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of Cannabis among adults with chronic pain and an overview of general harms: a systematic review. Ann Intern Med. 2017 Sep 05;167(5):319-31. doi: 10.7326/M17-0155. PMID: 28806817.

100. Okusanya BO, Asaolu IO, Ehiri JE, et al. Medical Cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review. Syst Rev. 2020 Jul 28;9(1):167. doi: 10.1186/s13643-020-01425-3. PMID: 32723354.

101. Longo R, Oudshoorn A, Befus D. Cannabis for chronic pain: a rapid systematic review of randomized control trials. Pain Manag Nurs. 2020;22(2):141-9. doi: 10.1016/j.pmn.2020.11.006. PMID: 33353819.

102. Wong SSC, Chan WS, Cheung CW. Analgesic effects of Cannabinoids for chronic non-cancer pain: a systematic review and meta-analysis with meta-regression. J Neuroimmune Pharmacol. 2020 Dec;15(4):801-29. doi: 10.1007/s11481-020-09905-y. PMID: 32172501.

103. Kurlyandchik I, Tiralongo E, Schloss J. Safety and efficacy of Medicinal Cannabis in the treatment of Fibromyalgia: a systematic review. J Altern Complement Med. 2020;27(3):198-213. doi: 10.1089/acm.2020.0331. PMID: 33337931.

104. Campbell J, King NB. “Unsettling circularity”: Clinical trial enrichment and the evidentiary politics of chronic pain. BioSocieties. 2017 2017/06/01;12(2):191-216. doi: 10.1057/biosoc.2016.7.

105. Katz N. Enriched enrollment randomized withdrawal trial designs of analgesics: focus on methodology. Clin J Pain. 2009 Nov-Dec;25(9):797-807. doi: 10.1097/AJP.0b013e3181b12dec. PMID: 19851161.

PREPUBLICATION COPY

106. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011 Jul 22;343:d4002. doi: 10.1136/bmj.d4002. PMID: 21784880.

107. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy. ClinicalTrials.gov Identifier: NCT00710424. Last update posted: 2012. https://www.clinicaltrials.gov/ct2/show/results/NCT00710424?view=results.

108. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med. 2001 Mar 30;20(6):825-40. doi: 10.1002/sim.650. PMID: 11252006.

109. Seide SE, Röver C, Friede T. Likelihood-based random-effects meta-analysis with few studies: empirical and simulation studies. BMC Med Res Methodol. 2019 Jan 11;19(1):16. doi: 10.1186/s12874-018-0618-3. PMID: 30634920.

110. Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine (Phila Pa 1976). 2008 Jan 1;33(1):90-4. doi: 10.1097/BRS.0b013e31815e3a10. PMID: 18165753.

111. Furlan A, Chaparro LE, Irvin E, et al. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag. 2011 Sep-Oct;16(5):337-51. doi: 10.1155/2011/465281. PMID: 22059206.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ANCOVA	analysis of covariance
BPI-SF	Brief Pain Inventory – Short Form
CBC	cannabichromene
CBD	cannabidiol
CBDV	cannabidivarin
CBG	cannabigerol
CI	confidence interval
CUD	cannabis use disorder
DAS28	28-Joint Disease Activity Scale
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FM	fibromyalgia
GHQ-12	Short General Health Questionnaire
GNDS	Guy's Neurological Disability Scale
HADS-D	Hospital Anxiety and Depression Scale
IA	inflammatory arthritis
KQ	Key Question
LAO	long acting opioid
MCID	minimal clinically important difference
MCP	New Mexico Medical Cannabis Program
MD	mean difference
MME	morphine milligram equivalents
MS	multiple sclerosis
NA	not applicable
NPP	neuropathic pain
NR	not reported
NRS	numerical rating scale
ODI	Oswestry Disability Index
OME	oral morphine equivalent
OR	odds ratio
PBC	plant-based compound
PDI	Pain Disability Index
PICOTS	populations, interventions, comparators, outcomes, timing, and settings
PL	profile likelihood

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

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Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) ALL

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

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

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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
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
('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

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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

((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"))

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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. 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 Agency for Healthcare Research and Quality (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.

Key Question 1. In adults or adolescents with chronic or subacute pain, what are the benefits of cannabinoids for treatment of chronic or subacute pain?

Key Question 2. In adults or adolescents with chronic or subacute pain, what are the harms of cannabinoids for treatment of chronic or subacute pain?

Key Question 3. 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?

Key Question 4. 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 (>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

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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

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will be made based on the strength of the RCT evidence. When the RCT evidence on a given Key Question and outcome is insufficient, we will include observational studies that meet inclusion criteria. When the strength of evidence is low, moderate, or high based on RCTs, we will update our protocol to exclude observational studies. We do not anticipate excluding observational studies assessing harms. For all Key Questions, we excluded uncontrolled observational studies, case series, and case reports. Systematic reviews were used to supplement searches and identify primary studies.

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

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through June 30, 2024. Searches were initially run in September 2020 with ongoing, automated monthly searches to identify newly published studies. For the 2023 update, search strategies were updated to include terms for subacute pain and applied to databases from inception to identify studies on subacute pain. No edits were needed to add adolescents, as there were previously no age restrictions in the strategies; however, a separate search was conducted from inception focused on adolescents and reviewed. Additionally, we re-assessed previously excluded studies for eligibility based on revised inclusion criteria. Search strategies are shown in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and reviewing the two prior AHRQ pain reports[3,4] for studies that met our inclusion criteria. A Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies for the original version of this report. As part of living systematic review methods, the electronic searches were automated to be run on a biweekly basis, with results emailed directly to the EPC librarian and the research team for processing. Citations were uploaded into DistillerSR® software for study selection management.

The updated criteria listed above were used to determine eligibility for inclusion and exclusion of abstracts. Using Distiller® SR, the review team conducted manual online assessment of study citations. All citations deemed potentially relevant by at least one of the reviewers were retrieved for full-text review. To ensure accuracy, any citation deemed not relevant for full-text review were reviewed by a second researcher. We initially planned to explore using the Distiller® AI feature to automate exclusion of abstracts that are clearly not relevant. Briefly, Distiller®SR AI is training in the background, learning from the human decisions on abstract eligibility. We planned to utilize the Distiller® AI decisions to assist with dual review when it reached a level of 95 percent accuracy (this typically takes 2000 citations, but varies by topic).[5] However, the biweekly citation counts have been low, so the AI feature has not been required.

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

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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 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,[6] and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force.[7] 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.[8] 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[3,4] 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).[3,4,9-11]

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.[12] 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,[13] 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[3,4,9-11] 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

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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
No effect/trivial effect	Below thresholds for small effect
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

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

Findings that were not statistically significant were interpreted as follows:

- In determining the strength of evidence (SOE), the precision of evidence was downgraded two levels if inadequate sample size (optimal information size) *and* the 95% confidence interval includes both potentially meaningful benefit and harm (e.g. for a relative effect, the lower bound is ≤ 0.75 *and* the upper bound is ≥ 1.25)[14]
- If the magnitude of effect is below the threshold for a small effect, the finding is considered to have "No effect"[3]
- 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."[15]

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.[8] To ensure

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consistency and validity of the evaluation, the strength of evidence is reviewed by the entire team of investigators prior to assigning a final grade on the following factors:

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

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

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Plain-language statements are used in the Main Points, the Evidence Summary and the Discussion to convey the SOE. High SOE is described as "is associated with" or simply "reduces/increases;" moderate SOE is described as "probably;" and low SOE is described as "may be."[16]

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.

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Assessing Applicability

Applicability is assessed in accordance with the AHRQ Methods Guide,[17] 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.

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Appendix B References

1. Chou R, Ahmed AY, Iyer S, et al. Living Systematic Reviews: Practical Considerations for the Agency for Healthcare Research and Quality Evidence-based Practice Center Program from Year 2 of an Ongoing Review [White Paper in Progress]. In: Quality AfHRa, editor: Pacific Northwest Evidence-based Practice Center; 2023.
2. Chou R, Ahmed AY, Morasco BJ, et al. Living Systematic Review on Cannabis and Other Plant-based Treatments for Chronic and Subacute Pain. PROSPERO 2021 CRD42021229579 Available from: . https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021229579.
3. Chou R, Hartung D, Turner J, Blazina I, Chan B, Levander X, McDonagh M, Selph S, Fu R, Pappas M. Opioid Treatments for Chronic Pain [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Apr. Report No.: 20-EHC011. PMID: 32338848.
4. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid pharmacologic treatments for chronic pain. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER228. PMID: 32338847.
5. Taieb V, Smela-Lipińska B, O'Blenis P, et al. Use of artificial intelligence with DistillerSR software for a systematic literature review of utilities in infectious disease. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018 Oct;21(Supplement 3):S387. doi: 10.1016/j.jval.2018.09.2299.
6. Furlan AD, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine. 2009 Aug 15;34(18):1929-41. doi: 10.1097/BRS.0b013e3181b1c99f. PMID: 19680101.
7. U.S. Preventive Services Task Force. Methods and processes. 2019. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes.
8. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2018. https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide. Accessed June 1, 2019.
9. Skelly AC, Chou R, Dettori JR, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review update. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER227. PMID: 32338846.
10. Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, Fu R, Dana T, Kraegel P, Griffin J, Grusing S, Brodt E. Noninvasive Treatments for Low Back Pain [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Feb. Report No.: 16-EHC004-EF. PMID: 26985522.
11. Skelly AC, Chou R, Dettori JR, Turner JA, Friedly JL, Rundell SD, Fu R, Brodt ED, Wasson N, Winter C, Ferguson AJR. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Jun. Report No.: 18-EHC013-EF. PMID: 30179389.
12. Morton SC, Murad MH, O'Connor E, et al. Quantitative synthesis—an update: Agency for Healthcare Research and Quality (US), Rockville (MD); 2018.
13. Huizenga HM, Visser I, Dolan CV. Testing overall and moderator effects in random effects meta-regression. The British journal of mathematical and statistical psychology. 2011 Feb;64(Pt 1):1-19. doi: 10.1348/000711010x522687. PMID: 21506942.
14. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283-93. doi: 10.1016/j.jclinepi.2011.01.012. PMID: 21839614.

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15. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2 Suppl):53s-70s. doi: 10.1378/chest.11-2288. PMID: 22315256.

16. Gerrity M, Fiordalisi C, Pillay J, et al. AHRQ methods for effective health care. Roadmap for Narratively Describing Effects of Interventions in Systematic Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.

17. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.

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Appendix C. Included Studies List

1. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011 Jul-Aug;11(4):353-68. doi: 10.1111/j.1533-2500.2010.00427.x. PMID: 21087411.
2. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006 Jan;45(1):50-2. PMID: 16282192.
3. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Health. 2018 Jul;3(7):e341-e50. doi: 10.1016/s2468-2667(18)30110-5. PMID: 29976328.
4. Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Pain Med. 2020;21(10):2212-8. doi: 10.1093/pm/pnaa303. PMID: 33118602.
5. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. Clin Gastroenterol Hepatol. 2017 Jul;15(7):1079-86.e4. doi: 10.1016/j.cgh.2016.09.147. PMID: 27720917.
6. Eibach L, Scheffel S, Cardebring M, et al. Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial. Clin Pharmacol Ther. 2020 Aug 08;109(4):1055-62. doi: 10.1002/cpt.2016. PMID: 32770831.
7. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ. 2008 Jan 26;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80. PMID: 18182416.
8. Gruber SA, Smith RT, Dahlgren MK, et al. No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. Exp Clin Psychopharmacol. 2021;29(2):147-56. doi: 10.1037/pha0000435. PMID: 33764103.
9. Hansen JS, Boix F, Hasselstrom JB, et al. Pharmacokinetics and pharmacodynamics of cannabis-based medicine in a patient population included in a randomized, placebo-controlled, clinical trial. Clin Transl Sci. 2023b;06:06. doi: https://dx.doi.org/10.1111/cts.13685. PMID: 38054364.
10. Hansen JS, Gustavsen S, Roshanisefat H, et al. Cannabis-based medicine for neuropathic pain and spasticity—A multicenter, randomized, double-blinded, placebo-controlled trial. Pharmaceuticals (Basel). 2023a;16(8):1079. doi: 10.3390/ph16081079. PMID: 37630995.
11. Holt A, Nouhravesh N, Strange JE, et al. Cannabis for chronic pain: cardiovascular safety in a nationwide Danish study. European Heart Journal. 2024doi: 10.1093/eurheartj/ehad834. PMID: 38200679.
12. Kliuk-Ben Bassat O, Schechter M, Ashtamker N, et al. Medical cannabis for pain management in patients undergoing chronic hemodialysis: randomized, double-blind, cross-over, feasibility study. Clin Kidney J. 2023;16(4):701-10. doi: 10.1093/ckj/sfac275. PMID: 37007688.
13. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.
14. Lee C, Lin M, Martins KJB, et al. Opioid use in medical cannabis authorization adult patients from 2013 to 2018: Alberta, Canada. BMC Public Health. 2021;21(1):843. doi: 10.1186/s12889-021-10867-w. PMID: 33933061.

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15. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014 Jan;47(1):166-73. doi: 10.1016/j.jpainsymman.2013.02.018. PMID: 23742737.

16. Merlin JS, Long D, Becker WC, et al. Marijuana use is not associated with changes in opioid prescriptions or pain severity among people living with HIV and chronic pain. J Acquir Immune Defic Syndr. 2019 06 01;81(2):231-7. doi: 10.1097/QAI.0000000000001998. PMID: 30865181.

17. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007 Dec 15;133(1-3):210-20. PMID: 17997224.

18. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012 Nov;13(8):677-84. doi: 10.1007/s10194-012-0490-1. PMID: 23070400.

19. Pramhas S, Thalhammer T, Terner S, et al. Oral cannabidiol (CBD) as add-on to paracetamol for painful chronic osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Lancet Reg Health Eur. 2023;35doi: 10.1016/j.lanepe.2023.100777. PMID: 38033459.

20. Rintala DH, Fiess RN, Tan G, et al. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil. 2010 Oct;89(10):840-8. doi: 10.1097/PHM.0b013e3181f1c4ec. PMID: 20855984.

21. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9. PMID: 16186518.

22. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78(5-6):320-9. doi: 10.1159/000481089. PMID: 29073592.

23. Schubert EA, Johnstone MT, Benson MJ, et al. Medicinal cannabis for Australian patients with chronic refractory pain including arthritis. Br J Pain. 2023;17(2):206-17. doi: https://dx.doi.org/10.1177/20494637221147115. PMID: 37057257.

24. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.

25. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.

26. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008 Feb;9(2):164-73. PMID: 17974490.

27. Tait J, Erridge S, Holvey C, et al. Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK Medical Cannabis Registry. Expert Rev Neurother. 2023:1-11. doi: 10.1080/14737175.2023.2195551. PMID: 37021592.

28. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024. PMID: 22921260.

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29. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59. doi: 10.1111/pme.12569. PMID: 25288189.

30. Ueberall MA, Essner U, Silván CV, et al. Comparison of the effectiveness and tolerability of nabiximols (THC:CBD) oromucosal spray versus oral dronabinol (THC) as add-on treatment for severe neuropathic pain in real-world clinical practice: retrospective analysis of the German pain e-registry. J Pain Res. 2022a;15:267-86. doi: 10.2147/JPR.S340968. PMID: 35140513.

31. Ueberall MA, Vila Silvan C, Essner U, et al. Effectiveness, safety, and tolerability of nabiximols oromucosal spray vs typical oral long-acting opioid analgesics in patients with severe neuropathic back pain: analysis of 6-month real-world data from the German pain e-registry. Pain Med. 2022b;23(4):745-60. doi: 10.1093/pm/pnab263. PMID: 34480564.

32. Vela J, Dreyer L, Petersen KK, et al. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. Pain. 2021 Jun 1;163(6):1206-14. PMID: 34510141.

33. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS ONE. 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795. PMID: 29145417.

34. Walczyńska-Dragon K, Kurek-Górecka A, Niemczyk W, et al. Cannabidiol Intervention for Muscular Tension, Pain, and Sleep Bruxism Intensity—A Randomized, Double-Blind Clinical Trial. J Clin Med. 2024;13(5). doi: 10.3390/jcm13051417.

35. Ware MA, Wang T, Shapiro S, et al. Cannabis for the management of pain: assessment of safety study (COMPASS). J Pain. 2015 Dec;16(12):1233-42. doi: 10.1016/j.jpain.2015.07.014. PMID: 26385201.

36. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. J Neurol. 2006 Oct;253(10):1337-41. PMID: 16988792.

37. Xu DH, Cullen BD, Tang M, et al. The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. Curr Pharm Biotechnol. 2020;21(5):390-402. doi: 10.2174/1389201020666191202111534. PMID: 31793418.

38. Zajicek JP, Hobart JC, Slade A, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32. doi: 10.1136/jnnp-2012-302468. PMID: 22791906.

39. Zubcevic K, Petersen M, Bach FW, et al. Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment. Eur J Pain. 2022doi: 10.1002/ejp.2072. PMID: 36571471.

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Appendix D. Results – Study Level Summary Tables and Meta-Analyses

Appendix D-1. Individual Study Summary Tables

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

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Blake, 2006 Moderate RCT Inflammatory arthritis-rheumatoid arthritis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 5.4 sprays/day (31) B: Placebo (27) 5 weeks Whole plant extracted	Pain severity (mean [SD NR] 0 to 10 NRS scale): 3.1 vs. 4.1, MD −1.04[b] (95% CI −1.9 to −0.18)	Function (mean [SD NR] 0 to 10 28−Joint Disease Activity Score scale): 5 vs. 5.9, MD −0.76[c] (95% CI −1.23 to −0.28)	SAE: 0/31 (0%) vs. 2/27 (7.41%), 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)
Langford, 2013 Low RCT Neuropathic pain- multiple sclerosis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.8 sprays/day (167) B: Placebo (172) 15 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 83/167 (49.75%) vs. 77/172 (44.77%), RR 1.11 (95% CI 0.89 to 1.39) Pain severity (mean [SD] 0 to 10 NRS scale): 4.54 (2.24) vs. 4.73 (2.26), MD −0.19 (SE 0.24) (95% CI −0.67 to 0.29)	Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.12, p=0.56 Function (0 to 100 SF−36 Physical Functioning scale): Treatment difference −0.45, p=0.785	WAE: 15/167 (8.98%) vs. 12/172 (6.98%), RR 1.29 (95% CI 0.62 to 2.67)
Lynch, 2014 High RCT (crossover) Neuropathic pain-chemotherapy induced	A: THC/CBD oromucosal spray (dose NR), mean dose 8 sprays/day (8) B: Placebo (8) 4 weeks Whole plant extracted	Pain severity (mean, 0 to 10 NRS−PI scale): 6 (95% CI 6.98 to 5.02) vs. 6.38 (95% CI5.67 to 7.09)	Function (mean [SD] 0 to 100 SF−36 Physical Functioning scale): 35.5 (9.19) vs. 46.5 (8.5), MD −11 (4.43) (95% CI −20.49 to −1.51)	SAE: 0/8 (0%) vs. 0/8 (0%), 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)

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

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

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

[b] Difference in median differences.

[c] Difference in mean differences.

[d] Mean sprays calculated by systematic review team.

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Chaves, 2020 Low RCT Fibromyalgia	A: 1.2 mg THC/0.02 mg CBD sublingual drops, mean 3.6 drops/day (8) B: Placebo (9) 8 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 FIQ scale): 3.75 (2.49) vs. 7.67 (1.84), MD −3.92 (1.05) (95% CI −6.17 to −1.68)	Function (mean [SD] 0 to 10 FIQ scale): 5.83 (2.02) vs. 4.07 (2.25), MD 1.76 (1.04) (95% CI −0.46 to 3.98)	WAE: 0/8 (0%) vs. 0/9 (0%), RR 1.11 (95% CI 0.02 to 50.43)
de Vries, 2017 Moderate RCT Visceral pain- chronic pancreatitis and postsurgical abdominal pain	A: THC oral tablet (Dronabinol), range 15 to 24 mg/day (30) B: Placebo (32) 7 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 2.4 (2.28) vs. 3.5 (2.42), MD −1.1 (SE 0.68) (95% CI −2.46 to 0.26)	NR	WAE: 7/30 (23.33%) vs. 2/32 (6.25%), RR 3.73 (95% CI 0.84 to 16.57)
Frank, 2008 Moderate RCT (crossover) Neuropathic pain	A: THC oral capsule (Nabilone), max dose 2 mg/day (48) B: Dihydrocodeine 30 mg, max dose 240 mg/day (48) 6 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): Treatment effect 5.7 (95% CI 0.5 to 10.9)	Function (mean [SD NR] 0 to 100 SF−36 Physical Functioning scale): Treatment effect 10.8 (95% CI 2.3 to 19.2)	SAE: 0/48 (0%) vs. 0/48 (0%), RR 1.00 (95% CI 0.02 to 49.40) WAE: 2/48 (4%) vs. 6/48 (12.5%), RR 0.34 (95% CI 0.07 to 1.57)

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Hansen, 2023 Low RCT Neuropathic pain	A: THC 2.5 mg capsule (dronabinol), median dose 22.5 mg/day (32) B: Synthetic CBD 5 mg capsule, median dose 45 mg/day (31) C: CBD/THC capsule, median dose 35 mg synthetic CBD /17.5 mg THC (dronabinol)/day (31) D: Placebo (40)	Pain response ≥30% (NRS scale): 7/24 (29.2%) vs. 11/27 (40.7%) vs.14/28 (50%) vs.16/35 (45.7%), RR (95% CI) A vs. B: 0.72 (0.33 to 1.55) A vs. C: 0.58 (0.28 to 1.20) A vs. D: 0.64 (0.31 to 1.31) B vs. C: 0.81 (0.45 to 1.46) B vs. D: 0.89 (0.50 to 1.59) C vs. D: 1.09 (0.65 to 1.83) Pain severity change from baseline (mean [SDI] 0 to 10 NRS scale): −1.4 (2) vs. −1.4 (1.6) vs. −1.6 (1.8) vs. −1.8 (1.8)	NR	SAE: 2/32 (6.5%) vs. 0/31 (0%) vs. 0/31 (0%) vs. 2/40 (5%), RR (95% CI) A vs. B: 4.85 (0.24 to 97.11) A vs. C: 4.85 (0.24 to 97.11) A vs. D: 1.25 (0.18 to 8.39) B vs. C: 1.00 (0.02 to 48.87) B vs. D: 0.26 (0.013 to 5.15) C vs. D: 0.26 (0.013 to 5.15) WAE: 5/32 (15.6%) vs. 0/31 (0%) vs. 3/31 (9.7%) vs. 1/40 (2.5%), RR (95% CI) A vs. B: 10.67 (0.61 to 185.14) A vs. C: 1.61 (0.42 to 6.19) A vs. D: 6.25 (0.77 to 50.84) B vs. C: 0.14 (0.0077 to 2.65) B vs. D: 0.43 (0.018 to 10.14) C vs. D: 3.87 (0.42 to 35.43)

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Pini, 2012 Low RCT (crossover) Headache- medication overuse headache	A: THC 0.5 mg oral capsule (Nabilone) daily (26) B: Ibuprofen 400 mg/day (26) 8 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 5.55 (2.5) vs. 6.75 (2.4), MD −1.2 (0.68) (95% CI −2.57 to 0.17)	NR	WAE: 1/30 (3.33%) vs. 1/30 (3.33%), RR 1.00 (95% CI 0.66 to 15.26)
Rintala, 2010 High RCT (crossover) Neuropathic pain- spinal cord injury	A: THC 5 mg oral capsule (Dronabinol), max dose 20 mg/day (7) B: Diphenhydramine 25 mg, max dose 75 mg/day (5) 47 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 BPI scale): 5.8 vs. 5.8	NR	SAE: 1/7 (14.29%) vs. 1/5 (20%), RR 0.71 (95% CI 0.57 to 8.91) WAE: 1/7 (14.29%) vs. 0/5 (0%), RR 2.25 (95% CI 0.11 to 46.13)
Schimrigk, 2017 Low RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg oral capsule (Dronabinol), mean dose 13 mg/day (124) B: Placebo (116) 16 weeks Synthetic	Pain severity (mean [SD] 0 to 10 NRS scale): 4.48 (2.04) vs. 4.92 (2.04), MD NR, p=0.676	NR	SAE: 12/124 (9.68%) vs. 7/116 (6.03%), 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)
Skrabek, 2008 Moderate RCT Fibromyalgia	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 2 mg/day (15) B: Placebo (18) 4 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 VAS scale): 4.8 vs. 5.6, MD −1.43, p<0.05	NR	SAE: 0/15 (0%) vs. 0/18 (0%), 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)
Toth, 2012 Low RCT Neuropathic pain- diabetic neuropathy	A: THC 0.5 mg oral capsule (Nabilone), max dose 4 mg/day (13) B: Placebo (13) 5 weeks Synthetic	Pain response ≥30% (NRS scale): 11/13 (84.62%) vs. 5/13 (38.46%), RR 2.2 (95% CI 1.06 to 4.55) Pain severity (mean [SD] 0 to 10 NRS scale): 3.5 (1.3) vs. 5.4 (1.7), MD −1.9 (0.59) (95% CI −3.13 to −0.68)	Pain interference (mean [SD] 0 to 10 MBPI scale): 2.5 (1.6) vs. 3.6 (0.9), MD −1.1 (0.51) (95% CI −2.15 to −0.05)	NR
Turcotte, 2015 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), max dose 2 mg/day (8) B: Placebo (7) 9 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): 35 vs. 57[b]	Pain interference (mean [SD NR] 0 to 100 VAS impact scale): 41 vs. 40[b]	SAE: 0/8 (0%) vs. 0/7 (0%), 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)

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Wissel, 2006 High RCT (crossover) Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 1 mg/day (13) B: Placebo (13) 4 weeks Synthetic	Pain severity (median [SD NR] 11 Point Box Test): 4 vs. 6, p<0.05	NR	WAE: 2/13 (15.38%) vs. 0/13 (0%), RR 5.00 (95% CI 0.26 to 95.02)
Zajicek, 2012 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg capsule, max dose 25 mg/day (143) B: Placebo (134) 12 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 CRS scale): 4.1 (2.9) vs. 4.7 (3.0), MD −0.6 (95% CI −1.3 to 0.1)	NR	SAE: 7/143 (4.9%) vs. 3/134 (2.24%), 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)
Zubcevic, 2022 Low RCT Peripheral neuropathic pain	A: THC 2.5 mg capsule (dronabinol), max dose 25 mg/day (28) B: Synthetic CBD 5 mg capsule, max dose 50 mg/day (27) C: CBD/THC capsule, max dose 50 mg CBD/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 = relative risk; VAS = visual analog scale; WAE = withdrawal due to due adverse events.

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

[b] Estimated from graph.

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Bassat, 2023 High RCT (crossover) Chronic pain-mixed	A: 3 drops (2.5 mg THC/15 mg CBD) sublingual oil, max dose 18 drops per day (15 mg THC/90 mg CBD) (7) B: 3 drops (2.5 mg THC/15 mg CBD) ≥97% purified sublingual oil, max dose 18 drops per day (15 mg THC/90 mg CBD) (5) C: Placebo (9) 16 weeks Whole plant extracted	NR	NR	SAE: 6/9 (67%) vs. 4/6 (67%) vs. 3/10 (30%) WAE: 1/4 (25%) vs. 1/5 (20%) vs. 1/6 (16.7%)
Pramhas, 2023 Moderate RCT Musculoskeletal – knee osteoarthritis	A: Purified CBD capsule (600 mg/day) (43) B: Placebo (43) 8 weeks Plant-derived	Pain severity change from baseline (mean [95% CI] 0 to 10 WOMAC Pain subscale): −2.5 (−3.3 to −1.8) vs. −2.4 (−3.2 to −1.7)	Physical Function change from baseline (mean [95% CI] 0 to 10 WOMAC scale): −1.5 (−2.4 to −0.7 vs. −1.7 (−2.5 to −0.8) SF-36 Physical Functioning change from baseline (mean [95% CI]): 8 (4.3 11.5) vs. 7.3 (4 to 10.7)	WAE: 9/43 (20.9%) vs. 6/43 (11.6%) RR: 1.5 (95% CI 0.58 to 3.84)
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)	Function/disability (0 to 3 HAQ-DI scale): mean NR, MD 0.03 (95% CI −0.11 to 0.18)	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)

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Walczyńska-Dragon, 2024 Moderate RCT Temporomandibular disorders - Sleep bruxism and muscle-related temporomandibular disorders	A: CBD 10% gel (40 mg CBD/day) (20) B: CBD 5% gel (20% CBD/day) (20) C: Placebo (20) Unknown derivative	Pain severity change from baseline (median [interquartile range] 0 to 10 VAS scale): −5.6 (−2.4) vs. −2.5 (0.63) vs. −0.5 (1.03)	NR	NR
Xu, 2020 High RCT (crossover) Neuropathic pain- mixed	A: CBD cream (250 mg/3 oz) up to 4 times daily (15) B: Placebo (14) 4 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 NPS scale): 3.33 (2.02) vs. 5.55 (2.81), MD −2.22 (95% CI −4.07 to −0.37)	NR	SAE: 0/15 (0%) vs. 0/14 (0%), RR 0.94 (95% CI 0.02 to 44.33)

Abbreviations: CBD = cannabidiol; HAQ-DI = Health Assessment Questionnaire – Disability Index; MD = mean difference; NPS = neuropathic pain scale; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SD = standard deviation; THC = tetrahydrocannabinol; VAS = visual analog scale; WAE = withdrawal due to adverse event; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

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

Table D-4. Other cannabinoids study primary outcomes

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

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

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

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Table D-5. Observational study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Bestard, 2011 Moderate Prospective cohort Neuropathic pain-mixed	A: THC oral capsule (Nabilone), mean dose 3.05 mg/day (49) B: Gabapentin, mean dose 2,295.5 mg/day (52) C: Gabapentin + THC capsule, mean dose NR + 3.02 mg/day (55) 6 months Synthetic	Pain intensity (mean [SD] 0 to 100 VAS scale): 28.0 (10.5) vs. 33.8 (11.6) vs. 33.1 (20.2), MD −5.8 (95% CI −10.18 to −1.42) for A vs. B, −5.1 (95% CI −11.48 to 1.28) for A vs. C	Pain interference (mean [SD] 0 to 10 BPI scale): 4.5 (2.3) vs. 4.6 (2.2) vs. 4.5 (2.2), MD −0.1 (95% CI −0.99 to 0.79) for A vs. B, 0.00 (95% CI −0.88 to 0.88) for A vs. C Function (mean [SD] 0 to 100 SF-36 scale): 48.3 (27.2) vs. 46.5 (25.1) vs. 43.7 (26.4), MD 1.80 (95% CI −8.53 to 12.13) for A vs. B, 4.60 (95% CI −5.83 to 15.03) for A vs. C	SAE: 0/49 (0%) vs. 0/52 (0%) vs. 0/55 (0%) A vs. B RR 1.06 (95% CI 0.21 to 52.41) B vs. C RR 1.06 (95% CI 0.02 to 52.30) A vs. C RR 1.12 (95% CI 0.02 to 55.41) WAE: 5/49 (10%) vs. 12/52 (23%) vs. 5/55 (9%) A vs. B RR 0.44 (95% CI 0.17 to 1.16) B vs. C RR 2.54 (95% CI 0.96 to 6.71) A vs. C RR 1.12 (95% CI 0.35 to 3.65)
Campbell, 2018 Moderate	A: Self-reported frequent cannabis use of ≥20 days/mo B: No cannabis use Overall N Baseline: 1,514 4-year followup: 1,217 Groups unclear 4 years Unclear THC concentration; patient-driven choice	A vs. B (reference) Pain intensity (Adjusted mean [SE]; BPI, 0-10 scale): 5.2 (0.14) vs. 4.9 (0.03); Beta: 0.37 (95% CI, −0.23 to 1.10), p=0.20	A vs. B Pain Interference (Adjusted mean [SE]; BPI pain interference, 0-10 scale): 5.2 (0.19) vs. 5.4 (0.04); Beta: −0.63 (95% CI, −1.46 to 0.19), p=0.13	NR
Gruber, 2021 High Prospective cohort Mixed (primarily musculoskeletal)	A: THC/CBD: Medicinal cannabis program, mean dose THC 13.3 mg/day, CBD 28.9 mg/day (37) B: Usual care, dose NA (9) 12 weeks Mixed cannabis products	Pain intensity (mean [SD] 0 to 100 VAS scale): 34.07 (22.36) vs. 48.78 (30.42); MD −14.71 (95% CI, −32.71 to 3.29)	A vs. B Function (mean [SD], 0 to 10 PDI scale): 18.13 (12.26) vs. 19.22 (12.73); MD −1.09 (95% CI −10.33 to 8.16) SF-36 Function (mean [SD], 0 to 100 scale[a]): 70.00 (22.87) vs. 69.44 (26.98); MD 0.56 (95% CI −17.17 to 18.29)	NR

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Holt, 2024 Moderate Retrospective cohort Mixed (arthritis, neurological, headaches, unspecified pain diagnoses)	A: Patients with chronic pain initiating medical cannabis (THC, THC:CBD, and CBD) during 2018-21 (5,391) B: Matched controls not initiating cannabis (26,941)	NR	NR	NR
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

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Schubert, 2023 High Prospective cohort Chronic refractory pain, including arthritis	A: CBD only (174) B: CBD dominant (two fold ratio increase in main cannabinoid) (37) C: Balanced (113) D: THC dominant (THC only) (27) Prescribed products were either oral liquids, capsules, flos, or granulate	Pain intensity, improved, n (%): 37 (21.3) vs. 8 (21.6) vs. 27 (23.9) vs. 5 (13.5)	Pain interference, improved, n (%): 64 (36.8) vs. 14 (37.8) vs. 49 (43.4) vs. 13 (35.1) Physical function, improved, n (%):57 (32.8) vs. 11 (29.7) vs. 40 (35.4) vs. 12 (32.4)	NR
Tait, 2023 Moderate Prospective cohort Chronic non-cancer pain	A: A. Cannabis-based sublingual/oral medium-chain triglyceride-based oil containing CBD and THC (348) B. Inhaled dried cannabis flower containing trace CBD and THC (36) C. A + B (377) Dried flower concentration: 20% THC, 0% (trace) CBD Cannabis-based oils ranged from all THC, all CBD, and ratios ranging from 1:1 to 1:20	A vs. B vs. C Pain, VAS score (scale 0-10; median, IQR) 1 month: 7.00 (5.00-8.00) vs. 5.50 (3.00-6.75) vs. 6.00 (5.00-7.75) 3 months: 6.00 (4.00-7.00) vs. 5.00 (3.00-7.00) vs. 6.00 (4.00-7.00) 6 months: 6.00 (3.00-7.25) vs. 3.00 (1.50-5.00) vs. 5.00 (3.00-7.00)	A vs. B. vs. C BPI-Interference score (scale 0-10; median, IQR) 1 month: 5.86 (3.64-7.36) vs. 5.14 (2.21-5.93) vs. 5.79 (3.57-7.43) 3 months: 5.29 (3.43-6.82) vs. 4.14 (2.43-6.29) vs. 5.00 (2.86-6.93) 6 months: 4.71 (3.14-6.43) vs. 2.14 (1.50-3.64) vs. 4.50 (2.64-6.64) Likelihood of improvement, adjusted OR A vs. B: 1.61 (95% CI 0.21 to 12.18); A vs. C: 1.90 (95% CI 0.68 to 5.29)	NR

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Ueberall, 2022a Moderate Retrospective cohort Peripheral neuropathic pain- mixed	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 and 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)	A vs. B Pain-related disabilities (mean relative change [improvement] rates at week 24, 0 to 100 VAS scale): 76.0% vs. 68.3%, p<0.001	A vs. B WAE: 5.9% vs. 14.8%, RR 2.5, p<0.001
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	A vs. B 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)	A vs. B 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)

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Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
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	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), RR 21.10 95% CI 1.24 to 357.80)

Abbreviations: BPI = brief pain inventory; CI = confidence interval; CBD = cannabidiol; IQR = interquartile range; MD = mean difference; NR = not reported; OR = odds ratio; 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.

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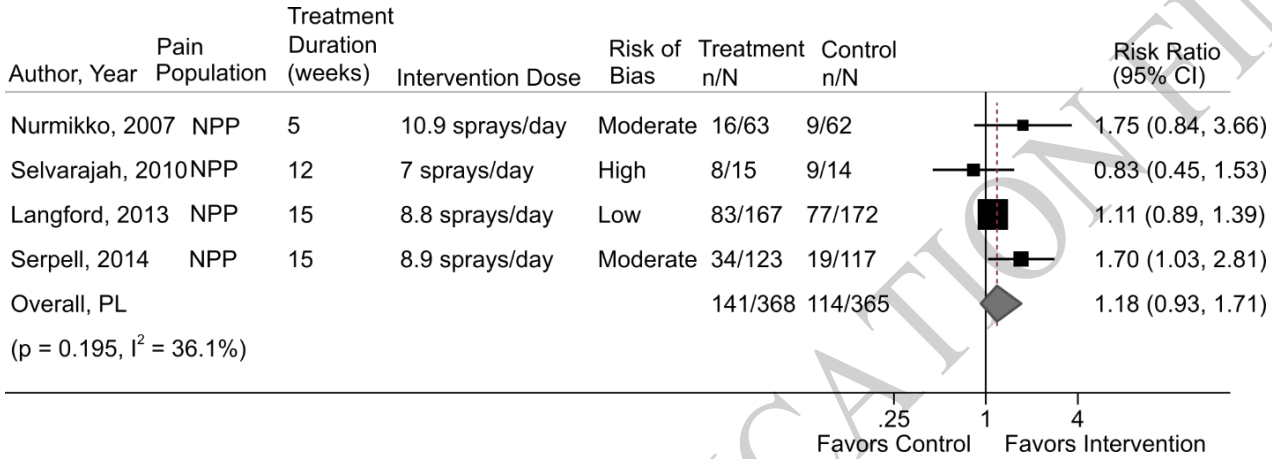
Appendix D-2. Meta-Analyses

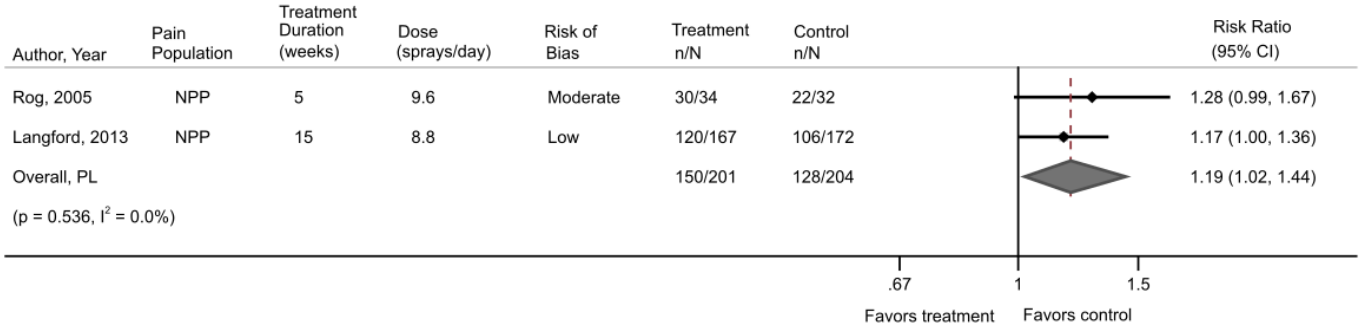
Comparable THC to CBD Ratio Studies

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



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

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



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

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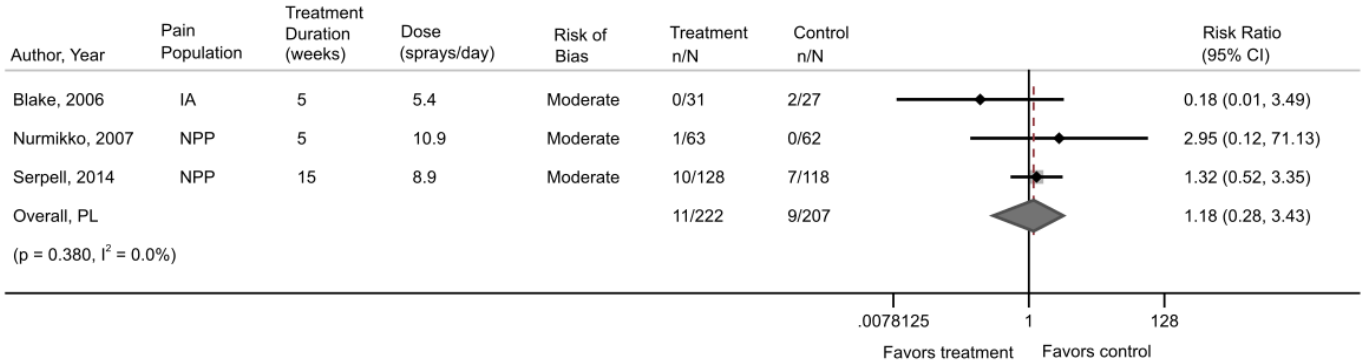
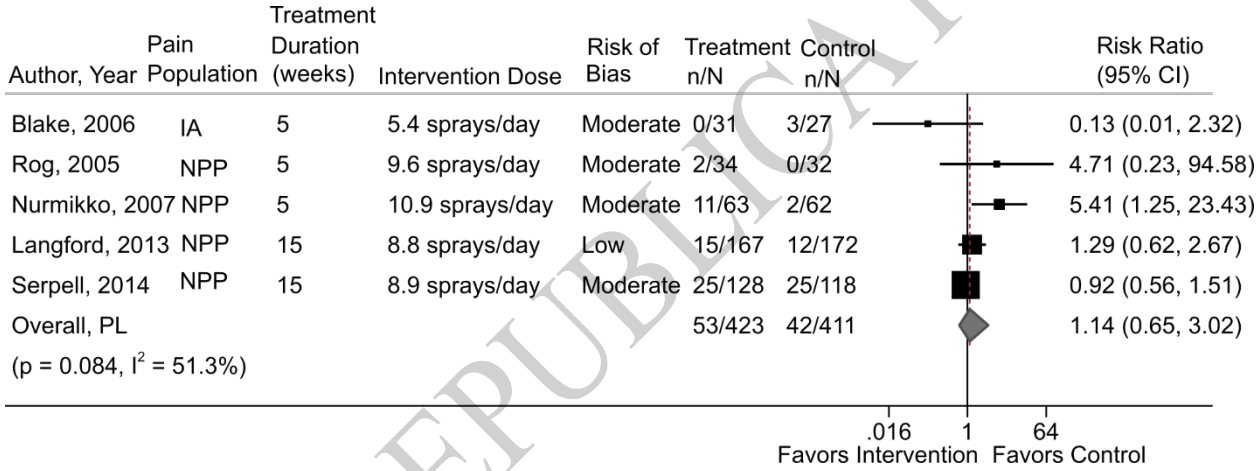
Figure D-3. Serious adverse events for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)



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

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



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

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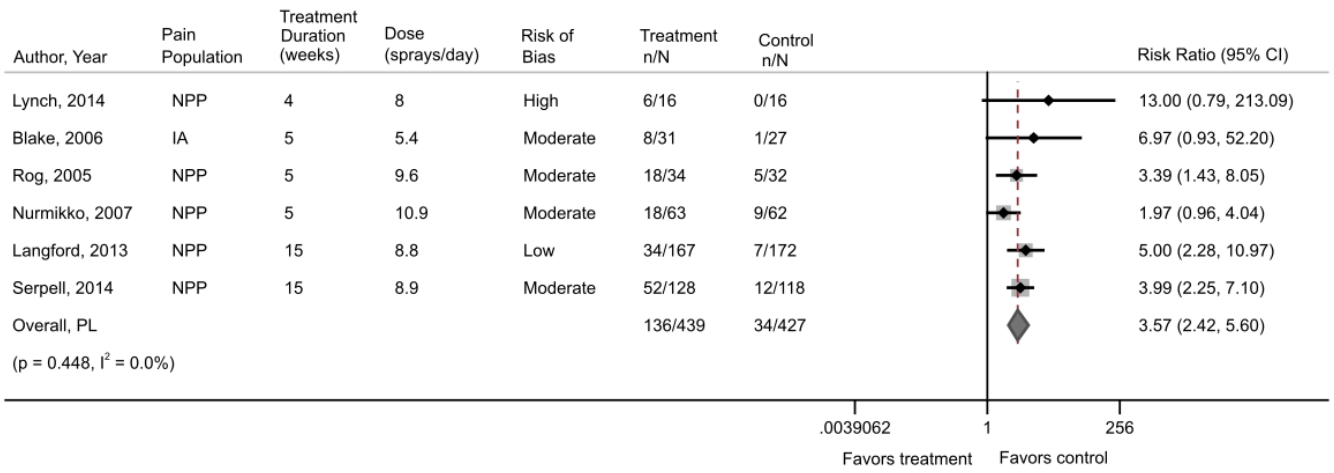
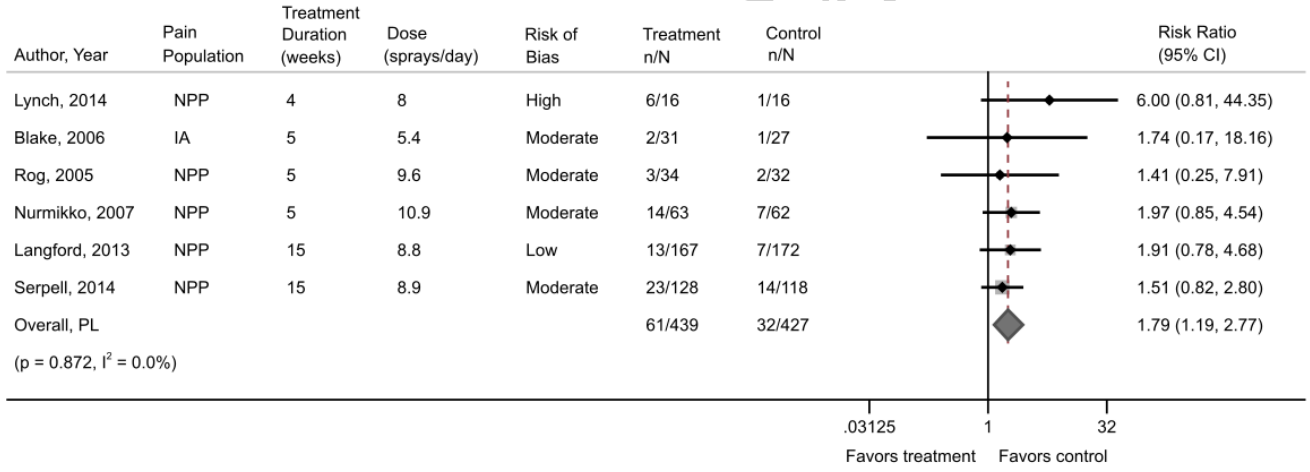
Figure D-5. Dizziness for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)



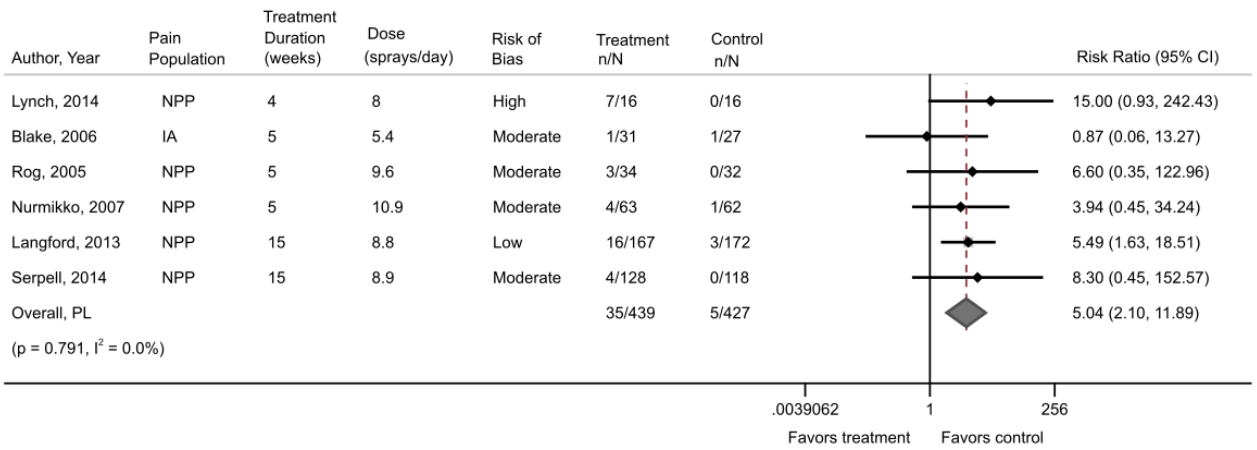
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

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



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

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



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

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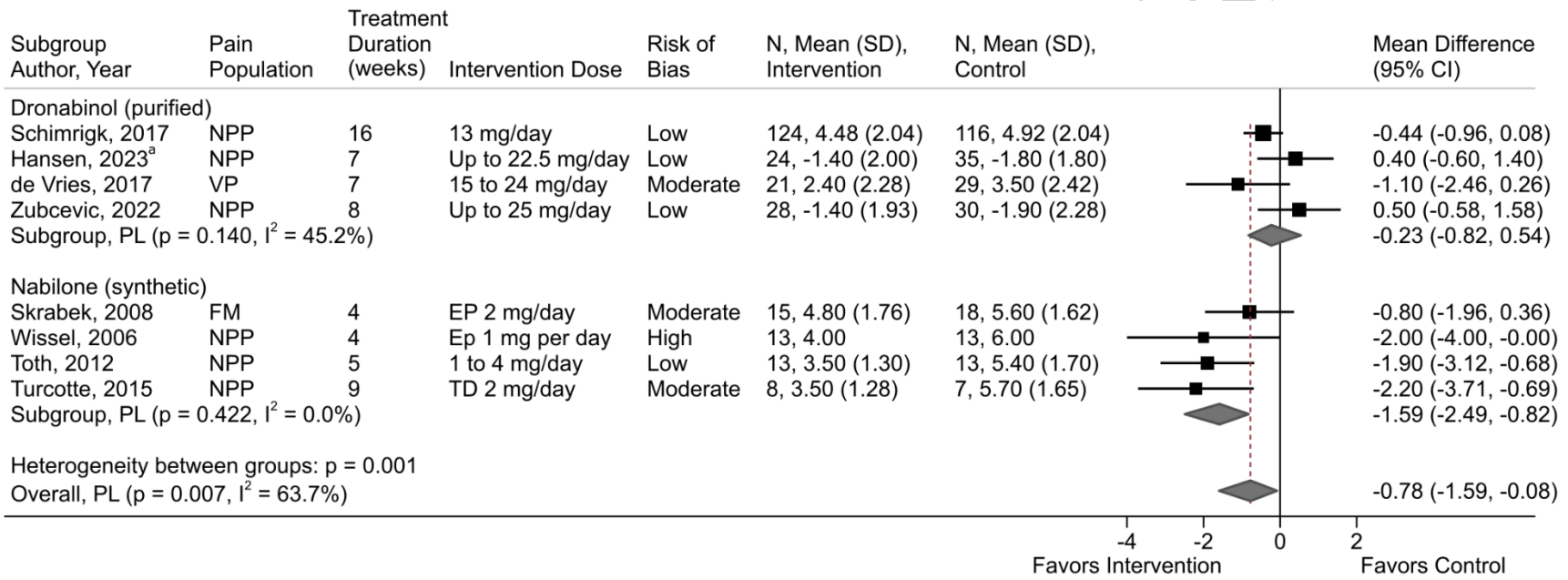
High THC to CBD Ratio Studies

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



Abbreviations: CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; RCT = randomized controlled trial; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain

[a] Study is new to the 2024 update.

Table D-6. Interaction effect of randomized controlled trials assessing synthetic cannabinoids: nabilone versus dronabinol

Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−1.46	0.498	−2.92	0.027	−2.67 to −0.237

Table D-7. 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%

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THC to CBD Ratio	Outcome	N; k Studies	Point Estimate	PL 95% CI	BC 95% CI	I-Squared
Comparable	WAEs	N=834; k=5	RR 1.14	0.65 to 3.02	0.31 to 6.16	51%
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 (all)	Pain severity	N=801; k=10	MD −0.98	−1.80 to −0.32	−1.89 to −0.25	68%
High (synthetic or purified)	Pain severity	N=507; k=8	MD −0.78	−1.59 to −0.08	−1.71 to 0.01	64%
High (all)	WAEs	N=764; k=7	RR 2.32	1.41 to 4.43	1.13 to 5.83	0%
High (synthetic or purified)	WAEs	N=487; k=6	RR 1.92	1.10 to 4.80	0.69 to 9.12	0%
High (all)	Dizziness	N=709; k=5	RR 3.10	1.43 to 6.23	1.17 to 7.43	76%
High (all)	Sedation	N=458; k=5	RR 1.57	1.11 to 2.29	0.99 to 2.78	0%

Abbreviations: BC = Bartlett's correction; CBD = cannabidiol; CI = confidence interval; MD = mean difference; PL = profile likelihood; RR = relative risk; SAE = serious adverse event; THC = tetrahydrocannabinol; WAE = study withdrawals due to adverse event

Table D-8. Interaction effect of randomized controlled trials: synthetic or purified versus extracted interventions

Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−1.02	0.960	−1.07	0.318	−3.24 to 1.19

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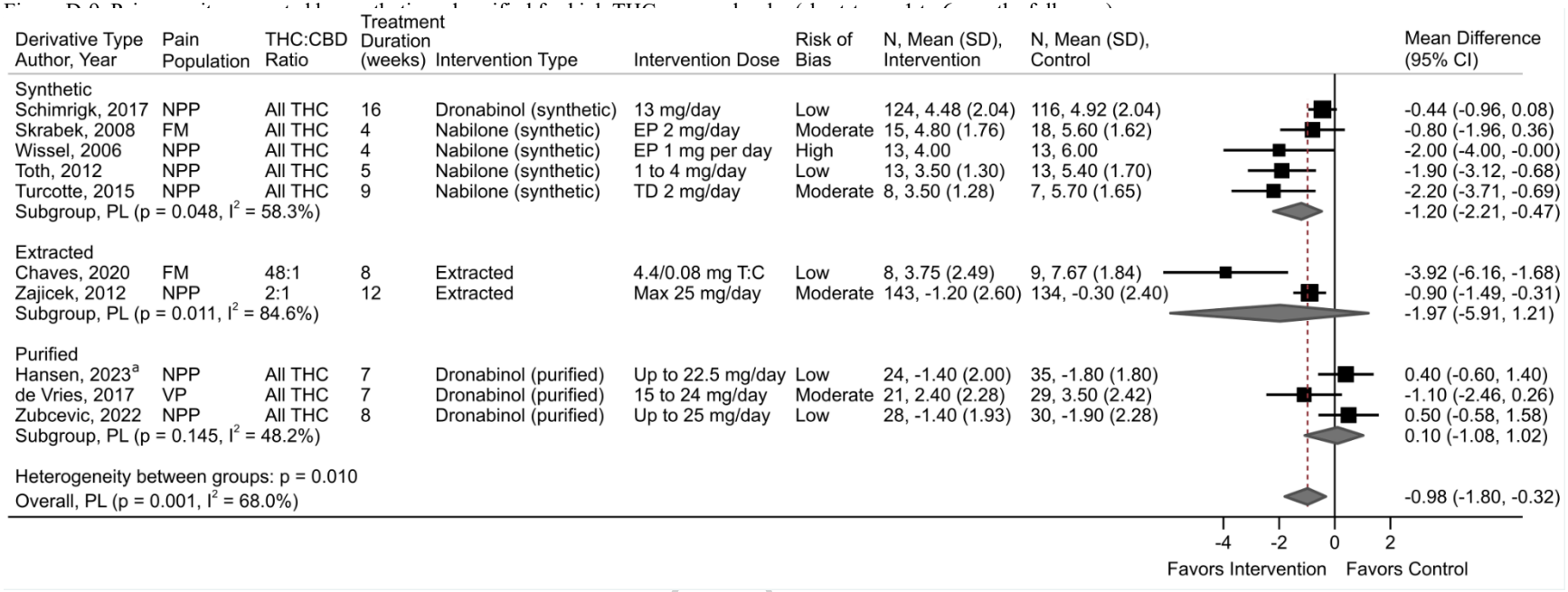

Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain.

[a] Study is new to the 2024 update.

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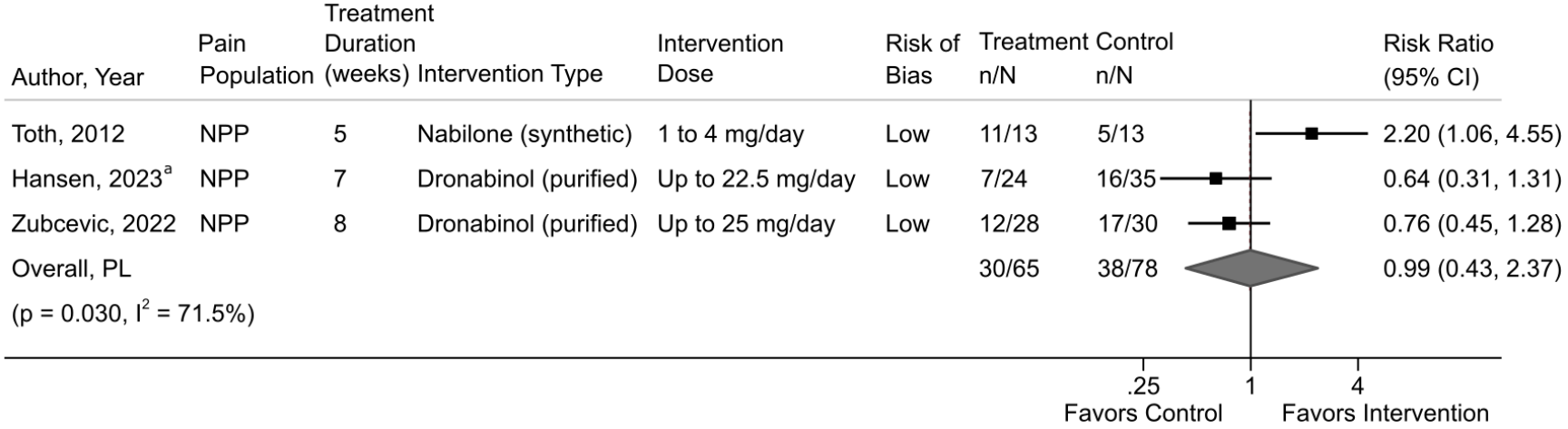
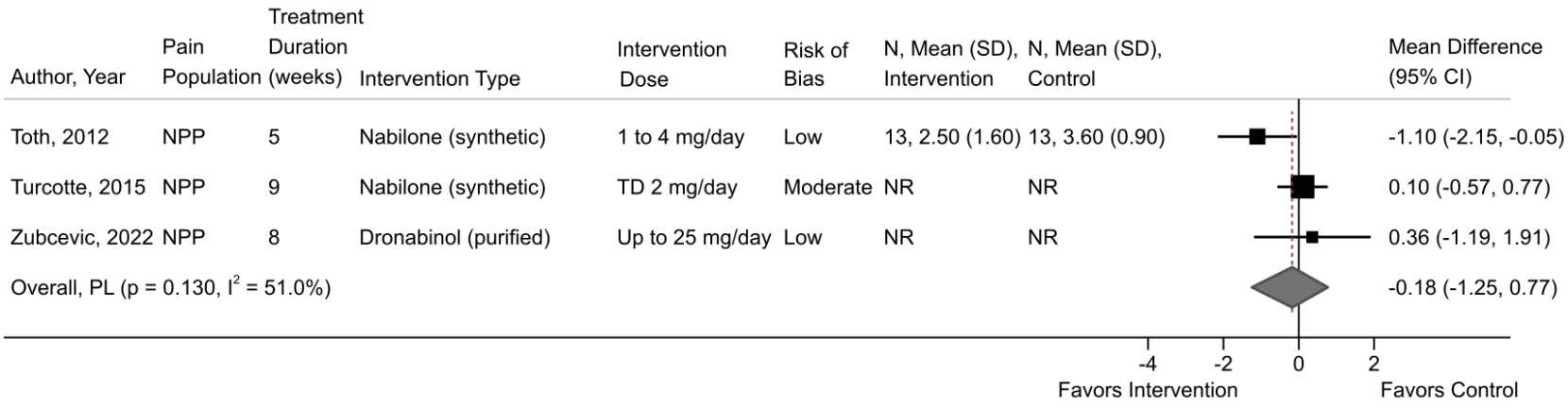
Figure D-10. Proportion of patients with pain response (≥30% improvement) with high THC versus placebo (short-term, 1 to 6 months



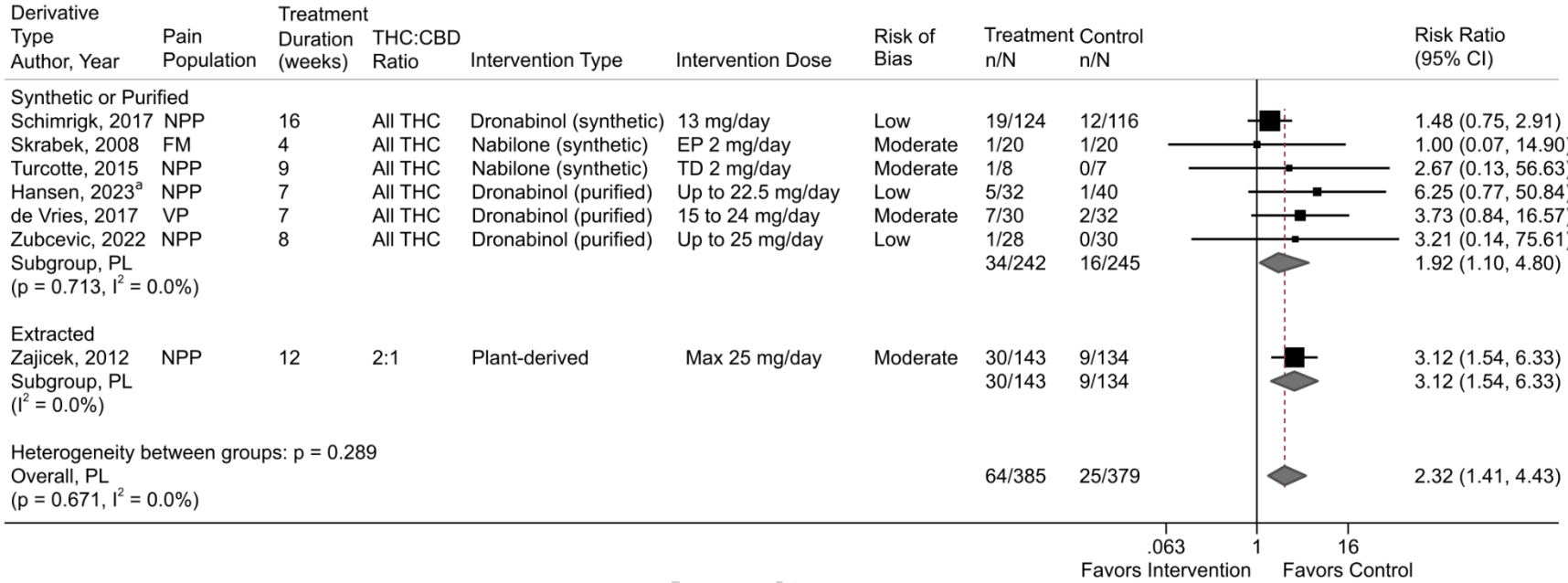
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol
[a] Study is new to the 2024 update.

Figure D-11 Overall function for high THC versus placebo (short-term, 1 to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; NR = not reported; SD = standard deviation; THC = tetrahydrocannabinol

Figure D-12. Study withdrawal due to adverse events for high THC versus placebo (short-term, 1 to 6 months followup)



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

[a] Study is new to the 2024 update.

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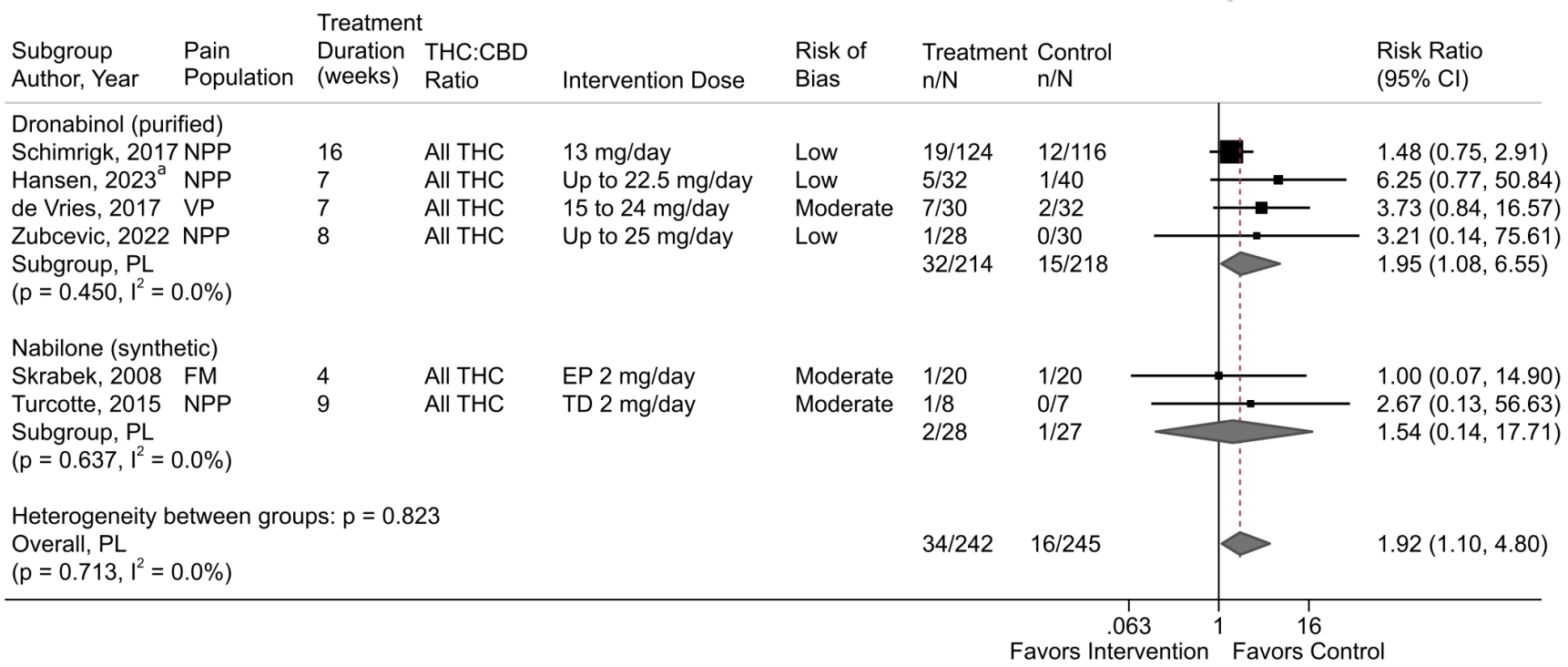
Figure D-13. Study withdrawal due to adverse events for dronabinol or nabilone versus placebo (short-term, 1 to 6 months followup)



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

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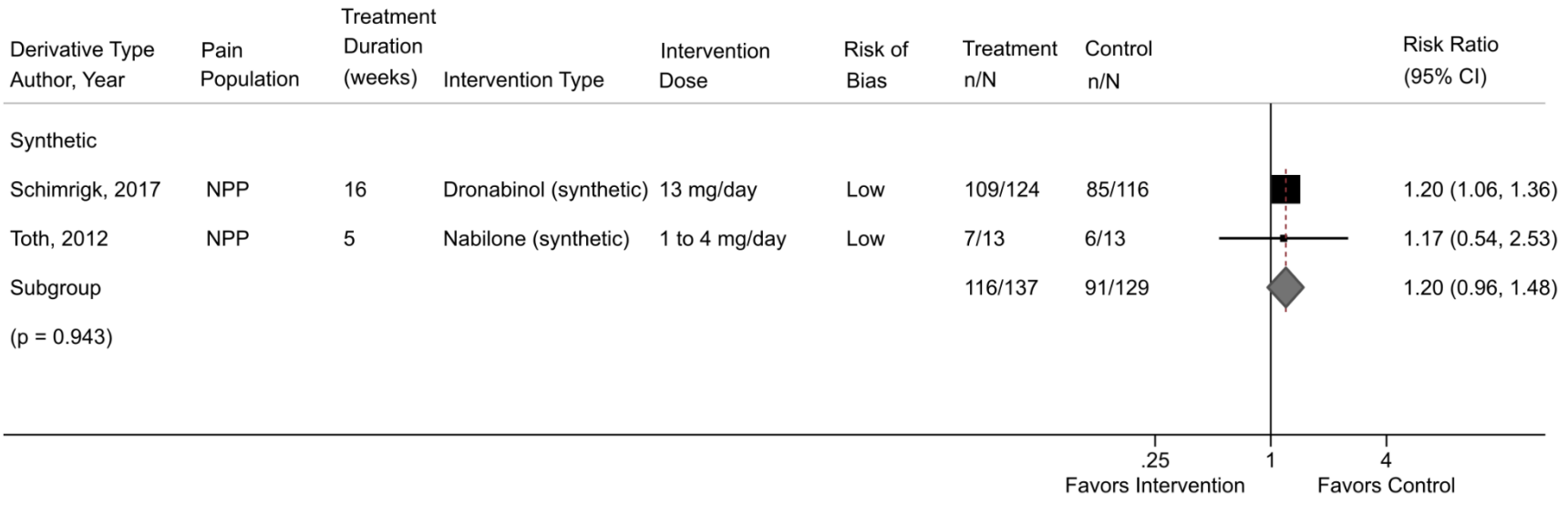

Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol
[a] Study is new to the 2024 update.

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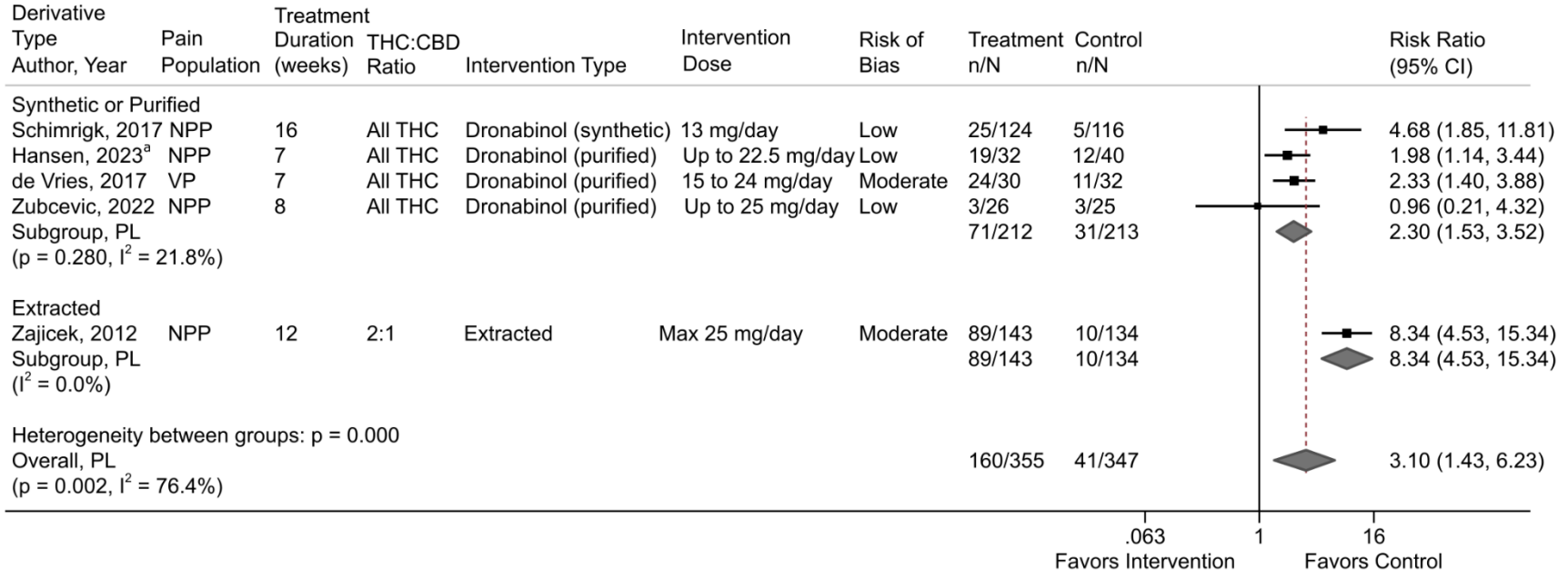
Figure D-15. Dizziness for high THC versus placebo (short-term, 1 to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol; VP = visceral pain

[a] Study is new to the 2024 update.

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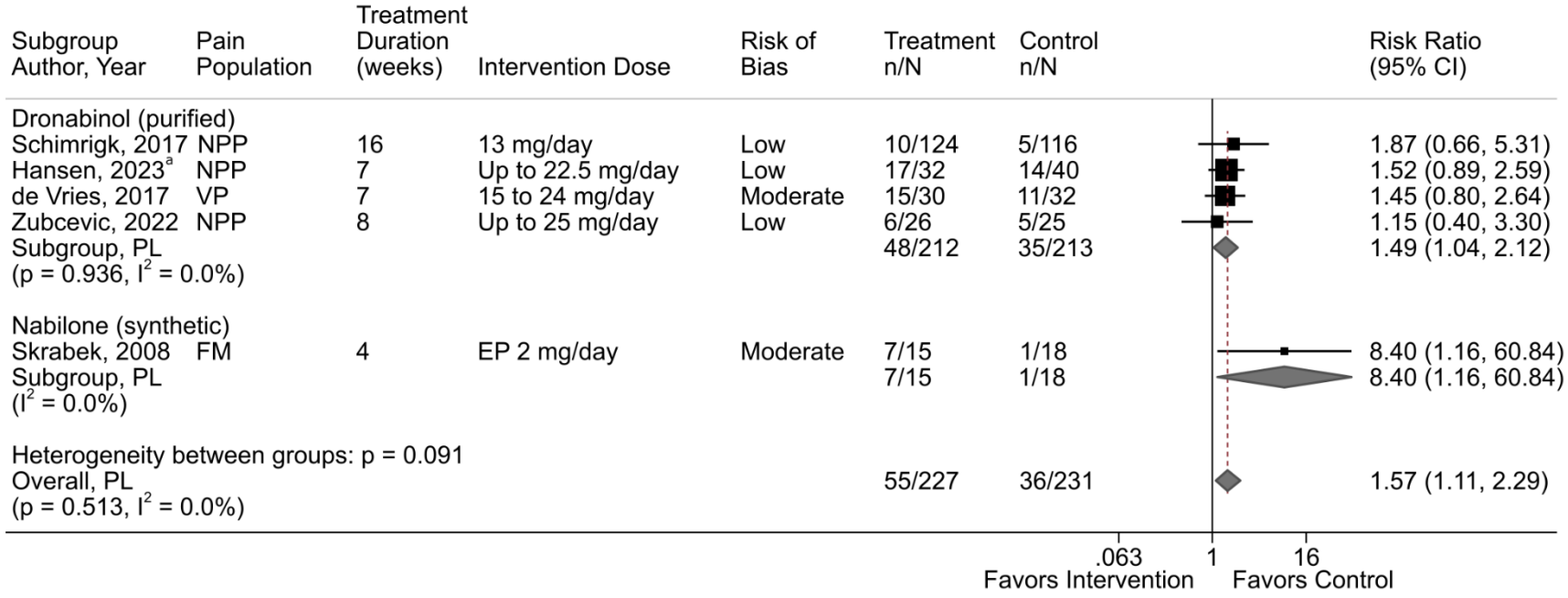

Abbreviations: CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL= profile likelihood; VP = visceral pain

[a] Study is new to the 2024 update.

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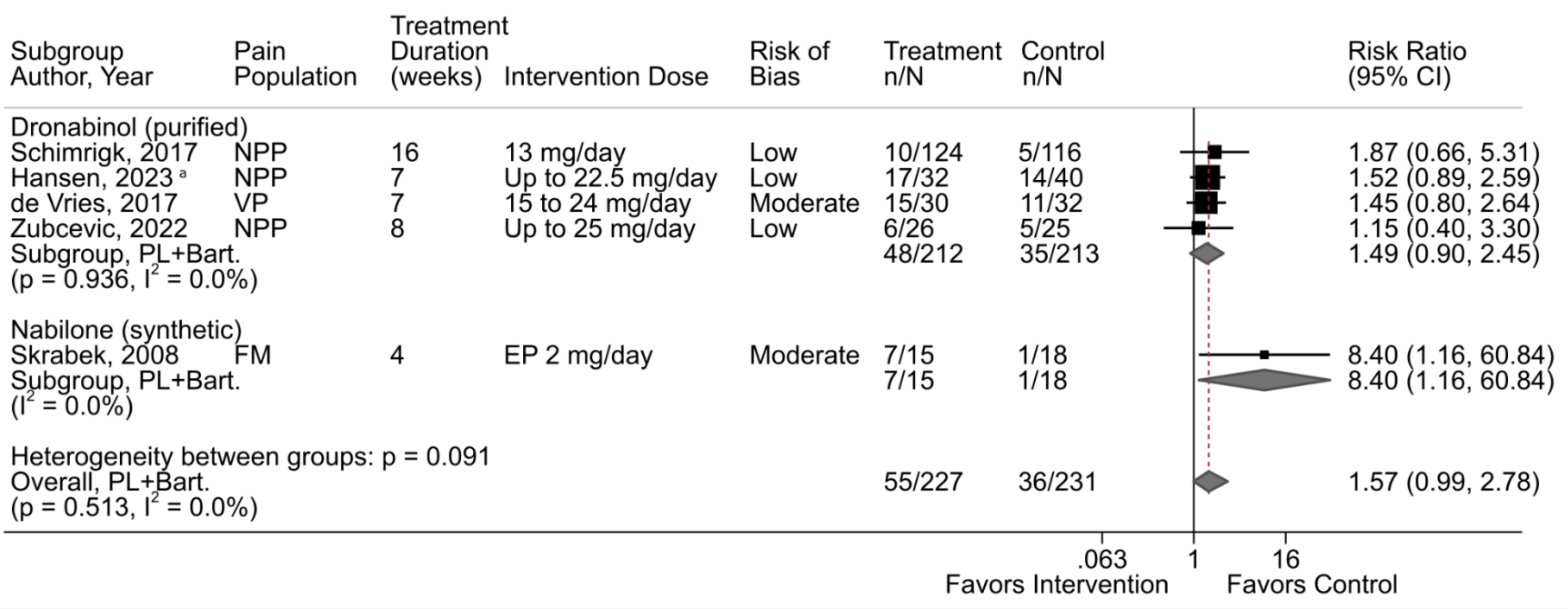

Abbreviations: Bart = Bartlett's correction; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol; VP = visceral pain

[a] Study is new to the 2024 update.

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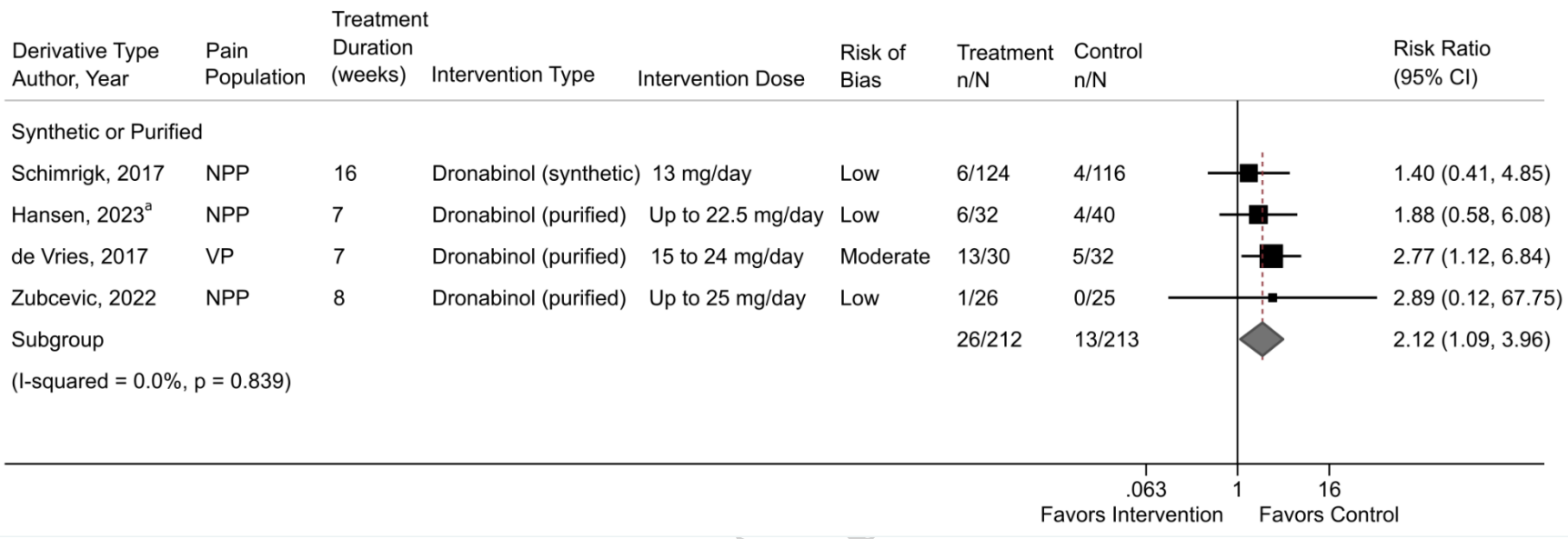

Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol; VP = visceral pain
[a] Study is new to the 2024 update.

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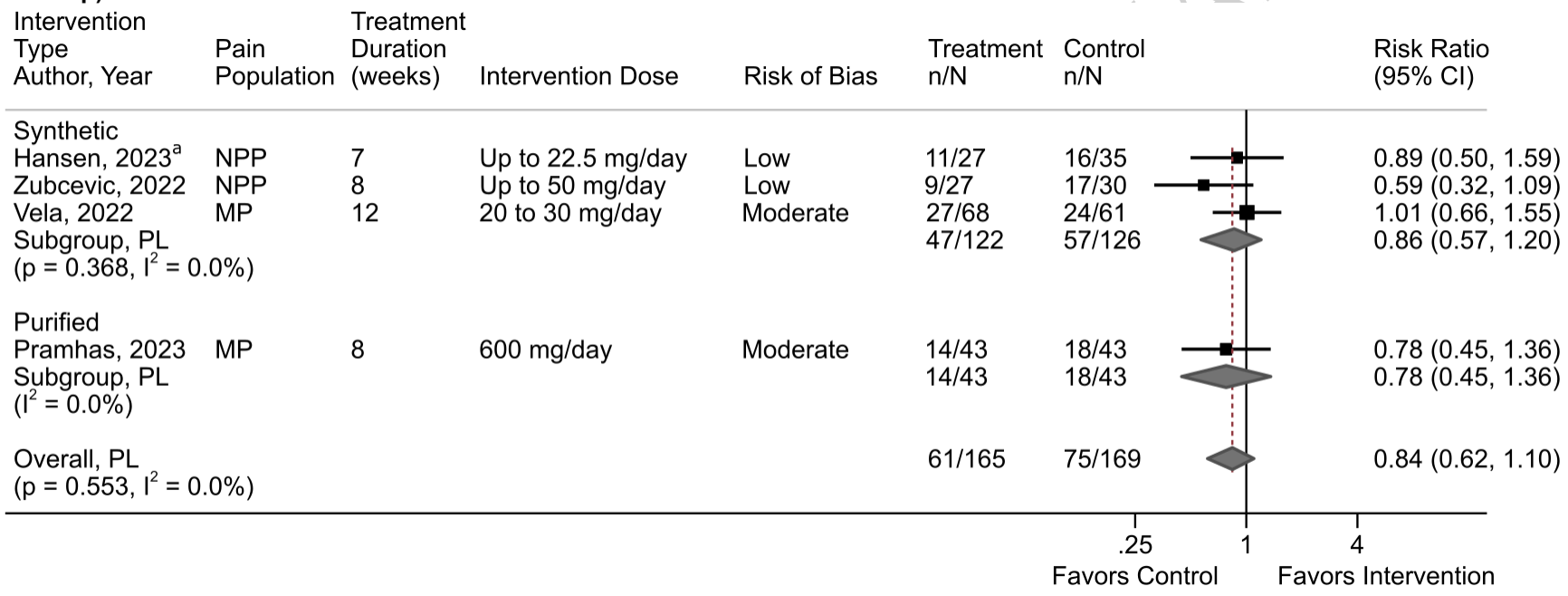
Low THC to CBD Ratio Studies

Figure D-19. Proportion of patients with pain response (≥30% improvement) for low THC versus placebo (short-term, 1 to 6 months followup)



Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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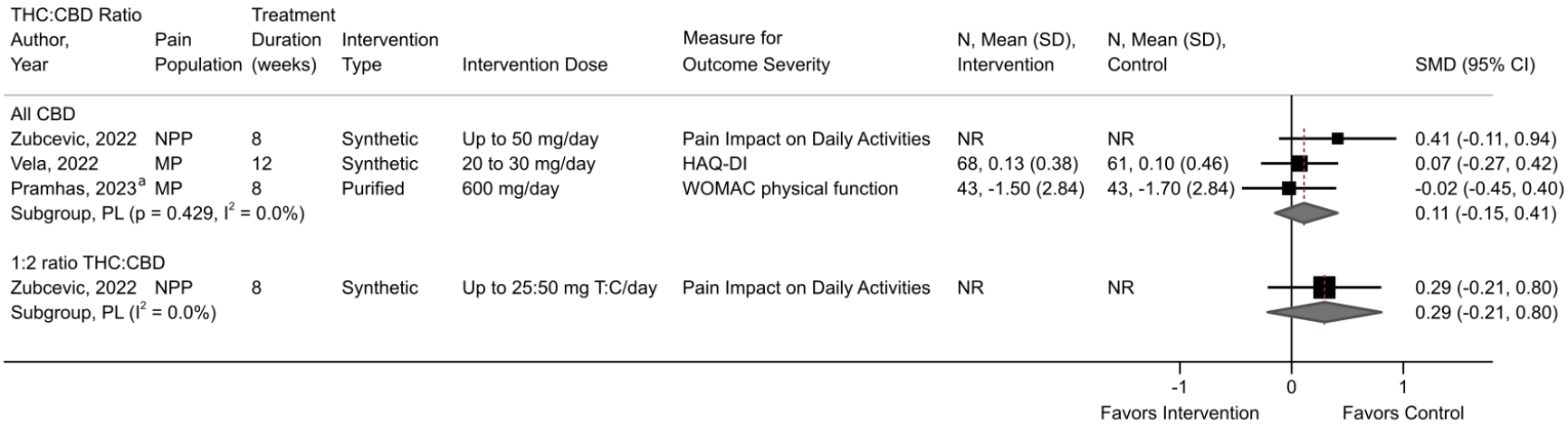
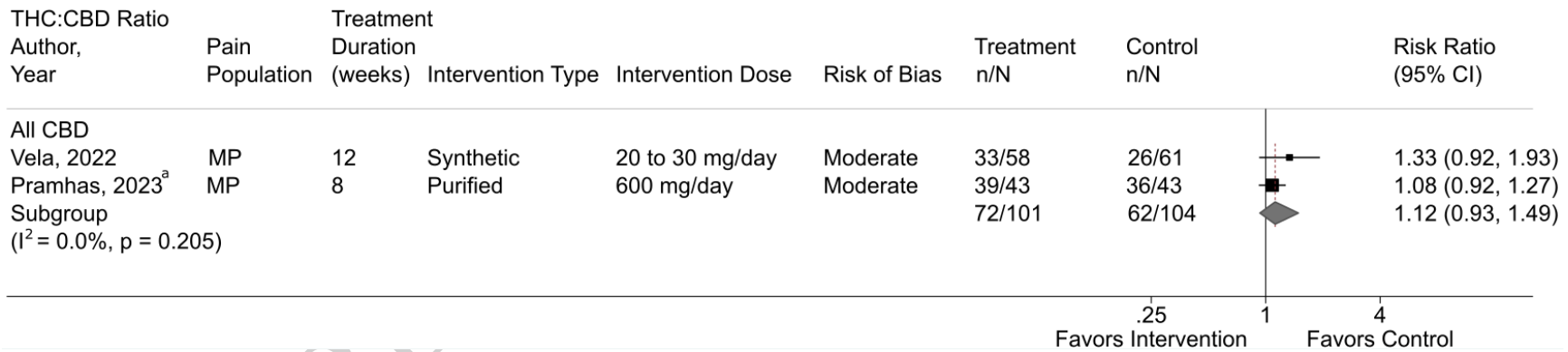


Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

Figure D-21. Any adverse event for low THC versus placebo (short-term, 1 to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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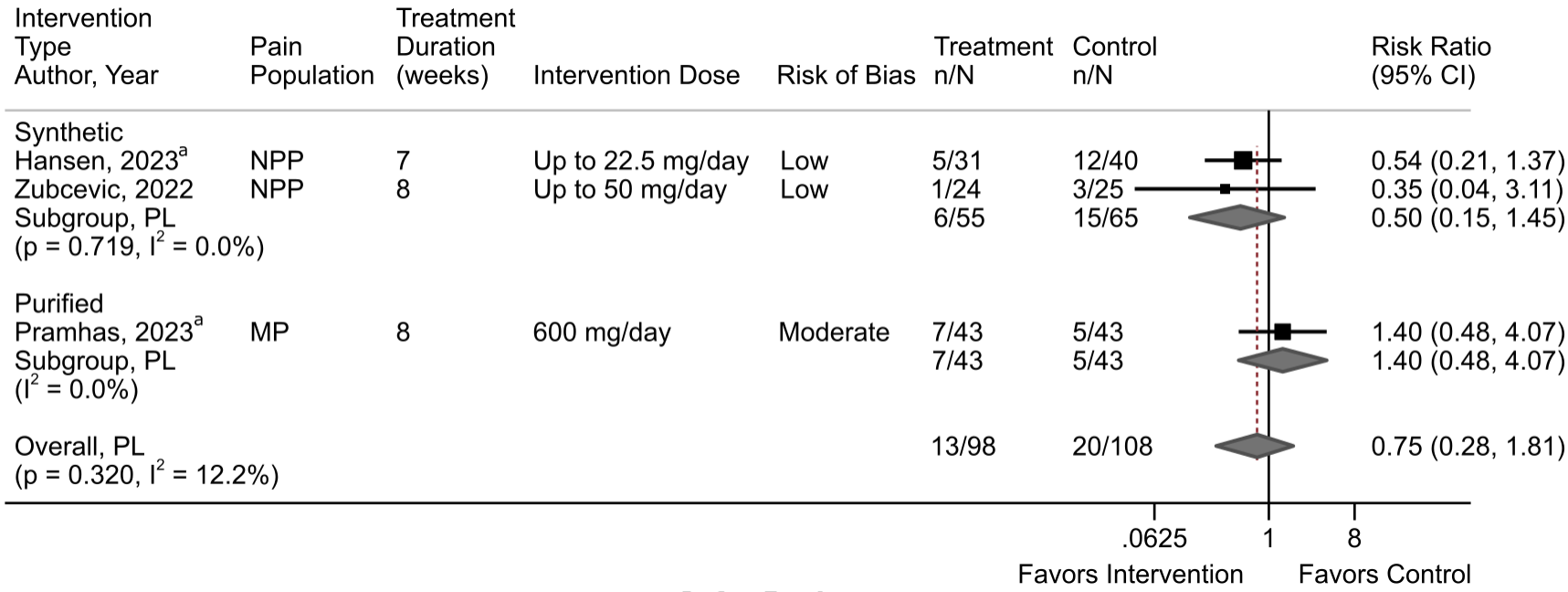

Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol
[a] Study is new to the 2024 update.

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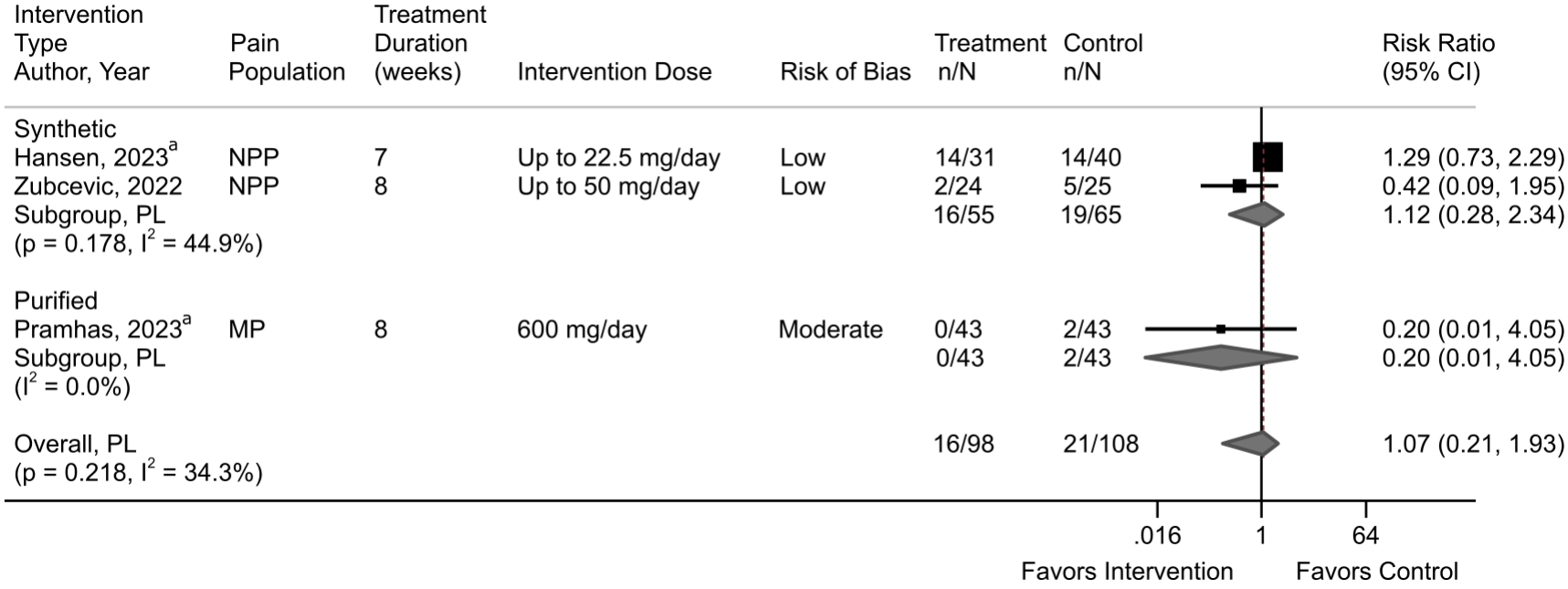
Figure D-23. Sedation for low THC versus placebo (short-term, 1 to 6 months followup)



Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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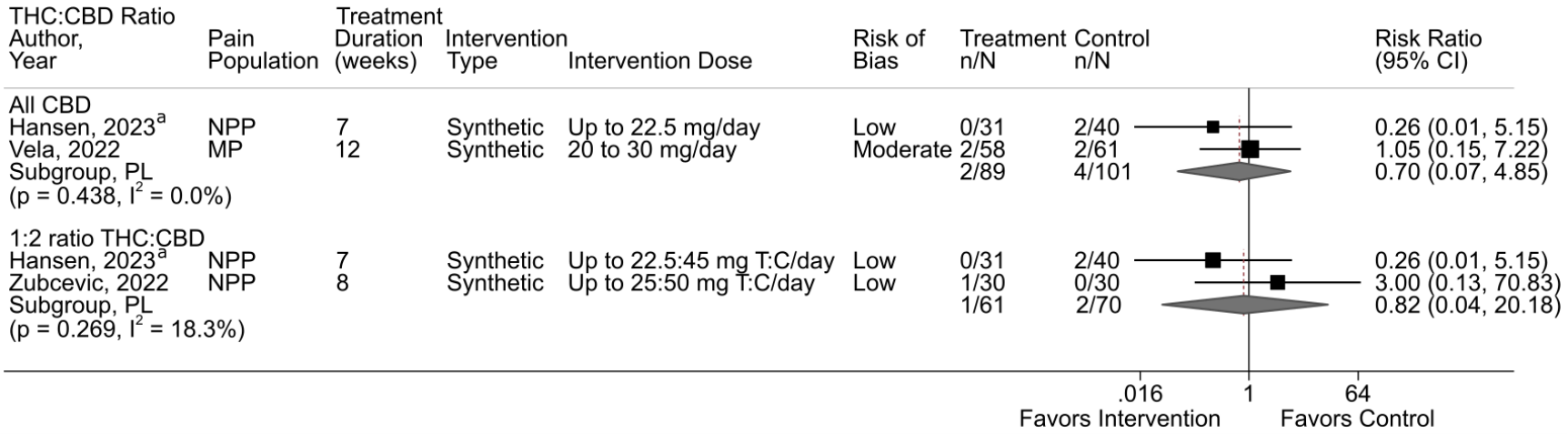

Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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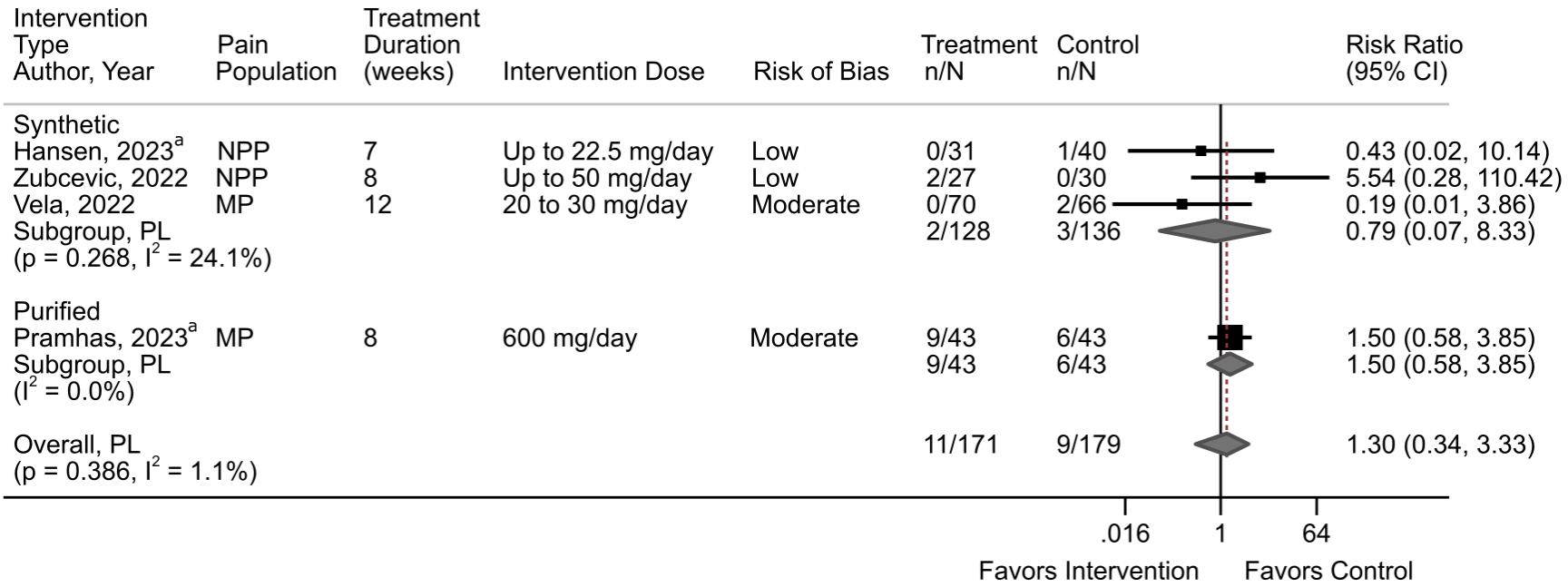

Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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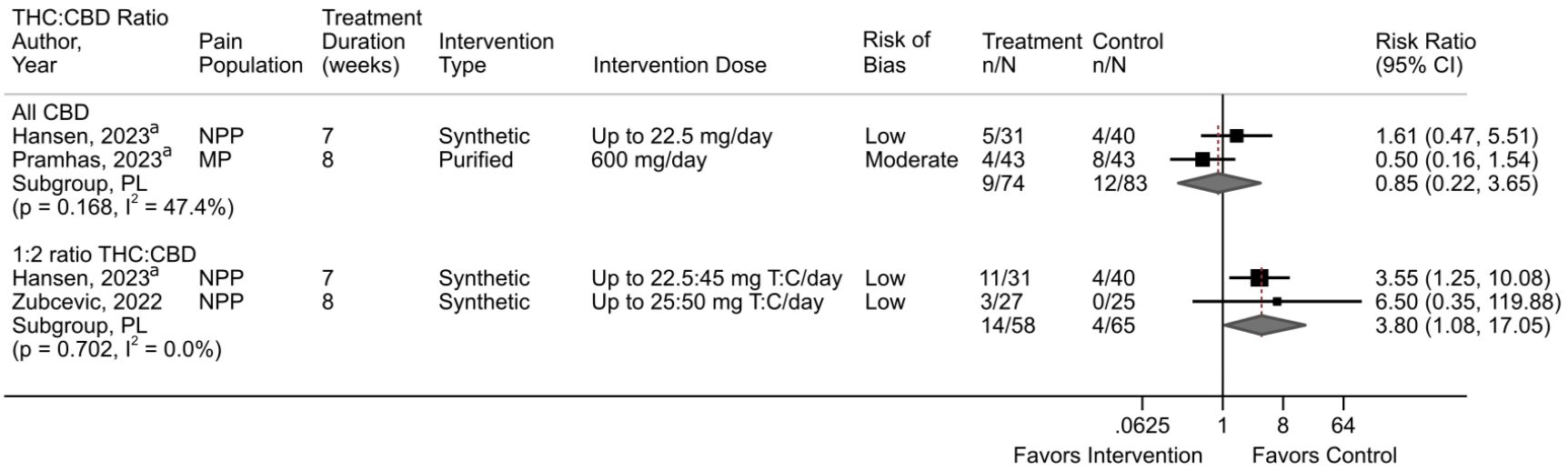

Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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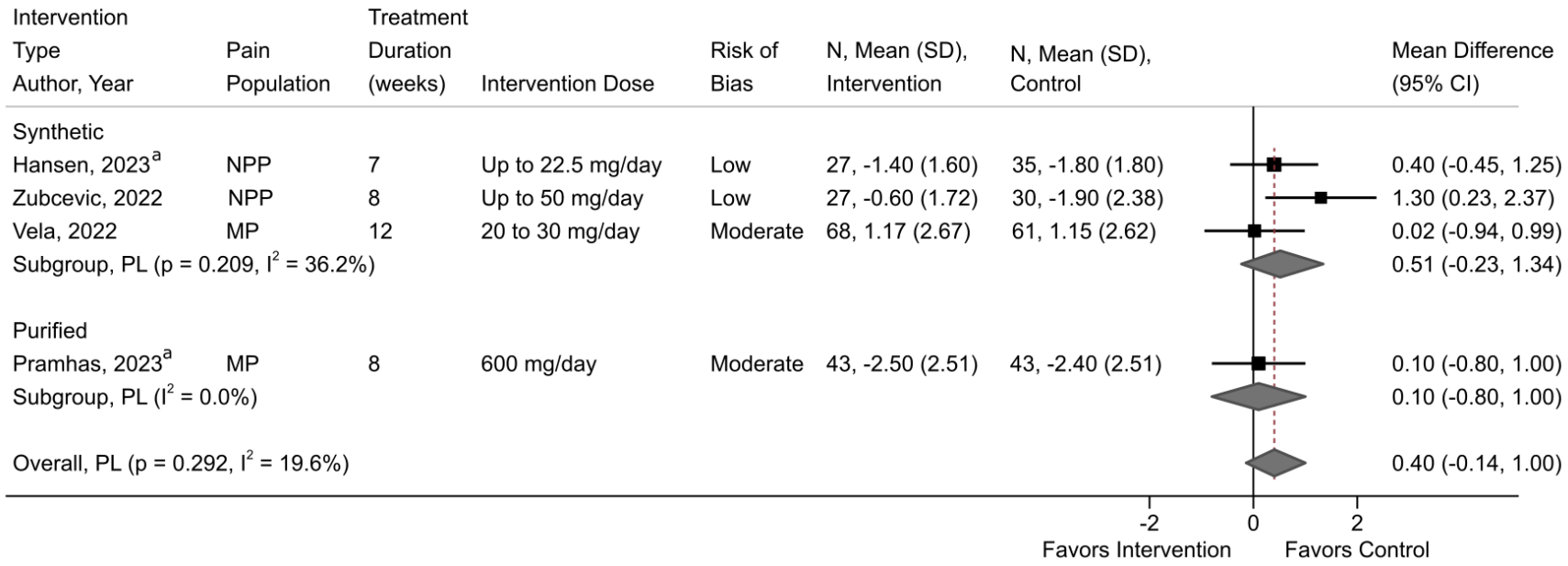

Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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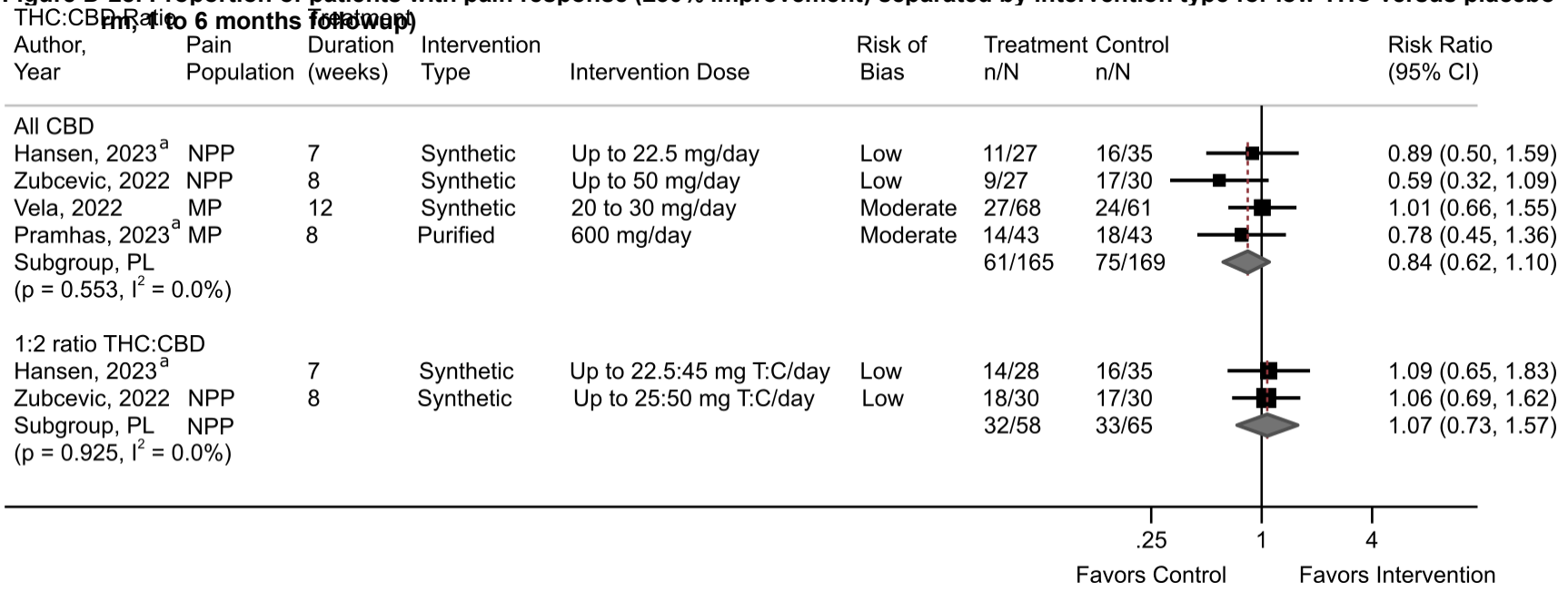
Figure D-28. Proportion of patients with pain response (≥30% improvement) separated by intervention type for low THC versus placebo (ITT, 1 to 6 months follow-up)



Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; TD = total dose; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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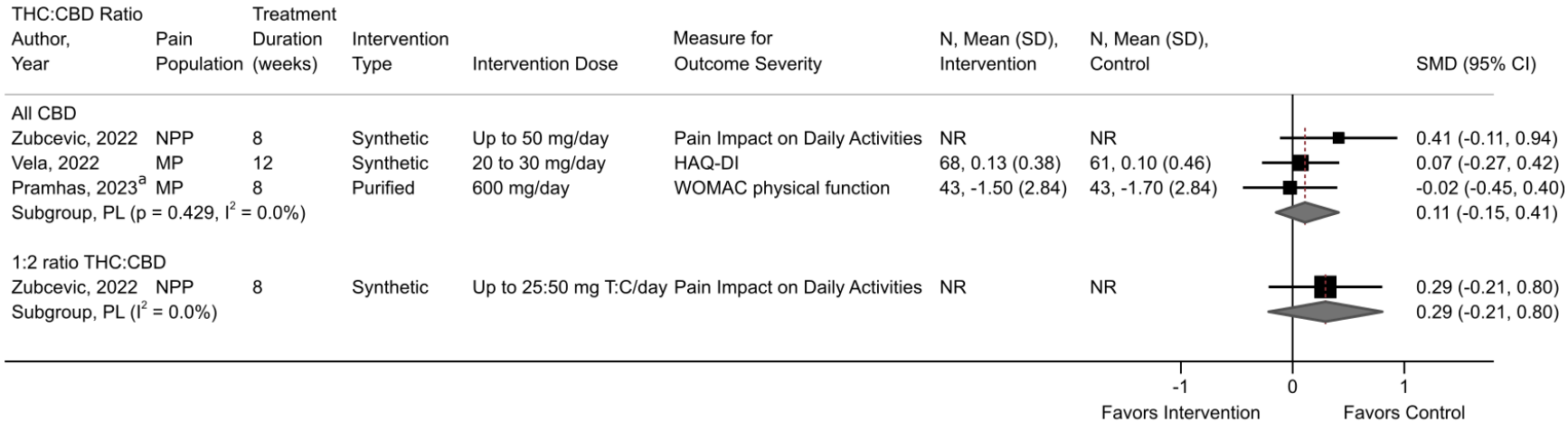

Abbreviations: CBD = cannabidiol; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire – Disability Index; MP = musculoskeletal pain; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SMD = standard mean difference; T:C = THC to CBD ratio; THC = tetrahydrocannabinol; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

[a] Study is new to the 2024 update.

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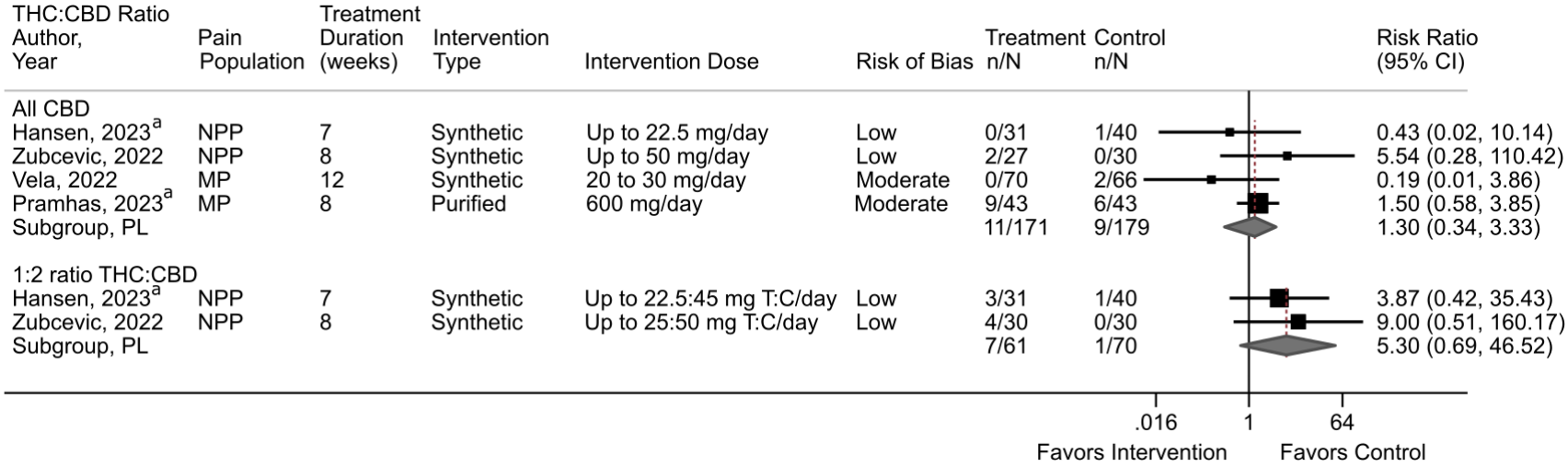
Figure D-30. Study withdrawal due to adverse events separated by intervention type for low THC versus placebo (short-term, 1 to 6



Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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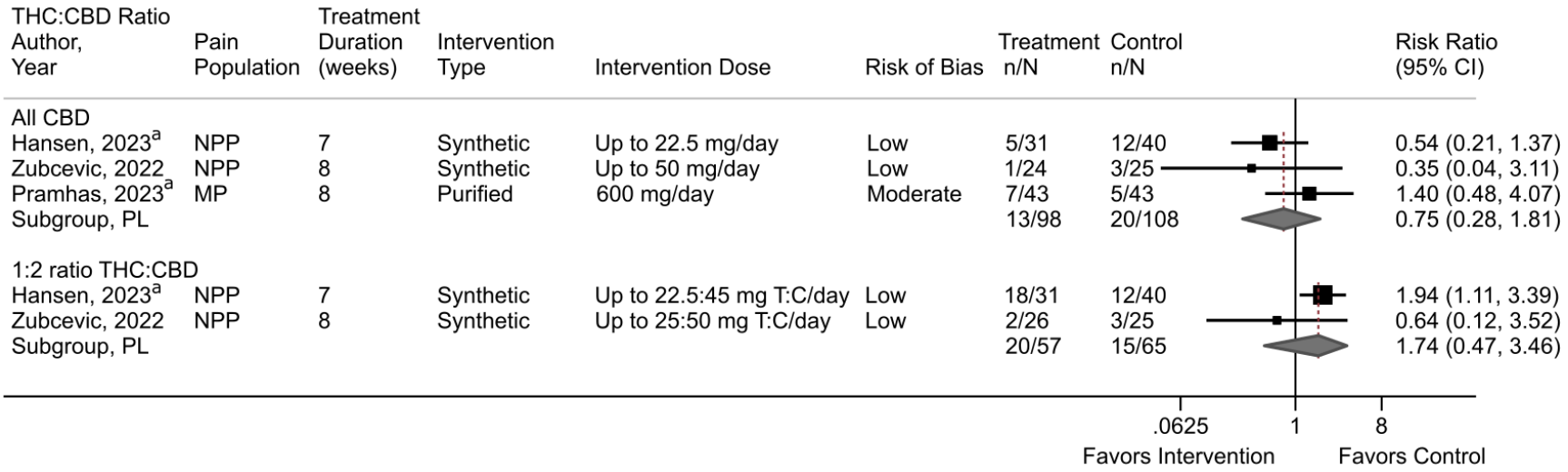

Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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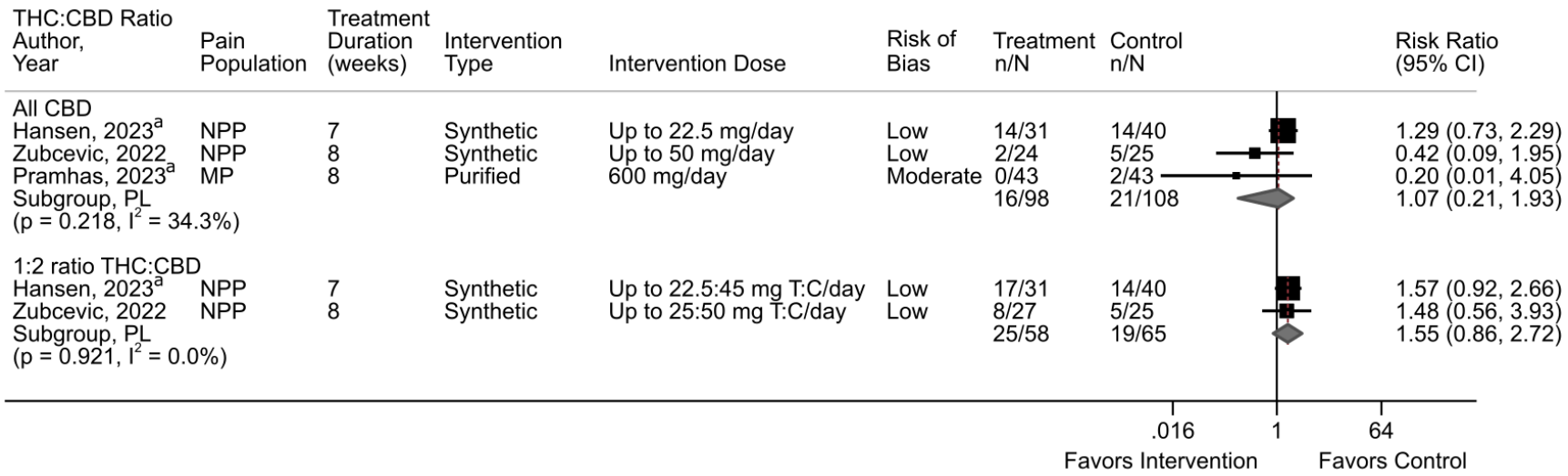

Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

[a] Study is new to the 2024 update.

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Appendix E. Evidence Tables

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

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Appendix F. Risk of Bias Assessment

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

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Appendix G. Details on Strength of Evidence

Table G-1. Key Questions 1 and 2: Cannabinoids to treat chronic pain – extracted comparable THC to CBD ratio oromucosal spray

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Pain response (≥30% improvement from baseline)	4 RCTs (N=733)[1-4]	Moderate	Direct	Consistent	Imprecise	Unknown	Potential small effect, not statistically significant, with THC:CBD 38% versus 31%, RR 1.18 (0.93 to 1.71); I^2=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=39%) Subgroup analysis removing high risk of bias studies: Moderate benefit MD -0.63 (−1.15 to −0.24; I^2=52%)	Moderate
Comparable THC to CBD Ratio vs. Placebo	Function or Disability	6 RCTs (N=616) [1-5,7]	Moderate	Direct	Consistent	Precise	Unknown	No effect 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	No effect 12.5% vs. 10.2%, RR 1.14 (0.65 to 3.02); I^2=51%	Low
Comparable THC to CBD Ratio vs. Placebo	SAEs	3 RCTs (N=866)[2,5]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 5.0% vs. 4.3%, RR 1.18 (0.26 to 3.4; I^2=0%)	Low

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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; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

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Table G-2. Key Questions 1 and 2: Cannabinoids to treat chronic pain – synthetic or purified, oral high THC to CBD ratio products

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Synthetic or Plant Purified THC vs. Placebo	Pain response (≥30% improvement from baseline)	3 RCTs (N=143)[8-10]	Low	Direct	Very serious inconsistency	Imprecise	Unknown	Unable to assess, due to inconsistency from three trials (one trial of nabilone, 85% vs. 38%, RR 2.20 [1.06 to 4.55] and two trials of dronabinol, 43% vs. 57%, RR 0.76 (0.45 to 1.28) and 29% vs. 46%, RR 0.64 [0.31 to 1.31]) Pooled estimate RR: 0.99 (0.43 to 2.37)	Insufficient
Synthetic or Plant Purified THC vs. Placebo	Pain severity	8 RCTs (N=507)[8-15]	Moderate	Direct	Consistent	Imprecise	Unknown	Small effect with synthetic THC 0 to 10 scale, MD −0.78 (−1.59 to −0.08; I^2=64%)	Low
Synthetic or Plant Purified THC vs. Placebo	Function/disability	3 RCTs (N=unclear)[8,9,14] 1 RCT (N=13) not Included in meta-analysis[15]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect (scale 0 to 10) MD: −0.18, −1.25 to 0.77, I^2=51%)	Low
Synthetic or Plant Purified THC vs. Placebo	WAEs	6 RCTs (N=487)[9-14]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect 14% vs. 6%, RR 1.92 (1.10 to 4.80; I^2=0%)	Low
Synthetic or Plant Purified THC vs. Placebo	SAEs	2 RCTs (N=312)[10,12]	Low	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 9% vs. 6%, RR 1.53 (0.52 to 4.15)	Insufficient

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Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Synthetic or Plant Purified THC vs. Placebo	Dizziness	4 RCTs (N=425)[9-12]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 33% vs. 15%, RR 2.30 (1.53 to 3.52; I^2=22%)	Moderate
Synthetic or Plant Purified THC vs. Placebo	Nausea	4 RCTs (N=425)[9-12]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 12% vs. 6%, RR 2.12 (1.09 to 3.96; I^2=0%)	Low
Synthetic or Plant Purified THC vs. Placebo	Sedation	5 RCTs (N=458)[9-13]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with dronabinol 24% vs. 16%, RR 1.57 (1.11 to 2.29; I^2=0%)	Low

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

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Table G-3. Key Questions 1 and 2: Cannabinoids to treat chronic pain – extracted, oral or sublingual high THC to CBD ratio products

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Extracted THC vs. Placebo	Pain severity	2 RCTs (N=294)[16,17]	Moderate	Direct	Inconsistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD −1.97 (−5.91 to 1.21; I^2=72%)	Insufficient
	Function/disability	1 RCT (N=18)[17]	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)[16]	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)[16]	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)[16]	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; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

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Table G-4. Key Questions 1 and 2: Cannabinoids to treat chronic pain – combined (synthetic, purified, or extracted high THC to CBD ratio products

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Combined (synthetic, purified, or extracted high THC to CBD ratio products	Pain severity	10 RCTs (N=801)[8-17]	Moderate	Direct	Consistent	Precise	Unknown	Moderate effect MD −0.98 (−1.80 to −0.32; I^2=68%)	Moderate

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

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Table G-5. Key Questions 1 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)	SOE Grade
Whole Plant Cannabis (Standardized to 12% THC) vs. Usual Care	Pain Severity change	1 cohort study (N=431, 302 contribute to pain outcome)[18]	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 chort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Large effect with cannabis 4.7% vs. 0%, RR 21.10 (1.24 to 357.80)	Insufficient
	SAE	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	No effect 13% vs. 19%, OR 0.64 (0.38 to 1.04)	Insufficient
	Dizziness	1 cohort study (N=431)[18]	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 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Moderate effect 16.7% vs. 9.7%, RR 1.72 (1.04 to 2.85)	Insufficient
	Sedation	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.5% vs. 4.63%, RR 2.91 (1.46 to 5.83)	Insufficient
	Cognitive Disorder	1 cohort study (N=431)[18]	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; MD = mean difference; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

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Table G-6. Key Question 1: Cannabinoids to treat chronic pain – synthetic or purified, oral low THC to CBD ratio products

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Oral Synthetic or Plant Purified CBD	Pain severity (change)	4 RCTs (N=334) [9,10,19,20]	Low	Direct	Consistent	Imprecise	Unknown	Not improved MD 0.40 (−0.14 to 1.00)	Moderate
	Pain response (≥30% improvement from baseline)	4 RCTs (N=334) [9,10,19,20]	Low	Direct	Consistent	Imprecise	Unknown	Likelihood not increased RR 0.84 (0.62 to 1.10)	Moderate
	Function/disability	3 RCTs (N=272) [9,19,20]	Low	Direct	Consistent	Imprecise	Unknown	Not improved SMD 0.11 (−0.14 to 0.41)	Moderate
	Any AE	2 RCTs (N=205) [19,20]	Moderate	Direct	Consistent	Imprecise	Unknown	No or minimal increase risk RR 1.12 (0.93 to 1.49)	Low
	SAEs	2 RCTs (N=190) [10,19]	Moderate	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 0.70 (0.07 to 4.85)	Insufficient
	WAEs	4 RCTs (N=350) [9,10,19,20]	Moderate	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 1.30 (0.34 to 3.33)	Insufficient
	Sedation	3 RCTs (N=206) [9,10,20]	Moderate	Direct	Consistent	Imprecise	Unknown	No or minimal increased risk RR 1.07 (0.21 to 1.93)	Low

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Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Oral purified THC + synthetic or purified CBD	Nausea	2 RCTs (N=157)[10,20]	Moderate	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 0.85 (0.22 to 3.65)	Insufficient
	Dizziness	3 RCTs (N=206)[9,10,20]	Moderate	Direct	Consistent	Imprecise	Unknown	No or minimal increased risk RR 0.75 (0.28 to 1.81)	Low
	Pain severity (change)	2 RCTs (N=123)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Not improved MD 0.12 (−0.71 to 0.93)	Low
	Pain response (≥30% improvement from baseline)	2 RCTs (N=123)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Not improved RR 1.07 (0.73 to 1.57)	Low
	Function/disability	1 RCT (N=60)[9]	Low	Direct	Unable to assess	Very imprecise	Unknown	Not improved SMD 0.29 (−0.21 to 0.80)	Low
	Any AE	No studies	--	--	--	--	--	--	No evidence
	SAEs	2 RCTs (N=131)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 0.82 (0.04 to 20.18)	Insufficient

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Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
	WAEs	2 RCTs (N=131)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 5.30 (0.69 to 46.52)	Insufficient
	Sedation	2 RCTs (N=123) [9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Potential increased risk RR 1.55 (0.86 to 2.72)	Low
	Nausea	2 RCTs (N=123) [9,10]	Low	Direct	Consistent	Imprecise	Unknown	Increased risk RR 3.80 (1.08 to 17.05)	Moderate
	Dizziness	2 RCTs (N=122)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Potential increased risk RR 1.74 (0.47 to 3.46)	Low
Topical (intraoral) CBD, unclear source	Pain severity (change)	1 RCT (n=60)[21]	Moderate	Direct	Unable to assess	Imprecise	Unknown	Unable to assess due to single small study with methodological limitations 2.0 (IQR 3.0) or 3.5 (2.0) vs. 5.5 (3.0)	Insufficient

Abbreviations: AE = adverse event; ANCOVA = analysis of covariance; CBD = cannabidiol; CI = confidence interval; IQR = interquartile range; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

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Table G-7. Key Questions 1 and 2: Cannabinoids to treat chronic pain – other or mixed cannabinoids

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Medical cannabis use vs. Non-use	Arrhythmia	1 cohort study (N=32,332)[22]	Moderate	Direct	Unknown	Precise	Unknown	Increased risk Adjusted RR 2.07 (1.34 to 2 .80)	Insufficient
Medical cannabis use vs. Non-use	Acute coronary syndrome	1 cohort study (N=32,332)[22]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect Adjusted RR 1.20 (0.35 to 2.04)	Insufficient
CBDV vs. Placebo	Pain Response (≥30% improvement from baseline)	1 RCT (N=31)[23]	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)[23]	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; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence.

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Table G-8. Key Questions 1 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)[24,25]	High	Direct	Inconsistent	Imprecise	Unknown	VAS (0-100): 41.5 vs 43.6 at 3 months[24] 34.1 vs 48.8; mean difference −14.71 (95% CI, −32.71 to 3.29)[25]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Long-term (12 months)	1 cohort (N=1,514)[26]	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[26]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Function or Disability (SF-36 Physical Function)	2 cohort studies (N=202)[24,25]	High	Direct	Consistent	Imprecise	Unknown	SF-36 Physical Functioning (mean, 0 to 100 scale) 46.5 vs. 43.7 at 6 months[24] 70.0 vs. 69.4; MD 0.56 (95% CI −17.2 to 18.3) at 3 months[25]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	WAEs	1 cohort study, short- and intermediate-term (N=156)[24]	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

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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)[24]	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)[24]	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)[24]	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; MD = mean difference; NA = not applicable; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

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Appendix G References

1. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.
2. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007 Dec 15;133(1-3):210-20. PMID: 17997224.
3. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.
4. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.
5. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006 Jan;45(1):50-2. PMID: 16282192.
6. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014 Jan;47(1):166-73. doi: 10.1016/j.jpainsymman.2013.02.018. PMID: 23742737.
7. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9. PMID: 16186518.
8. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024. PMID: 22921260.
9. Zubcevic K, Petersen M, Bach FW, et al. Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment. Eur J Pain. 2022doi: 10.1002/ejp.2072. PMID: 36571471.
10. Hansen JS, Gustavsen S, Roshanisefat H, et al. Cannabis-based medicine for neuropathic pain and spasticity—A multicenter, randomized, double-blinded, placebo-controlled trial. Pharmaceuticals (Basel). 2023a;16(8):1079. doi: 10.3390/ph16081079. PMID: 37630995.
11. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. Clin Gastroenterol Hepatol. 2017 Jul;15(7):1079-86.e4. doi: 10.1016/j.cgh.2016.09.147. PMID: 27720917.
12. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78(5-6):320-9. doi: 10.1159/000481089. PMID: 29073592.
13. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008 Feb;9(2):164-73. PMID: 17974490.
14. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59. doi: 10.1111/pme.12569. PMID: 25288189.

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15. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. J Neurol. 2006 Oct;253(10):1337-41. PMID: 16988792.

16. Zajicek JP, Hobart JC, Slade A, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32. doi: 10.1136/jnnp-2012-302468. PMID: 22791906.

17. Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Pain Med. 2020;21(10):2212-8. doi: 10.1093/pm/pnaa303. PMID: 33118602.

18. Ware MA, Wang T, Shapiro S, et al. Cannabis for the management of pain: assessment of safety study (COMPASS). J Pain. 2015 Dec;16(12):1233-42. doi: 10.1016/j.jpain.2015.07.014. PMID: 26385201.

19. Vela J, Dreyer L, Petersen KK, et al. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. Pain. 2021 Jun 1;163(6):1206-14. PMID: 34510141.

20. Pramhas S, Thalhammer T, Terner S, et al. Oral cannabidiol (CBD) as add-on to paracetamol for painful chronic osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Lancet Reg Health Eur. 2023;35doi: 10.1016/j.lanepe.2023.100777. PMID: 38033459.

21. Walczyńska-Dragon K, Kurek-Górecka A, Niemczyk W, et al. Cannabidiol Intervention for Muscular Tension, Pain, and Sleep Bruxism Intensity—A Randomized, Double-Blind Clinical Trial. J Clin Med. 2024;13(5)doi: 10.3390/jcm13051417.

22. Holt A, Nouhravesh N, Strange JE, et al. Cannabis for chronic pain: cardiovascular safety in a nationwide Danish study. European Heart Journal. 2024doi: 10.1093/eurheartj/ehad834. PMID: 38200679.

23. Eibach L, Scheffel S, Cardebring M, et al. Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial. Clin Pharmacol Ther. 2020 Aug 08;109(4):1055-62. doi: 10.1002/cpt.2016. PMID: 32770831.

24. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011 Jul-Aug;11(4):353-68. doi: 10.1111/j.1533-2500.2010.00427.x. PMID: 21087411.

25. Gruber SA, Smith RT, Dahlgren MK, et al. No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. Exp Clin Psychopharmacol. 2021;29(2):147-56. doi: 10.1037/pha0000435. PMID: 33764103.

26. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Health. 2018 Jul;3(7):e341-e50. doi: 10.1016/s2468-2667(18)30110-5. PMID: 29976328.

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Appendix H. 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; an open label proof of concept study with randomization between treatment groups: Cannabis, Oxycodone or Cannabis/Oxycodone 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 publication type
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
8. Effects of Cannabidiol (CBD) on Resting-state Electroencephalography (EEG) and Neuropathic Pain Severity in People With Spinal Cord Injury (SCI). 2022. **Exclusion reason:** Ineligible publication type
9. The Impact of THC on Pain Modulation in Fibromyalgia. 2022 PMID: CN-02504284. **Exclusion reason:** Ineligible publication type
10. Diabetic Neuropathic Pain Relief, 6 Weeks Dosage Sublingual Water-soluble CBD/PEA. A Randomized, Double-Blind, Placebo-Controlled Trial Using Cannabidiol and Palmitoylethanolamide for the Treatment of Painful Diabetic Peripheral Neuropathy of the Feet. 2023. **Exclusion reason:** Ineligible publication type
11. A Double-Blind, Randomised Placebo-Controlled Feasibility Trial Assessing Oral Cannabis for The Relief of Fibromyalgia Symptoms. 2023. **Exclusion reason:** Ineligible publication type
12. A Randomised, Double-Blind, Placebo-Controlled, Parallel-Arm Study to Evaluate the Efficacy, Safety and Tolerability of 150 mg Sublingual Cannabidiol in Adults with Mild-to-Moderate Pain. 2023. **Exclusion reason:** Ineligible publication type
13. Safety and Effect on Pain and Function According to RAPID-3 of IHL-675A in Patients With Rheumatoid Arthritis. A Phase II, Blinded, Randomised, Placebo Controlled Clinical Trial to Determine the Safety and Effect on Pain and Function According to RAPID-3 of IHL-675A in Patients With Rheumatoid Arthritis. 2023 PMID: CN-02580932. **Exclusion reason:** Ineligible publication type
14. Cannabinoid in cancer pain management. A double-blind, randomized, placebo-controlled, parallel arm study evaluating the safety and efficacy of cannabinoid-containing formulations in cancer pain management along with improvement in quality of life of patients with solid tumors. - Nil. 2023. **Exclusion reason:** Ineligible population

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15. The efficacy and safety of Cannabis Extract in muscle pain control. Evaluation of the efficacy and safety of Full Spectrum Cannabis Extract, in pain control, in patients with Muscular Temporomandibular Disorder Clinical, randomized, double-blind, placebo-controlled trial. 2023. **Exclusion reason:** Ineligible publication type

16. The Effectiveness of CBD and CBN in the Treatment of Facial Pain and Headache of Muscular Origin. The Evaluation of the Effectiveness of Cannabidiol (CBD) and Cannabinol (CBN) Oral Solutions in the Treatment of Facial Pain and Headache of Muscular Origin. 2023. **Exclusion reason:** Ineligible publication type

17. Investigating the effects of a cannabis-based medication on sleep problems in chronic pain. Long-term effects of a cannabis-based medication on insomnia in chronic back pain: a randomized crossover trial. 2023. **Exclusion reason:** Ineligible publication type

18. Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Traumatic or Post-operative Peripheral Neuropathy. 2023. **Exclusion reason:** Ineligible publication type

19. Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Central Neuropathy of Any Genesis. 2023. **Exclusion reason:** Ineligible publication type

20. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Back Pain. 2023. **Exclusion reason:** Ineligible publication type

21. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Traumatic or Post-operative Peripheral Neuropathy. 2023. **Exclusion reason:** Ineligible publication type

22. Efficacy and Tolerability of AP707 in Patients With Chronic Back Pain. 2023. **Exclusion reason:** Ineligible publication type

23. Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Diabetic Polyneuropathy. 2023. **Exclusion reason:** Ineligible publication type

24. The Study of Effectiveness of Zingiber cassumunar Roxb.(Plai) Mixed Cannabis sativa L. Leaf Oil for Chronic Pain in Elderly.Randomized controlled trial. 2023. **Exclusion reason:** Ineligible publication type

25. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Diabetic Polyneuropathy. 2023. **Exclusion reason:** Ineligible publication type

26. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Central Neuropathy of Any Genesis. 2023. **Exclusion reason:** Ineligible publication type

27. Effect of local cannabinoid administration on knee osteoarthritis. Effect of local cannabinoid administration on knee osteoarthritis: a randomized triple-blind placebo based clinical trial. 2023. **Exclusion reason:** Ineligible publication type

28. Cannabidiol for Postoperative Opioid Reduction in Primary Total Knee Arthroplasty. 2024. **Exclusion reason:** Ineligible publication type

29. Topical CBD's Effects on Soreness and Performance. 2024. **Exclusion reason:** Ineligible publication type

30. MIVetsCan: cannabidiol (CBD)-Care Trial. 2024. **Exclusion reason:** Ineligible publication type

31. The effect of Cannabinoid use on Neuropathic Pain in Low Back Pain. 2024. **Exclusion reason:** Ineligible publication type

32. The Effects and Mechanisms of a High CBD Cannabis Extract (BRC-002) for the Treatment of Pain and Health in Complex Regional Pain Syndrome. 2024. **Exclusion reason:** Ineligible publication type

33. Abelev S, Warne LN, Benson M, et al. Medicinal Cannabis for the treatment of chronic refractory pain: an investigation of the adverse event profile and health-related quality of life impact of an oral formulation. Med Cannabis Cannabinoids. 2022;5(1):20-31. doi: 10.1159/000521492. PMID: 35950052. **Exclusion reason:** Ineligible comparator

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34. Abo Ziad R, Grynbaum MB, Peleg R, et al. The Attitudes and Beliefs of Family Physicians Regarding the Use of Medical Cannabis, Knowledge of Side Effects, and Barriers to Use: A Comparison Between Residents and Specialists. Am J Ther. 2020;Publish Ahead of Printdoi: 10.1097/MJT.0000000000001236. PMID: 33416237. **Exclusion reason:** Ineligible study design

35. Aboud T, Schuster NM. Pain management in Multiple Sclerosis: a review of available treatment options. Curr Treat Options Neurol. 2019 Nov 27;21(12):62. doi: 10.1007/s11940-019-0601-2. PMID: 31773455. **Exclusion reason:** Systematic review used as source document

36. Abrams DI, Couey P, Dixit N, et al. Effect of inhaled Cannabis for pain in adults with Sickle Cell Disease: a randomized clinical trial. JAMA Netw Open. 2020 Jul 01;3(7):e2010874. doi: 10.1001/jamanetworkopen.2020.10874. PMID: 32678452. **Exclusion reason:** Inadequate duration

37. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007 Feb 13;68(7):515-21. doi: 10.1212/01.wnl.0000253187.66183.9c. PMID: 17296917. **Exclusion reason:** Inadequate duration

38. Abuhasira R, Ron A, Sikorin I, et al. Medical Cannabis for older patients-treatment protocol and initial results. J Clin Med. 2019 Nov 01;8(11):1819. doi: 10.3390/jcm8111819. PMID: 31683817. **Exclusion reason:** Ineligible population

39. Aebischer JH, Dieckmann NF, Jones KD, et al. Chronic pain clinical and prescriptive practices in the Cannabis era. Pain Manag Nurs. 2021 Dec 29;29:29. doi: 10.1016/j.pmn.2021.11.009. PMID: 34973920. **Exclusion reason:** Systematic review used as source document

40. Akgün K, Essner U, Seydel C, et al. Daily practice managing resistant multiple sclerosis spasticity with delta-9-tetrahydrocannabinol: cannabidiol oromucosal spray: a systematic review of observational studies. J Cent Nerv Syst Dis. 2019;11:1179573519831997. doi: 10.1177/1179573519831997. PMID: 30886530. **Exclusion reason:** Systematic review used as source document

41. Allan GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for Medical Cannabinoids: pain, nausea and vomiting, spasticity, and harms. Can Fam Physician. 2018 Feb;64(2):e78-e94. PMID: 29449262. **Exclusion reason:** Ineligible publication type

42. Almog S, Aharon-Peretz J, Vulfsons S, et al. The pharmacokinetics, efficacy, and safety of a novel selective-dose Cannabis inhaler in patients with chronic pain: a randomized, double-blinded, placebo-controlled trial. Eur J Pain. 2020 Sep;24(8):1505-16. doi: 10.1002/ejp.1605. PMID: 32445190. **Exclusion reason:** Inadequate duration

43. Aly E, Masocha W. Targeting the Endocannabinoid system for management of HIV-associated neuropathic pain: a systematic review. IBRO Neurosci Rep. 2021 Jun;10:109-18. doi: 10.1016/j.ibneur.2021.01.004. PMID: 34179865. **Exclusion reason:** Systematic review used as source document

44. Amato L, Minozzi S, Mitrova Z, et al. Systematic review of safeness and therapeutic efficacy of Cannabis in patients with Multiple Sclerosis, neuropathic pain, and in oncological patients treated with chemotherapy. Epidemiol Prev. 2017;41(5-6)doi: 10.19191/EP17.5-6.AD01.069. PMID: 29119763. **Exclusion reason:** Ineligible publication type

45. AminiLari M, Wang L, Neumark S, et al. Medical Cannabis and Cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials. Sleep. 2021doi: 10.1093/sleep/zsab234. PMID: 34546363. **Exclusion reason:** Systematic review used as source document

PRE-PUBLICATION FINAL

46. Anaya HJM, Ortiz MPT, Valencia DHF, et al. Efficacy of Cannabinoids in Fibromyalgia: a literature review. Colomb J Anesthesiol. 2021;49(4)doi: 10.5554/22562087.e980. **Exclusion reason:** Inadequate duration

47. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. J Pain. 2015 Dec;16(12):1221-32. doi: 10.1016/j.jpain.2015.07.009. PMID: 26362106. **Exclusion reason:** Inadequate duration

48. Anonymous. Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines. 2016. **Exclusion reason:** Ineligible study design

49. Anonymous. National Institute for Health and Care Excellence (UK). 2019 11;11:11. PMID: 35107907. **Exclusion reason:** Systematic review used as source document

50. Arkell TR, Downey LA, Hayley AC, et al. Assessment of Medical Cannabis and Health-Related Quality of Life. JAMA Netw Open. 2023;6(5):e2312522. doi: https://dx.doi.org/10.1001/jamanetworkopen.2023.12522. **Exclusion reason:** Ineligible study design

51. Arkell TR, Manning B, Downey LA, et al. A Semi-Naturalistic, Open-Label Trial Examining the Effect of Prescribed Medical Cannabis on Neurocognitive Performance. CNS Drugs. 2023doi: 10.1007/s40263-023-01046-z. **Exclusion reason:** Ineligible population

52. Arnold JC, McCartney D, Suraev A, et al. The safety and efficacy of low oral doses of cannabidiol: An evaluation of the evidence. Clin Transl Sci. 2022doi: https://dx.doi.org/10.1111/cts.13425. **Exclusion reason:** Systematic review used as source document

53. Arthur P, Kalvala AK, Surapaneni SK, et al. Applications of Cannabinoids in Neuropathic Pain: An Updated Review. Critical reviews in therapeutic drug carrier systems. 2024;41(1):1-33. doi: https://dx.doi.org/10.1615/CritRevTherDrugCarrierSyst.2022038592. **Exclusion reason:** Ineligible publication type

54. Aviram J, Atzmony D, Eisenberg E. Long-term effectiveness and safety of Medical Cannabis administered through the metered-dose Syqe Inhaler. Pain reports. 2022;7(3):e1011. doi: 10.1097/PR9.0000000000001011. PMID: 35620248. **Exclusion reason:** Ineligible comparator

55. Aviram J, Glezerman M, Hayam E, et al. Evaluating Sex Differences in Efficacy, Safety and Pharmacokinetics in Patients Treated with Cannabis by a Metered-Dose Inhaler. Pharmaceuticals (Basel). 2023;16(10)doi: https://dx.doi.org/10.3390/ph16101426. **Exclusion reason:** Ineligible comparator

56. Aviram J, Lewitus GM, Pud D, et al. Specific Phytocannabinoid compositions are associated with analgesic response and adverse effects in chronic pain patients treated with Medical Cannabis. Pharmacol Res. 2021 Jul;169:105651. doi: 10.1016/j.phrs.2021.105651. PMID: 34000362. **Exclusion reason:** Ineligible comparator

57. Aviram J, Lewitus GM, Vysotski Y, et al. Sex differences in Medical Cannabis-related adverse effects. Pain. 2021doi: 10.1097/j.pain.0000000000002463. PMID: 34538843. **Exclusion reason:** Ineligible comparator

58. Aviram J, Pud D, Gershoni T, et al. Medical Cannabis treatment for chronic pain: outcomes and prediction of response. Eur J Pain. 2020 Oct 16;16:16. doi: 10.1002/ejp.1675. PMID: 33065768. **Exclusion reason:** Ineligible comparator

59. Aviram J, Samuelly-Leichtag G. Efficacy of Cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. Pain Physician. 2017 Sep;20(6):E755-E96. PMID: 28934780. **Exclusion reason:** Systematic review used as source document

60. Bains S, Mukhdomi T. Medicinal Cannabis for Treatment of Chronic Pain. StatPearls Publishing. 2024;01:01. PMID: 34662076. **Exclusion reason:** Ineligible publication type

PRE-PUBLICATION FINAL

61. Bajtel A, Kiss T, Toth B, et al. The safety of Dronabinol and Nabilone: a systematic review and meta-analysis of clinical trials. Pharmaceuticals (Basel). 2022 Jan 14;15(1):14. doi: 10.3390/ph15010100. PMID: 35056154. **Exclusion reason:** Systematic review used as source document

62. Bakewell BK, Sherman M, Binsfeld K, et al. The Use of Cannabidiol in Patients With Low Back Pain Caused by Lumbar Spinal Stenosis: An Observational Study. Cureus. 2022;14(9):e29196. doi: https://dx.doi.org/10.7759/cureus.29196. **Exclusion reason:** Ineligible study design

63. Bakhshaie J, Doorley JD, Choukas NR, et al. Cannabis Co-Use Among Black Individuals with Chronic Pain Who Use Opioids: Associations with Other Substance Use and Pain Related Outcomes. Journal of health care for the poor and underserved. 2024;35(2):564-82. doi: 10.1353/hpu.2024.a928633. **Exclusion reason:** Ineligible study design

64. Balestra AM, Chalk K, Denke C, et al. Influence of Cannabinoid Treatment on Trajectories of Patient-Related Outcomes in Chronic Pain: Pain Intensity, Emotional Distress, Tolerability and Physical Disability. Brain sci. 2023;13(4)doi: 10.3390/brainsci13040680. **Exclusion reason:** Ineligible comparator

65. Ball S, Vickery J, Hobart J, et al. The cannabinoid use in progressive inflammatory brain disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess. 2015;19(12):1-187. doi: 10.3310/hta19120. PMID: 25676540. **Exclusion reason:** Ineligible population

66. Balu A, Mishra D, Marcu J, et al. Medical Cannabis certification is associated with decreased opiate use in patients with chronic pain: a retrospective cohort study in Delaware. Cureus. 2021 Dec;13(12):e20240. doi: 10.7759/cureus.20240. PMID: 35004055. **Exclusion reason:** Ineligible comparator

67. Barakji J, Korang SK, Feinberg J, et al. Cannabinoids versus placebo for pain: A systematic review with meta-analysis and Trial Sequential Analysis. PLoS ONE. 2023;18(1):e0267420. doi: https://dx.doi.org/10.1371/journal.pone.0267420. **Exclusion reason:** Systematic review used as source document

68. Bargnes V, Hart P, Gupta S, et al. Safety and efficacy of medical cannabis in elderly patients: a retrospective review in a neurological outpatient setting. Neurology. 2019;92(15). **Exclusion reason:** Ineligible publication type

69. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of Multiple Sclerosis and neuropathic pain. Expert Opin Pharmacother. 2006 Apr;7(5):607-15. doi: 10.1517/14656566.7.5.607. PMID: 16553576. **Exclusion reason:** Ineligible publication type

70. Barnes RC, Banjara S, McHann MC, et al. Assessing dose and sex dependent antinociceptive effects of cannabidiol and amitriptyline, alone and in combination, and exploring mechanism of action involving serotonin 1A receptors. J Pharmacol Exp Ther. 2023;21:21. doi: https://dx.doi.org/10.1124/jpet.123.001855. PMID: 38129125. **Exclusion reason:** Ineligible population

71. Bawa Z, Lewis D, Gavin PD, et al. An open-label feasibility trial of transdermal cannabidiol for hand osteoarthritis. Sci. 2024;14(1)doi: 10.1038/s41598-024-62428-x. **Exclusion reason:** Ineligible comparator

72. Becker WC, Li Y, Caniglia EC, et al. Cannabis use, pain interference, and prescription opioid receipt among persons with HIV: a target trial emulation study. AIDS Care. 2021 Jun 28:1-9. doi: 10.1080/09540121.2021.1944597. PMID: 34180721. **Exclusion reason:** Ineligible population

PRE-PUBLICATION FINAL

73. Bellnier T, Brown GW, Ortega TR. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with Medical Cannabis. Ment Health Clin. 2018 Apr 26;8(3):110-5. doi: 10.9740/mhc.2018.05.110. PMID: 29955555. **Exclusion reason:** Ineligible comparator

74. Benedict G, Sabbagh A, Conermann T. Medical Cannabis used as an alternative treatment for chronic pain demonstrates reduction in chronic opioid use - a prospective study. Pain Physician. 2022 Jan;25(1):E113-E9. PMID: 35051158. **Exclusion reason:** Ineligible comparator

75. Bennici A, Mannucci C, Calapai F, et al. Safety of Medical Cannabis in neuropathic chronic pain management. Molecules (Basel). 2021;26(20):16. doi: 10.3390/molecules26206257. PMID: 34684842. **Exclusion reason:** Systematic review used as source document

76. Berger AA, Keefe J, Winnick A, et al. Cannabis and Cannabidiol (CBD) for the treatment of Fibromyalgia. Best Pract Res Clin Anaesthesiol. 2020doi: 10.1016/j.bpa.2020.08.010. PMID: 33004171. **Exclusion reason:** Ineligible publication type

77. Berman JS, Symonds C, Birch R. Efficacy of two Cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004 Dec;112(3):299-306. doi: 10.1016/j.pain.2004.09.013. PMID: 15561385. **Exclusion reason:** Inadequate duration

78. Bialas P, Fitzcharles M-A, Klose P, et al. Long-term observational studies with Cannabis-based medicines for chronic non-cancer pain: a systematic review and meta-analysis of effectiveness and safety. Eur J Pain. 2022doi: 10.1002/ejp.1957. PMID: 35467781. **Exclusion reason:** Systematic review used as source document

79. Bicket MC, Stone EM, McGinty EB. Association of cannabis use with patient-reported pain measures among adults with chronic pain in US states with medical cannabis programs. Reg Anesth Pain Med. 2023;03:03. doi: https://dx.doi.org/10.1136/rapm-2023-104833. PMID: 37923347. **Exclusion reason:** Ineligible intervention

80. Bicket MC, Stone EM, McGinty EE. Use of Cannabis and Other Pain Treatments Among Adults With Chronic Pain in US States With Medical Cannabis Programs. JAMA Netw Open. 2023;6(1):e2249797. doi: https://dx.doi.org/10.1001/jamanetworkopen.2022.49797. **Exclusion reason:** Ineligible study design

81. Bilbao A, Spanagel R. Medical Cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications. BMC medicine. 2022;20(1):259. doi: 10.1186/s12916-022-02459-1. PMID: 35982439. **Exclusion reason:** Systematic review used as source document

82. Blake A, Wan BA, Malek L, et al. A selective review of Medical Cannabis in cancer pain management. Ann Palliat Med. 2017 Dec;6(Suppl 2):S215-S22. doi: 10.21037/apm.2017.08.05. PMID: 28866904. **Exclusion reason:** Systematic review used as source document

83. Bobitt J, Kang H, Arora K, et al. Offering an Alternative to Persons with Chronic Pain: How Access to Cannabis May Provide an Off-Ramp from Undesired Prescription Opioid Use. Cannabis (Albuquerque, N.M.). 2023;6(2):113-22. doi: 10.26828/cannabis/2023/000125. PMID: 37484046. **Exclusion reason:** Ineligible study design

84. Boehnke KF, Clauw DJ. Cannabinoids for Chronic Pain: Translating Systematic Review Findings Into Clinical Action. Ann Intern Med. 2022doi: 10.7326/M22-1512. PMID: 35667063. **Exclusion reason:** Background only

PRE-PUBLICATION FINAL

85. Boehnke KF, Gagnier JJ, Matallana L, et al. Cannabidiol Use for Fibromyalgia: Prevalence of Use and Perceptions of Effectiveness in a Large Online Survey. J Pain. 2021doi: 10.1016/j.jpain.2020.12.001. PMID: 33400996. **Exclusion reason:** Ineligible study design

86. Boehnke KF, Gagnier JJ, Matallana L, et al. Substituting Cannabidiol for opioids and pain medications among individuals with Fibromyalgia: a large online survey. J Pain. 2021doi: 10.1016/j.jpain.2021.04.011. PMID: 33992787. **Exclusion reason:** Background only

87. Boehnke KF, Hauser W, Fitzcharles M-A. Cannabidiol (CBD) in Rheumatic Diseases (Musculoskeletal Pain). Curr Rheumatol Rep. 2022doi: 10.1007/s11926-022-01077-3. PMID: 35503198. **Exclusion reason:** Systematic review used as source document

88. Boehnke KF, Martel MO, Smith T, et al. Medicinal Cannabis Use for Rheumatic Conditions in the US Versus Canada: Rationale for Use and Patient?Health Care Provider Interactions. ACR Open Rheumatology. 2023;5(9):443-53. doi: 10.1002/acr2.11592. PMID: 37519131. **Exclusion reason:** Ineligible study design

89. Boehnke KF, Scott JR, Litinas E, et al. High-frequency Medical Cannabis use is associated with worse pain among individuals with chronic pain. J Pain. 2020 May - Jun;21(5-6):570-81. doi: 10.1016/j.jpain.2019.09.006. PMID: 31560957. **Exclusion reason:** Ineligible comparator

90. Boehnke KF, Wu CL, Clauw DJ. Thoughtfully Integrating Cannabis Products Into Chronic Pain Treatment. Anesthesia and Analgesia. 2024;138(1):5-15. doi: 10.1213/ANE.0000000000005904. **Exclusion reason:** Ineligible publication type

91. Bonomo Y, Norman A, Collins L, et al. Pharmacokinetics, safety, and tolerability of a Medicinal Cannabis formulation in patients with chronic non-cancer pain on long-term high dose opioid analgesia: a pilot study. Pain Ther. 2021;18:18. doi: 10.1007/s40122-021-00344-y. PMID: 34921662. **Exclusion reason:** Ineligible comparator

92. Boychuk DG, Goddard G, Mauro G, et al. The effectiveness of Cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache. 2015;29(1):7-14. doi: 10.11607/ofph.1274. PMID: 25635955. **Exclusion reason:** Ineligible publication type

93. Brenne J, Burney E, Mauer K, et al. Risks associated with chronic cannabis use on opioid use, length of stay, and revision rate for patients undergoing posterior lumbar interbody fusion. The spine journal : official journal of the North American Spine Society. 2024doi: https://dx.doi.org/10.1016/j.spinee.2024.01.011. **Exclusion reason:** Ineligible intervention

94. Busse JW, MacKillop J. Medical Cannabis and Cannabinoids for chronic pain: summary of a rapid recommendation. J Mil Veteran Fam Health. 2021;7:118-22. doi: 10.3138/jmvfh-2021-0056. **Exclusion reason:** Ineligible publication type

95. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. Jama. 2018 Dec 18;320(23):2448-60. doi: 10.1001/jama.2018.18472. PMID: 30561481. **Exclusion reason:** Systematic review used as source document

96. Campbell CM, Mun CJ, Hamilton KR, et al. Within-subject, double-blind, randomized, placebo-controlled evaluation of combining the cannabinoid dronabinol and the opioid hydromorphone in adults with chronic pain. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2023;48(11):1630-38. doi: https://dx.doi.org/10.1038/s41386-023-01597-1. **Exclusion reason:** Ineligible population

97. Campos MG, China M, Cláudio M, et al. Drug–Cannabinoid Interactions in Selected Therapeutics for Symptoms Associated with Epilepsy, Autism Spectrum Disorder, Cancer, Multiple Sclerosis, and Pain. Pharmaceuticals (Basel). 2024;17(5)doi: 10.3390/ph17050613. **Exclusion reason:** Ineligible publication type

PRE-PUBLICATION FINAL

98. Canavan C, Inoue T, McMahon S, et al. The efficacy, adverse events, and withdrawal rates of the pharmacological management of chronic spinal cord injury pain: a systematic review and meta-analysis. Pain Med. 2022 Feb 01;23(2):375-95. doi: 10.1093/pm/pnab140. PMID: 33844010. **Exclusion reason:** Systematic review used as source document

99. Carlisle C, Polley K, Panda C, et al. Alleviation of Pain, PAIN Interference, and Oxidative Stress by a Novel Combination of Hemp Oil, Calamari Oil, and Broccoli: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients. 2023;15(12)doi: https://dx.doi.org/10.3390/nu15122654. **Exclusion reason:** Ineligible intervention

100. Carpenter RW, Nance M, Frumkin MR, et al. Use and co-use of alcohol and cannabis following physical pain in the daily life of community adults engaged in regular substance use. Psychology of Addictive Behaviors. 2024;15:15. doi: https://dx.doi.org/10.1037/adb0000992. PMID: 38358657. **Exclusion reason:** Ineligible study design

101. Carreira DS, Garden S, Huffman A, et al. Cannabinoids in the Orthopedic Setting: A Literature Review. Orthopedics. 2022:1-7. doi: 10.3928/01477447-20220225-11. PMID: 35245146. **Exclusion reason:** Systematic review used as source document

102. Chan CJ. Efficacy of plant based Cannabis in reducing pain in patients with chronic pain: a meta analysis. Diss Abstr Int. 2020;81(10-B):No Pagination Specified. **Exclusion reason:** Ineligible publication type

103. Charoenporn V, Charernboon T, Mackie CJ. Medical Cannabis as a Substitute for Prescription Agents: A Systematic Review and Meta-analysis. J Subst Use. 2023;28(4):522-34. doi: 10.1080/14659891.2022.2070870. **Exclusion reason:** Systematic review used as source document

104. Chen MY, Kramer EB, Gibson LP, et al. Investigating the Relationship Between Cannabis Expectancies and Anxiety, Depression, and Pain Responses After Acute Flower and Edible Cannabis Use. Cannabis Cannabinoid Res. 2024;12:12. doi: https://dx.doi.org/10.1089/can.2023.0264. PMID: 38608236. **Exclusion reason:** Ineligible population

105. Christ MM. Pain medicine: Cannabis is effective in neuropathic pain. Arzneimitteltherapie. 2019;37(6):242-3. **Exclusion reason:** Not in English

106. Clermont-Gnamien S, Atlani S, Attal N, et al. The therapeutic use of Δ9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain. Presse Med. 2002;31(39 I):1840-5. PMID: 12496714. **Exclusion reason:** Not in English

107. Coates MD, Dalessio S, Walter V, et al. Symptoms and extraintestinal manifestations in active cannabis users with inflammatory bowel disease. Cannabis Cannabinoid Res. 2022;7(4):445-50. doi: 10.1089/can.2020.0155. PMID: 33998892. **Exclusion reason:** Ineligible population

108. Cooper ZD, Abrams DI. Considering abuse liability and neurocognitive effects of Cannabis and Cannabis-derived products when assessing Analgesic efficacy: a comprehensive review of randomized-controlled studies. Am J Drug Alcohol Abuse. 2019;45(6):580-95. doi: 10.1080/00952990.2019.1669628. PMID: 31687845. **Exclusion reason:** Systematic review used as source document

109. Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked Cannabis for spasticity in Multiple Sclerosis: a randomized, placebo-controlled trial. Cmaj. 2012 Jul 10;184(10):1143-50. doi: 10.1503/cmaj.110837. PMID: 22586334. **Exclusion reason:** Inadequate duration

110. Costales B, van Boemmel-Wegmann S, Winterstein A, et al. Clinical conditions and prescription drug utilization among early medical marijuana registrants in Florida. J Psychoactive Drugs. 2021:1-10. doi: 10.1080/02791072.2020.1864069. PMID: 33393877. **Exclusion reason:** Ineligible study design

PEER REVIEW FINAL

111. Coughlin LN, Ilgen MA, Jannausch M, et al. Progression of Cannabis withdrawal symptoms in people using Medical Cannabis for chronic pain. Addiction. 2021doi: 10.1111/add.15370. PMID: 33400332. **Exclusion reason:** Ineligible study design

112. Crestani F. Medical Cannabis for the treatment of Fibromyalgia. J Clin Rheumatol. 2018 Aug;24(5):281. doi: 10.1097/RHU.0000000000000823. PMID: 29757806. **Exclusion reason:** Ineligible study design

113. Cumenal M, Selvy M, Kerckhove N, et al. The safety of medications used to treat peripheral neuropathic pain, part 2 (opioids, Cannabinoids and other drugs): review of double-blind, placebo-controlled, randomized clinical trials. Expert Opin Drug Saf. 2020doi: 10.1080/14740338.2021.1842871. PMID: 33103931. **Exclusion reason:** Systematic review used as source document

114. Cunetti L, Manzo L, Peyraube R, et al. Chronic pain treatment with Cannabidiol in kidney transplant patients in Uruguay. Transplant Proc. 2018 Mar;50(2):461-4. doi: 10.1016/j.transproceed.2017.12.042. PMID: 29579828. **Exclusion reason:** Ineligible comparator

115. Cunningham CO, Starrels JL, Zhang C, et al. Medical marijuana and opioids (MEMO) study: protocol of a longitudinal cohort study to examine if medical cannabis reduces opioid use among adults with chronic pain. BMJ Open. 2020;10(12):e043400. doi: 10.1136/bmjopen-2020-043400. PMID: 33376181. **Exclusion reason:** Ineligible study design

116. Curtis SA, Brandow AM, Deveaux M, et al. Daily Cannabis users with Sickle Cell Disease show fewer admissions than others with similar pain complaints. Cannabis Cannabinoid Res. 2020;5(3):255-62. doi: 10.1089/can.2019.0036. PMID: 32923662. **Exclusion reason:** Ineligible study design

117. D'Souza RS, Alvarez GAM, Dombovy-Johnson M, et al. Evidence-Based Treatment of Pain in Chemotherapy-Induced Peripheral Neuropathy. Current pain and headache reports. 2023;27(5):99-116. doi: https://dx.doi.org/10.1007/s11916-023-01107-4. **Exclusion reason:** Ineligible publication type

118. Dagher M, Alayoubi M, Sigal GH, et al. Unveiling the link between chronic pain and misuse of opioids and cannabis. Journal of Neural Transmission. 2024;03:03. doi: https://dx.doi.org/10.1007/s00702-024-02765-3. PMID: 38570361. **Exclusion reason:** Ineligible study design

119. Darnall BD, Humphreys KN. An experimental method for assessing whether marijuana use reduces opioid use in patients with chronic pain. Addiction. 2018 Aug;113(8):1552-3. doi: 10.1111/add.14239. PMID: 29882256. **Exclusion reason:** Ineligible study design

120. Datta S, Ramamurthy PC, Anand U, et al. Wonder or evil?: multifaceted health hazards and health benefits of Cannabis Sativa and its Phytochemicals. Saudi J Biol Sci.28(12):7290-313. doi: 10.1016/j.sjbs.2021.08.036. PMID: 34867033. **Exclusion reason:** Ineligible publication type

121. Davidson WM, Mahavni A, Chrusciel T, et al. Characteristics of patients with non-cancer pain and long-term prescription opioid use who have used medical versus recreational marijuana. J Cannabis Res.6(1):7. doi: https://dx.doi.org/10.1186/s42238-024-00218-y. PMID: 38383471. **Exclusion reason:** Ineligible outcome

122. Dawson D, Stjepanovi D, Lorenzetti V, et al. The prevalence of cannabis use disorders in people who use medicinal cannabis: A systematic review and meta-analysis. Drug Alcohol Depend. 2024;257doi: 10.1016/j.drugalcdep.2024.111263. **Exclusion reason:** Systematic review used as source document

PREPUBLICATION DRAFT

123. Degenhardt L, Lintzeris N, Campbell G, et al. Experience of adjunctive Cannabis use for chronic non-cancer pain: findings from the pain and opioids in treatment (POINT) study. Drug Alcohol Depend. 2015 Feb 01;147:144-50. doi: 10.1016/j.drugalcdep.2014.11.031. PMID: 25533893. **Exclusion reason:** Ineligible study design

124. Denduluri SK, Woolson ST, Indelli PF, et al. Cannabinoid and Opioid Use Among Total Joint Arthroplasty Patients: A 6-Year, Single-Institution Study. Orthopedics. 2020 Oct 01:1-6. doi: 10.3928/01477447-20200928-02. PMID: 33002174. **Exclusion reason:** Ineligible population

125. Deshpande A, Mailis-Gagnon A, Zoheiry N, et al. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: systematic review of randomized controlled trials. Can Fam Physician. 2015 Aug;61(8):e372-81. PMID: 26505059. **Exclusion reason:** Ineligible publication type

126. Dimitrios L, Aris F. Efficacy, tolerability and safety of Cannabinoids for management of pain in adult patients with Multiple Sclerosis: a systematic review and meta-analysis. Signa Vitae. 2021;17:S10. doi: 10.22514/sv.2021.157. **Exclusion reason:** Ineligible publication type

127. Domnic G, Narayanan S, Mohana-Kumaran N, et al. Kratom (Mitragyna speciosa Korth.) an overlooked medicinal plant in Malaysia. J Subst Use. 2022;27(1):1-6. doi: 10.1080/14659891.2021.1885515. **Exclusion reason:** Systematic review used as source document

128. Dubois C, Danielson EC, Beestrum M, et al. Medical cannabis and its efficacy/effectiveness on the management of osteoarthritis pain and function. Current Medical Research and Opinion. 2024doi: 10.1080/03007995.2024.2363945. **Exclusion reason:** Systematic review used as source document

129. Dugosh KL, Short MM, Syracuse P, et al. Anxiety severity and prescription medication utilization in first-time medical marijuana users. Journal of Affective Disorders Reports. 2023;14doi: 10.1016/j.jadr.2023.100671. **Exclusion reason:** Ineligible population

130. Durán M, Capellà D. Cannabis and Cannabinoids in the treatment of neuropathic pain. DOLOR. 2005;20(4):213-6. **Exclusion reason:** Not in English

131. Dykukha I, Malessa R, Essner U, et al. Nabiximols in chronic neuropathic pain: a meta-analysis of randomized placebo-controlled trials. Pain Med. 2021 04 20;22(4):861-74. doi: 10.1093/pm/pnab050. PMID: 33561282. **Exclusion reason:** Systematic review used as source document

132. Eadie L, Lo LA, Christiansen A, et al. Duration of neurocognitive impairment with Medical Cannabis use: a scoping review. Front Psychiatry. 2021;12doi: 10.3389/fpsyt.2021.638962. PMID: 33790818. **Exclusion reason:** Systematic review used as source document

133. Edinoff AN, Fort JM, Singh C, et al. Alternative Options for Complex, Recurrent Pain States Using Cannabinoids, Psilocybin, and Ketamine: A Narrative Review of Clinical Evidence. Neurology int. 2022;14(2):423-36. doi: 10.3390/neurolint14020035. PMID: 35645354. **Exclusion reason:** Ineligible publication type

134. Eichorn NL, Shult HT, Kracht KD, et al. Making a joint decision: Cannabis as a potential substitute for opioids in Obstetrics and Gynecology. Best practice & research. Clinical obstetrics & gynaecology. 2022;S1521-6934(22):00100-6. doi: 10.1016/j.bpobgyn.2022.07.002. PMID: 35970747. **Exclusion reason:** Ineligible publication type

135. El-Mourad J, Lunghi C, Herrera NP, et al. Dosing of Cannabinoids Associated with an Opioid-Sparing Effect: A Systematic Review of Longitudinal Studies. Pain Manag Nurs. 2023doi: https://dx.doi.org/10.1016/j.pmn.2023.08.005. **Exclusion reason:** Systematic review used as source document

136. Ellis RJ, Toperoff W, Vaida F, et al. Smoked Medicinal Cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009 Feb;34(3):672-80. doi: 10.1038/npp.2008.120. PMID: 18688212. **Exclusion reason:** Inadequate duration

PRE-PUBLICATION DRAFT

137. Ergisi M, Erridge S, Harris M, et al. An updated analysis of clinical outcome measures across patients from the UK Medical Cannabis registry. Cannabis Cannabinoid Res. 2022 Jan 24;24:24. doi: 10.1089/can.2021.0145. PMID: 35073160. **Exclusion reason:** Ineligible population

138. Fallon MT, Albert Lux E, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain. 2017 Aug;11(3):119-33. doi: 10.1177/2049463717710042. PMID: 28785408. **Exclusion reason:** Ineligible population

139. Faraj M, Dautrich T, Lundahl L, et al. Effects of Two Cannabidiol Oil Products on Self-Reported Stress Relief: A Quasi-Experimental Study. Med Cannabis Cannabinoids. 2023;6(1):138-47. doi: 10.1159/000531886. **Exclusion reason:** Ineligible population

140. Fari G, Megna M, Scacco S, et al. Hemp Seed Oil in Association with &bgr;-Caryophyllene, Myrcene and Ginger Extract as a Nutraceutical Integration in Knee Osteoarthritis: a Double-Blind Prospective Case-Control Study. Medicina (Kaunas, Lithuania). 2023;59(2)doi: https://doi.org/10.3390/medicina59020191. **Exclusion reason:** Ineligible intervention

141. Feingold D, Brill S, Goor-Aryeh I, et al. Depression and Anxiety among chronic pain patients receiving prescription opioids and medical marijuana. J Affect Disord. 2017 Aug 15;218:1-7. doi: 10.1016/j.jad.2017.04.026. PMID: 28453948. **Exclusion reason:** Ineligible study design

142. Ferrie ML, Rogers AH, Zvolensky MJ, et al. Alcohol and marijuana co-use among adults with chronic low back pain: Associations with substance misuse, mental health, and pain experience. The American journal on addictions. 2022;31(6):546-9. doi: 10.1111/ajad.13343. PMID: 36184876. **Exclusion reason:** Ineligible study design

143. Fiani B, Sarhadi KJ, Soula M, et al. Current application of Cannabidiol (CBD) in the management and treatment of neurological disorders. Neurol Sci. 2020 Nov;41(11):3085-98. doi: 10.1007/s10072-020-04514-2. PMID: 32556748. **Exclusion reason:** Background only

144. Filippini G, Minozzi S, Borrelli F, et al. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. The Cochrane database of systematic reviews. 2022;5(5):CD013444. doi: 10.1002/14651858.CD013444.pub2. PMID: 35510826. **Exclusion reason:** Systematic review used as source document

145. First L, Douglas W, Habibi B, et al. Cannabis use and low-back pain: a systematic review. Cannabis Cannabinoid Res. 2020;5(4):283-9. doi: 10.1089/can.2019.0077. PMID: 33381642. **Exclusion reason:** Systematic review used as source document

146. Fishbain DA, Cutler RB, Rosomoff HL, et al. Validity of self-reported drug use in chronic pain patients. Clin J Pain. 1999 Sep;15(3):184-91. doi: 10.1097/00002508-199909000-00005. PMID: 10524471. **Exclusion reason:** Background only

147. Fisher E, Moore RA, Fogarty AE, et al. Cannabinoids, Cannabis, and Cannabis-based medicine for pain management: a systematic review of randomised controlled trials. Pain. 2021 Jul 1;162(Suppl 1):S45-s66. doi: 10.1097/j.pain.0000000000001929. PMID: 32804836. **Exclusion reason:** Systematic review used as source document

148. Fitzcharles M-A, Rampakakis E, Sampalis J, et al. Use of Medical Cannabis by patients with Fibromyalgia in Canada after Cannabis legalisation: a cross-sectional study. Clin Exp Rheumatol. 2021doi: 10.55563/clinexprheumatol/qcyet7. PMID: 33938797. **Exclusion reason:** Ineligible study design

PRE-PUBLICATION FINAL

149. Fitzcharles MA, Baerwald C, Ablin J, et al. Efficacy, tolerability and safety of Cannabinoids in chronic pain associated with rheumatic diseases (Fibromyalgia Syndrome, back pain, Osteoarthritis, Rheumatoid Arthritis): a systematic review of randomized controlled trials. Schmerz. 2016 Feb;30(1):47-61. doi: 10.1007/s00482-015-0084-3. PMID: 26767993. **Exclusion reason:** Ineligible publication type

150. Fitzcharles MA, Petzke F, Tolle TR, et al. Cannabis-based medicines and Medical Cannabis in the treatment of nociplastic pain. Drugs.81(18):2103-16. doi: 10.1007/s40265-021-01602-1. PMID: 34800285. **Exclusion reason:** Ineligible publication type

151. Fitzcharles MA, Shir Y, Joseph L, et al. The effects of nabilone on insomnia in fibromyalgia: results of a randomized controlled trial. Arthritis and rheumatism. 2009;60:1429. doi: https://doi.org/10.1002/art.26503. **Exclusion reason:** Ineligible publication type

152. Fitzcharles MA, Ste-Marie PA, Hauser W, et al. Efficacy, tolerability, and safety of Cannabinoid treatments in the rheumatic diseases: a systematic review of randomized controlled trials. Arthritis care & research. 2016 May;68(5):681-8. doi: 10.1002/acr.22727. PMID: 26548380. **Exclusion reason:** Ineligible publication type

153. Flachenecker P, Henze T, Zettl UK. Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice--results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. Eur Neurol. 2014;71(5-6):271-9. doi: 10.1159/000357427. PMID: 24525548. **Exclusion reason:** Ineligible population

154. Flachenecker P, Henze T, Zettl UK. Long-term effectiveness and safety of nabiximols (tetrahydrocannabinol/cannabidiol oromucosal spray) in clinical practice. Eur Neurol. 2014;72(1-2):95-102. doi: 10.1159/000360285. PMID: 24943098. **Exclusion reason:** Ineligible population

155. Francis A, Erridge S, Holvey C, et al. Assessment of Clinical Outcomes in Patients With Osteoarthritis: Analysis From the UK Medical Cannabis Registry. J Pain Pall Care Pharmacother. 2024:1-14. doi: https://dx.doi.org/10.1080/15360288.2024.2340076. **Exclusion reason:** Ineligible comparator

156. Gado F, Mohamed KA, Meini S, et al. Variously substituted 2-oxopyridine derivatives: extending the structure-activity relationships for allosteric modulation of the Cannabinoid CB2 receptor. Eur J Med Chem. 2020;211:113116. doi: 10.1016/j.ejmech.2020.113116. PMID: 33360803. **Exclusion reason:** Ineligible study design

157. Gambino A, Cabras M, Panagiotakos E, et al. Evaluating the suitability and potential efficiency of Cannabis Sativa oil for patients with primary Burning Mouth Syndrome: a prospective, open-label, single-arm pilot study. Pain Med. 2020doi: 10.1093/pm/pnaa318. PMID: 33123730. **Exclusion reason:** Ineligible comparator

158. Garmon EH, Olson K. Narrative review of Kratom, an emerging psychoactive substance with perianesthetic implications. Anesthesia and analgesia. 2022;XXXdoi: 10.1213/ANE.0000000000006177. PMID: 35986675. **Exclusion reason:** Ineligible publication type

159. Gedin F, Blome S, Ponten M, et al. Placebo Response and Media Attention in Randomized Clinical Trials Assessing Cannabis-Based Therapies for Pain: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(11):e2243848. doi: https://dx.doi.org/10.1001/jamanetworkopen.2022.43848. **Exclusion reason:** Systematic review used as source document

160. Gershoni T, Pud D, Aviram J, et al. Wellness of patients with chronic pain is not only about pain intensity. Pain practice : the official journal of World Institute of Pain. 2022;00:1-10. doi: 10.1111/papr.13168. PMID: 36181347. **Exclusion reason:** Ineligible comparator

PRE-PUBLICATION FINAL

161. Gilman JM, Schuster RM, Potter KW, et al. Effect of medical marijuana card ownership on pain, Insomnia, and Affective Disorder symptoms in adults: a randomized clinical trial. JAMA Netw Open. 2022;5(3):e222106. doi: 10.1001/jamanetworkopen.2022.2106. PMID: 35302633. **Exclusion reason:** Ineligible intervention

162. Giossi R, Carrara F, Padroni M, et al. Systematic review and meta-analysis seem to indicate that Cannabinoids for chronic primary pain treatment have limited benefit. Pain Ther. 2022doi: 10.1007/s40122-022-00434-5. PMID: 36129666. **Exclusion reason:** Systematic review used as source document

163. Glare P, Chye R, Bloch M, et al. Tolerability and Efficacy of a 10:25 Preparation of DELTA9-Tetrahydrocannabinol and Cannabidiol for Treatment of Chronic Back or Neck Pain: A Multiple-Dose Escalation Study. Med Cannabis Cannabinoids. 2023;6(1):66-76. doi: 10.1159/000531232. PMID: 37465637. **Exclusion reason:** Ineligible study design

164. Goedel WC, Macmadu A, Shihipar A, et al. Association of medical cannabis licensure with prescription opioid receipt: A population-based, individual-level retrospective cohort study. Int J Drug Policy. 2021;100:103502. doi: 10.1016/j.drugpo.2021.103502. PMID: 34695720. **Exclusion reason:** Ineligible intervention

165. Goldstein F, Galluzzi K, Bach B, et al. Analgesic Effect of delta-9-Tetrahydrocannabinol Alone and of a 1: 1 delta-9-Tetrahydrocannabinol: cannabidiol Formulation in Chronic Neuropathic Pain: two Pilot Studies. J Pain. 2024;25(4):32. doi: https://doi.org/10.1016/j.jpain.2024.01.153. **Exclusion reason:** Ineligible publication type

166. Greis A, Larsen E, Liu C, et al. Perceived efficacy, reduced prescription drug use, and minimal side effects of Cannabis in patients with chronic orthopedic pain. Cannabis Cannabinoid Res. 2021;12:12. doi: 10.1089/can.2021.0088. PMID: 34767730. **Exclusion reason:** Ineligible comparator

167. Greis A, Renslo B, Wilson-Poe AR, et al. Medical Cannabis use reduces opioid prescriptions in patients with chronic back pain. Cureus. 2022;14(1):e21452. doi: 10.7759/cureus.21452. PMID: 35223236. **Exclusion reason:** Ineligible comparator

168. Grossman S, Tan H, Gadiwalla Y. Cannabis and orofacial pain: a systematic review. Br J Oral Maxillofac Surg. 2021doi: 10.1016/j.bjoms.2021.06.005. PMID: 35305839. **Exclusion reason:** Systematic review used as source document

169. Grotenhermen F. Treatment of severe chronic pain with Cannabis preparations. Arztl Prax Neurol Psychiatr. 2002(5):28-30. **Exclusion reason:** Not in English

170. Guevara-López UM, Elizarrarás-Rivas J, Ramírez-García SA, et al. Empirical use of cannabis to control chronic pain of musculoskeletal origin. Revista Mexicana de Anestesiologia. 2024;47(2):96-101. doi: 10.35366/115316. **Exclusion reason:** Not in English

171. Guillouard M, Authier N, Pereira B, et al. Cannabis use assessment and its impact on pain in Rheumatologic diseases: a systematic review and meta-analysis. Rheumatology (Oxford). 2020doi: 10.1093/rheumatology/keaa534. PMID: 33159797. **Exclusion reason:** Systematic review used as source document

172. Gundin JS, Rubio-Valera M, Romero LG, et al. Off-label use of Cannabinoids efficacy and safety. Eur J Clin Pharm. 2017;19(3):158-63. **Exclusion reason:** Ineligible study design

173. Gustavsen S, Hb S, K L, et al. Safety and efficacy of low-dose medical cannabis oils in multiple sclerosis. Mult Scler Relat Disord. 2020;48:102708. doi: 10.1016/j.msard.2020.102708. PMID: 33387864. **Exclusion reason:** Ineligible population

174. Gutierrez T, Hohmann AG. Cannabinoids for the treatment of neuropathic pain: Are they safe and effective? Future Neurol. 2011;6(2):129-33. doi: 10.2217/fnl.11.6. **Exclusion reason:** Ineligible publication type

PRE-PUBLICATION FINAL

175. Guy D, Wootten JC, Wong M, et al. Pharmacodynamic effects following co-administration of cannabinoids and opioids: A scoping review of human experimental studies. Pain Med. 2024;01:01. doi: https://dx.doi.org/10.1093/pm/pnae024. PMID: 38561178. **Exclusion reason:** Systematic review used as source document

176. Habib G, Khazin F, Artul S. The effect of Medical Cannabis on pain level and quality of sleep among Rheumatology clinic outpatients. Pain Res Manag. 2021;2021:1756588. doi: 10.1155/2021/1756588. PMID: 34531934. **Exclusion reason:** Ineligible comparator

177. Häckel A. Cannabis for chronic back pain?: Pivotal study for whole Cannabis extract started. MMW Fortschr Med. 2021;163(14):63. doi: 10.1007/s15006-021-0197-9. **Exclusion reason:** Ineligible publication type

178. Haddad F, Dokmak G, Karaman R. The efficacy of Cannabis on Multiple Sclerosis-related symptoms. Life (Basel, Switzerland). 2022;12(5)doi: 10.3390/life12050682. PMID: 35629350. **Exclusion reason:** Ineligible publication type

179. Haffar A, Khan IA, Abdelaal MS, et al. Topical Cannabidiol (CBD) After Total Knee Arthroplasty Does Not Decrease Pain or Opioid Use: A Prospective Randomized Double-Blinded Placebo-Controlled Trial. J Arthroplasty. 2022 Apr 4doi: 10.1016/j.arth.2022.03.081. PMID: 35390457. **Exclusion reason:** Ineligible population

180. Haleem R, Wright R. A scoping review on clinical trials of pain reduction with Cannabis administration in adults. J Clin Med Res. 2020 Jun;12(6):344-51. doi: 10.14740/jocmr4210. PMID: 32587650. **Exclusion reason:** Systematic review used as source document

181. Hall N, James B, Bhuiyan MAN, et al. Topical cannabidiol is well tolerated in individuals with a history of elite physical performance and chronic lower extremity pain. J Cannabis Res. 2023;5(1):11. doi: https://dx.doi.org/10.1186/s42238-023-00179-8. **Exclusion reason:** Ineligible comparator

182. Hameed M, Prasad S, Jain E, et al. Medical Cannabis for Chronic Nonmalignant Pain Management. Current pain and headache reports. 2023doi: https://dx.doi.org/10.1007/s11916-023-01101-w. **Exclusion reason:** Ineligible publication type

183. Hansen JS, Hansen RM, Petersen T, et al. The effect of Cannabis-based medicine on neuropathic pain and spasticity in patients with Multiple Sclerosis and spinal cord injury: study protocol of a national multicenter double-blinded, placebo-controlled trial. Brain sci. 2021;11(9)doi: 10.3390/brainsci11091212. PMID: 34573231. **Exclusion reason:** Ineligible publication type

184. Hansen JS, Kasch H, Finnerup NB, et al. The effect of medical cannabis on neuropathic pain and spasticity in patients with multiple sclerosis and spinal cord injury: a danish multicentre double-blinded placebo-controlled study. Med Cannabis Cannabinoids. 2019;2(2):79. doi: https://doi.org/10.1159/000500623. **Exclusion reason:** Ineligible publication type

185. Haroutounian S, Arendt-Nielsen L, Belton J, et al. International association for the study of pain presidential task force on Cannabis and Cannabinoid Analgesia: research agenda on the use of Cannabinoids, Cannabis, and Cannabis-based medicines for pain management. Pain. 2021 Jul 01;162(Suppl 1):S117-S24. doi: 10.1097/j.pain.0000000000002266. PMID: 34138827. **Exclusion reason:** Background only

186. Harris E. Medical Cannabis Did Not Reduce Pain Prescriptions, Procedures. Jama. 2023;330(6):496. doi: 10.1001/jama.2023.12554. PMID: 37467000. **Exclusion reason:** Ineligible publication type

187. Harris M, Erridge S, Ergisi M, et al. UK Medical Cannabis Registry: an analysis of clinical outcomes of Medicinal Cannabis therapy for chronic pain conditions. Expert Rev Clin Pharmacol. 2021:1-13. doi: 10.1080/17512433.2022.2017771. PMID: 34937477. **Exclusion reason:** Ineligible comparator

PRE-PUBLICATION FINAL

188. Hasin DS, Wall MM, Alschuler D, et al. Chronic Pain, Cannabis Legalization and Cannabis Use Disorder in Veterans Health Administration Patients, 2005 to 2019. medRxiv : the preprint server for health sciences. 2023;80(4):380-8. doi: 10.1101/2023.07.10.23292453. PMID: 37503049. **Exclusion reason:** Ineligible comparator

189. Hasin DS, Wall MM, Alschuler DM, et al. Chronic pain, cannabis legalisation, and cannabis use disorder among patients in the US Veterans Health Administration system, 2005 to 2019: a repeated, cross-sectional study. The Lancet Psychiatry. 2023;10(11):877-86. doi: 10.1016/S2215-0366(23)00268-7. **Exclusion reason:** Ineligible outcome

190. Hassan S, Zheng Q, Rizzolo E, et al. Does integrative medicine reduce prescribed opioid use for chronic pain? A systematic literature review. Pain Med. 2020 Apr 01;21(4):836-59. doi: 10.1093/pm/pnz291. PMID: 31755962. **Exclusion reason:** Ineligible intervention

191. Haungs A, Elizondo J. Does smoking Cannabis help with chronic neuropathic pain? Evid Based Pract. 2018;21(2):E7-E8. doi: 10.1097/01.EBP.0000541985.24333.b1. **Exclusion reason:** Ineligible publication type

192. Hauser W, Fitzcharles M-A. Register-based studies on Cannabis-based medicines and Medical Cannabis need reliable diagnoses and Cannabis treatment details. Eur J Pain. 2022;26(1):3-4. doi: 10.1002/ejp.1881. PMID: 34743399. **Exclusion reason:** Ineligible publication type

193. Hauser W, Fitzcharles M-A, Radbruch L, et al. Cannabinoids in pain management and palliative medicine: an overview of systematic reviews and prospective observational studies. Dtsch Arztebl Int. 2017 Sep;114(38):627-34. doi: 10.3238/arztebl.2017.0627. PMID: 29017688. **Exclusion reason:** Systematic review used as source document

194. Hauser W, Fitzcharles MA, Radbruch L, et al. Cannabinoids in Pain Management and Palliative Medicine. Dtsch Arztebl Int. 2017 Sep 22;114(38):627-34. doi: 10.3238/arztebl.2017.0627. PMID: 29017688. **Exclusion reason:** Systematic review used as source document

195. Hayaki J, Abrantes AM, Anderson B, et al. Chronic Pain and Cannabis Use Frequency, Intensity, and Severity in Young Adults. Subst Use Misuse. 2023:1-7. doi: https://dx.doi.org/10.1080/10826084.2023.2287240. PMID: 38017655. **Exclusion reason:** Ineligible comparator

196. Hayes C, Martin JH. Lack of efficacy of Cannabidiol for relieving back pain: time to re-set expectations? Med J Aust. 2021doi: 10.5694/mja2.51025. PMID: 33846981. **Exclusion reason:** Ineligible publication type

197. Hefner K, Sofuoglu M, Rosenheck R. Concomitant Cannabis abuse/dependence in patients treated with opioids for non-cancer pain. The American journal on addictions. 2015 Sep;24(6):538-45. doi: 10.1111/ajad.12260. PMID: 26246069. **Exclusion reason:** Ineligible intervention

198. Hegde V, Bracey DN, Pollet AK, et al. Cannabis Use Does Not Affect Outcomes After Total Hip Arthroplasty. The Journal of arthroplasty. 2023;38(9):1808-11. doi: 10.1016/j.arth.2023.03.040. PMID: 36940759. **Exclusion reason:** Ineligible population

199. Heineman JT, Forster GL, Stephens KL, et al. A randomized controlled trial of topical Cannabidiol for the treatment of thumb basal joint arthritis. J Hand Surg Am. 2022 May 27doi: 10.1016/j.jhsa.2022.03.002. PMID: 35637038. **Exclusion reason:** Inadequate duration

200. Hendricks O, Andersen TE, Christiansen AA, et al. Efficacy and safety of Cannabidiol followed by an open label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with Rheumatoid Arthritis or Ankylosing Spondylitis: protocol for a multicentre, randomised, placebo-controlled study. BMJ Open. 2019 Jun 04;9(6):e028197. doi: 10.1136/bmjopen-2018-028197. PMID: 31167870. **Exclusion reason:** Ineligible study design

PRE-PUBLICATION FINAL

201. Hershkovich O, Hayun Y, Oscar N, et al. The role of cannabis in treatment-resistant fibromyalgia women. Pain practice : the official journal of World Institute of Pain. 2022doi: https://dx.doi.org/10.1111/papr.13179. **Exclusion reason:** Ineligible study design

202. Hesselink JM, Kopsky DJ. Enhancing acupuncture by low dose Naltrexone. Acupunct Med. 2011 Jun;29(2):127-30. doi: 10.1136/aim.2010.003566. PMID: 21415049. **Exclusion reason:** Ineligible publication type

203. Hill KP, Hurley-Welljams-Dorof WM. Low to moderate quality evidence demonstrates the potential benefits and adverse events of Cannabinoids for certain medical indications. Evid Based Med. 2016 Feb;21(1):17. doi: 10.1136/ebmed-2015-110264. PMID: 26490847. **Exclusion reason:** Ineligible publication type

204. Hill KP, Palastro MD, Johnson B, et al. Cannabis and pain: a clinical review. Cannabis Cannabinoid Res. 2017;2(1):96-104. doi: 10.1089/can.2017.0017. PMID: 28861509. **Exclusion reason:** Systematic review used as source document

205. Hjorthøj C, La Cour P, Nordentoft M, et al. Cannabis-based medicines and Medical Cannabis for patients with neuropathic pain and other pain disorders: nationwide register-based pharmacoepidemiologic comparison with propensity score matched controls. Eur J Pain. 2021doi: 10.1002/ejp.1874. PMID: 34624164. **Exclusion reason:** Ineligible outcome

206. Hodges JS, DeAngelis BN, Borodovsky J, et al. Impact of Early-Life Adversity on Cannabis Use: Exploring the Mediating and Moderating Effects of Chronic Pain. Cannabis Cannabinoid Res. 2024doi: https://dx.doi.org/10.1089/can.2023.0218. **Exclusion reason:** Ineligible intervention

207. Hoggart B, Ratcliffe S, Ehler E, et al. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. J Neurol. 2015 Jan;262(1):27-40. doi: 10.1007/s00415-014-7502-9. PMID: 25270679. **Exclusion reason:** Ineligible study design

208. Hojsted J, Ekholm O, Kurita GP, et al. Addictive behaviors related to opioid use for chronic pain: a population-based study. Pain. 2013;154(12):2677-83. doi: 10.1016/j.pain.2013.07.046. PMID: 23906554. **Exclusion reason:** Ineligible intervention

209. Holdcroft A, Smith M, Jacklin A, et al. Pain relief with oral Cannabinoids in familial Mediterranean fever. Anaesthesia. 1997 May;52(5):483-6. doi: 10.1111/j.1365-2044.1997.139-az0132.x. PMID: 9165969. **Exclusion reason:** Ineligible study design

210. Horsted T, Lichon Hesthaven K, Leutscher PDC. Safety and Effectiveness of Cannabinoids to Danish Patients with Treatment Refractory Chronic Pain - A Retrospective Observational Real-world Study. Eur J Pain. 2022doi: https://dx.doi.org/10.1002/ejp.2054. **Exclusion reason:** Ineligible study design

211. Huang IC, Alberts NM, Buckley MG, et al. Change in pain status and subsequent opioid and marijuana use among long-term adult survivors of childhood cancer. JNCI Cancer Spectr. 2020;4(6):pkaa070. doi: 10.1093/jncics/pkaa070. PMID: 33409451. **Exclusion reason:** Ineligible study design

212. Hughes PR, Nwokocha J. Medical Cannabis or Cannabinoids for chronic pain: BMJ rapid recommendation. American Family Physician. 2022;106(2):208-9. PMID: 35977118. **Exclusion reason:** Ineligible publication type

213. Hunter D, Oldfield G, Tich N, et al. Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis. Osteoarthritis Cartilage. 2018;26:S26. doi: 10.1016/j.joca.2018.02.067. **Exclusion reason:** Ineligible publication type

214. Hwang JK, Clarke H. Cannabis and pain: a review. J Pain Manag. 2016;9(4):395-413. **Exclusion reason:** Ineligible publication type

215. Iskedjian M, Bereza B, Gordon A, et al. Meta-analysis of Cannabis based treatments for neuropathic and Multiple Sclerosis-related pain. Curr Med Res Opin. 2007 Jan;23(1):17-24. doi: 10.1185/030079906x158066. PMID: 17257464. **Exclusion reason:** Ineligible publication type

PRE-PUBLICATION FINAL

216. Issa MA, Narang S, Jamison RN, et al. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clin J Pain. 2014 Jun;30(6):472-8. doi: 10.1097/AJP.0000000000000022. PMID: 24281276. **Exclusion reason:** Inadequate duration

217. Jain N, Moorthy A. Cannabinoids in Rheumatology: friend, foe or a bystander? Musculoskeletal care. 2022doi: 10.1002/msc.1636. PMID: 35476898. **Exclusion reason:** Ineligible publication type

218. Jashinski J, Grossman E, Quaye A, et al. Randomised, pragmatic, waitlist controlled trial of Cannabis added to prescription opioid support on opioid dose reduction and pain in adults with chronic non-cancer pain: study protocol. BMJ Open. 2022;12(6):e064457. doi: 10.1136/bmjopen-2022-064457. PMID: 35680252. **Exclusion reason:** Ineligible publication type

219. Jawahar R, Oh U, Yang S, et al. A systematic review of pharmacological pain management in Multiple Sclerosis. Drugs. 2013 Oct;73(15):1711-22. doi: 10.1007/s40265-013-0125-0. PMID: 24085618. **Exclusion reason:** Systematic review used as source document

220. Jeddi HM, Busse JW, Sadeghirad B, et al. Cannabis for medical use versus opioids for chronic non-cancer pain: a systematic review and network meta-analysis of randomised clinical trials. BMJ Open. 2024;14(1):e068182. doi: https://dx.doi.org/10.1136/bmjopen-2022-068182. **Exclusion reason:** Systematic review used as source document

221. Jensen TS, Madsen CS, Finnerup NB. Pharmacology and treatment of neuropathic pains. Curr Opin Neurol. 2009 Oct;22(5):467-74. doi: 10.1097/WCO.0b013e3283311e13. PMID: 19741531. **Exclusion reason:** Ineligible publication type

222. Johal H, Devji T, Chang Y, et al. Cannabinoids in chronic non-cancer pain: a systematic review and meta-analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020 Feb 19;13:1179544120906461. doi: 10.1177/1179544120906461. PMID: 32127750. **Exclusion reason:** Systematic review used as source document

223. Jugl S, Okpeku A, Costales B, et al. A mapping literature review of Medical Cannabis clinical outcomes and quality of evidence in approved conditions in the USA from 2016 to 2019. Med Cannabis Cannabinoids. 2021;4(1):21-42. doi: 10.1159/000515069. PMID: 34676348. **Exclusion reason:** Systematic review used as source document

224. Kafil TS, Nguyen TM, MacDonald JK, et al. Cannabis for the treatment of ulcerative colitis. Cochrane Database Syst Rev. 2018 Nov 08;11(11):CD012954. doi: 10.1002/14651858.CD012954.pub2. PMID: 30406638. **Exclusion reason:** Ineligible population

225. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. Jama. 2003 Oct 01;290(13):1757-62. doi: 10.1001/jama.290.13.1757. PMID: 14519710. **Exclusion reason:** Inadequate duration

226. Karuppagounder V, Chung J, Abdeen A, et al. Therapeutic Effects of Non-Euphorigenic Cannabis Extracts in Osteoarthritis. Cannabis Cannabinoid Res. 2023;8(6):1030-44. doi: https://dx.doi.org/10.1089/can.2021.0244. PMID: 35994012. **Exclusion reason:** Ineligible population

227. Kaskie B, Kang H, Bhagianadh D, et al. Cannabis use among older persons with Arthritis, Cancer and Multiple Sclerosis: are we comparing apples and oranges? Brain sci. 2021;11(5)doi: 10.3390/brainsci11050532. PMID: 33922425. **Exclusion reason:** Ineligible study design

PRE-PUBLICATION FINAL

228. Kawka M, Erridge S, Holvey C, et al. Clinical outcome data of first cohort of chronic pain patients treated with Cannabis-based sublingual oils in the United Kingdom - analysis from the UK Medical Cannabis Registry. J Clin Pharmacol. 2021doi: 10.1002/jcph.1961. PMID: 34473850. **Exclusion reason:** Ineligible comparator

229. Khalid N, Patel P, Singh A. Cannabis Versus Opioids for Pain. StatPearls Publishing. 2024;01:01. PMID: 34424653. **Exclusion reason:** Ineligible publication type

230. Khurshid H, Qureshi IA, Jahan N, et al. A systematic review of Fibromyalgia and recent advancements in treatment: is Medicinal Cannabis a new hope? Cureus. 2021;13(8):e17332. doi: 10.7759/cureus.17332. PMID: 34567876. **Exclusion reason:** Systematic review used as source document

231. Kim J. In patients with chronic neuropathic pain, cannabinoids improve sleep and reduce pain vs. placebo. Ann Intern Med. 2023;176(5):JC57. doi: https://dx.doi.org/10.7326/J23-0026. **Exclusion reason:** Ineligible publication type

232. Kinnucan JAR, Swaminath A, Sangha MS, et al. Real world dispensary data for IBD patients using medical cannabis. Am J Gastroenterol. 2021;116(SUPPL):S436. doi: https://doi.org/10.14309/01.ajg.0000777220.73380.41. **Exclusion reason:** Ineligible publication type

233. Kliuk-Ben Bassat O, Brill S, Vaisman N, et al. POS-676 exploratory study to assess the safety of sublingual oil based Medical Cannabis BOL-DP-O-04 in dialysis patients who have chronic pain. Kidney international reports. 2021;6(4):S295. doi: 10.1016/j.ekir.2021.03.707. **Exclusion reason:** Ineligible publication type

234. Kluwe L, Scholze C, Schmidberg LM, et al. Medical Cannabis Alleviates Chronic Neuropathic Pain Effectively and Sustainably without Severe Adverse Effect: A Retrospective Study on 99 Cases. Med Cannabis Cannabinoids. 2023:89-96. doi: 10.1159/000531667. **Exclusion reason:** Ineligible study design

235. Kocot-Kepska M, Zajaczkowska R, Mika J, et al. Topical treatments and their molecular/cellular mechanisms in patients with peripheral neuropathic pain-narrative review. Pharmaceutics. 2021;13(4)doi: 10.3390/pharmaceutics13040450. PMID: 33810493. **Exclusion reason:** Ineligible publication type

236. Korownyk CS, Montgomery L, Young J, et al. PEER simplified chronic pain guideline: management of chronic low back, osteoarthritic, and neuropathic pain in primary care. Can Fam Physician. 2022;68(3):179-90. doi: 10.46747/cfp.6803179. PMID: 35292455. **Exclusion reason:** Systematic review used as source document

237. Kruger DJ, Kruger JS. Consumer experiences with Delta-8-THC: medical use, pharmaceutical substitution, and comparisons with Delta-9-THC. Cannabis Cannabinoid Res. 2021;19:19. doi: 10.1089/can.2021.0124. PMID: 34797727. **Exclusion reason:** Ineligible study design

238. Kulesza B, Mazurek M, Kurzepa J. Can cannabidiol (CBD) help with low back pain? Annals of Agricultural & Environmental Medicine. 2023;30(3):549-54. doi: https://dx.doi.org/10.26444/aaem/168674. PMID: 37772533. **Exclusion reason:** Systematic review used as source document

239. Kurlyandchik I, Tiralongo E, Schloss J. Safety and efficacy of Medicinal Cannabis in the treatment of Fibromyalgia: a systematic review. J Altern Complement Med. 2020;27(3):198-213. doi: 10.1089/acm.2020.0331. PMID: 33337931. **Exclusion reason:** Systematic review used as source document

240. Lake S, Walsh Z, Kerr T, et al. Frequency of Cannabis and illicit opioid use among people who use drugs and report chronic pain: a longitudinal analysis. PLoS Med. 2019 Nov 19;16(11):e1002967. doi: 10.1371/journal.pmed.1002967. PMID: 31743343. **Exclusion reason:** Ineligible study design

PRE-PUBLICATION FINAL

241. Lamb LC, Di Fiori MM, Feeney JM. Cannabis to reduce opiate use in patients with acute rib fractures. Journal of the American College of Surgeons. 2018;227(4):S259. doi: 10.1016/j.jamcollsurg.2018.07.531. **Exclusion reason:** Ineligible publication type

242. Lee C, Danielson EC, Beestrum M, et al. Medical Cannabis and Its Efficacy/Effectiveness for the Treatment of Low-Back Pain: a Systematic Review. Current Pain and Headache Reports. 2023doi: 10.1007/s11916-023-01189-0. **Exclusion reason:** Systematic review used as source document

243. Lee G, Grovey B, Furnish T, et al. Medical Cannabis for neuropathic pain. Curr Pain Headache Rep. 2018 Feb 01;22(1):8. doi: 10.1007/s11916-018-0658-8. PMID: 29388063. **Exclusion reason:** Systematic review used as source document

244. Lewis M, Baroutian S, Hanning SM. Phytocannabinoids for the Treatment of Neuropathic Pain: A Scoping Review of Randomised Controlled Trials Published Between 2012 and 2023. Curr Pain Headache Rep. 2023;14:14. doi: https://dx.doi.org/10.1007/s11916-023-01196-1. PMID: 38095748. **Exclusion reason:** Systematic review used as source document

245. Liang AL, Gingher EL, Coleman JS. Medical Cannabis for Gynecologic pain conditions: a systematic review. Obstet Gynecol. 2022 Feb 01;139(2):287-96. doi: 10.1097/AOG.0000000000004656. PMID: 35104069. **Exclusion reason:** Systematic review used as source document

246. Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symptom Manage. 2018 Feb;55(2):179-88.e1. doi: 10.1016/j.jpainsymman.2017.09.001. PMID: 28923526. **Exclusion reason:** Ineligible population

247. Lick D, Mirza N, Trevor R. Are cannabinoids effective for treatment of noncancer musculoskeletal pain? Evid Based Pract. 2022;25(7):40-1. doi: 10.1097/EBP.0000000000001631. PMID: 32655704. **Exclusion reason:** Ineligible publication type

248. Ling H-Q, Chen Z-H, He L, et al. Comparative efficacy and safety of 11 drugs as therapies for adults with neuropathic pain after spinal cord injury: a bayesian network analysis based on 20 randomized controlled trials. Frontiers in neurology. 2022;13:818522. doi: 10.3389/fneur.2022.818522. PMID: 35386408. **Exclusion reason:** Systematic review used as source document

249. Link K, Knowles LM, Alschuler KN, et al. Characterizing cannabis use in a sample of adults with multiple sclerosis and chronic pain: An observational study. Mult Scler Relat Disord. 2023;75doi: 10.1016/j.msard.2023.104742. **Exclusion reason:** Ineligible intervention

250. Longo R, Oudshoorn A, Befus D. Cannabis for chronic pain: a rapid systematic review of randomized control trials. Pain Manag Nurs. 2020;22(2):141-9. doi: 10.1016/j.pmn.2020.11.006. PMID: 33353819. **Exclusion reason:** Systematic review used as source document

251. Longworth J, Szafron M, Gruza A, et al. Cannabis and cannabinoid medications for the treatment of chronic orofacial pain: A scoping review: Cannabinoids and Chronic Orofacial Pain. Dentistry Review. 2023;3(1)doi: 10.1016/j.dentre.2023.100063. **Exclusion reason:** Systematic review used as source document

252. Lopez-Sendon Moreno JL, Garcia Caldentey J, Trigo Cubillo P, et al. A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's Disease. J Neurol. 2016;263(7):1390-400. doi: 10.1007/s00415-016-8145-9. PMID: 27159993. **Exclusion reason:** Ineligible population

253. Lowin T. Cannabidiol (CBD) and potential in medicinal use in rheumatoid arthritis. Medicinal Usage of Cannabis and Cannabinoids. 2023:511-21. **Exclusion reason:** Ineligible study design

PRE-PUBLICATION FINAL

254. Lucas P, Boyd S, Milloy MJ, et al. Cannabis significantly reduces the use of prescription opioids and improves quality of life in authorized patients: results of a large prospective study. Pain Med. 2020doi: 10.1093/pm/pnaa396. PMID: 33367882. **Exclusion reason:** Ineligible population

255. Luchetti M, Zanarella C, Moretti C, et al. Cannabinoids for the treatment of neuropathic pain. Acta Anaesthesiol Ital. 2008;59(2):187-95. **Exclusion reason:** Not in English

256. Lyes M, Yang KH, Castellanos J, et al. Microdosing psilocybin for chronic pain: a case series. Pain. 2022doi: 10.1097/j.pain.0000000000002778. PMID: 36066961. **Exclusion reason:** Ineligible study design

257. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol. 2011 Nov;72(5):735-44. doi: 10.1111/j.1365-2125.2011.03970.x. PMID: 21426373. **Exclusion reason:** Ineligible publication type

258. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol. 2015 Jun;10(2):293-301. doi: 10.1007/s11481-015-9600-6. PMID: 25796592. **Exclusion reason:** Ineligible publication type

259. Maayah ZH, Takahara S, Ferdaoussi M, et al. The anti-inflammatory and Analgesic effects of formulated full-spectrum Cannabis extract in the treatment of neuropathic pain associated with Multiple Sclerosis. Inflamm Res. 2020 Jun;69(6):549-58. doi: 10.1007/s00011-020-01341-1. PMID: 32239248. **Exclusion reason:** Ineligible publication type

260. MacCallum CA, Eadie L, Barr AM, et al. Practical strategies using Medical Cannabis to reduce harms associated with long term opioid use in chronic pain. Front Pharmacol. 2021;12doi: 10.3389/fphar.2021.633168. PMID: 33995035. **Exclusion reason:** Ineligible publication type

261. MacKay M, Zurier R, Kamen D, et al. A Phase 2, Double-blind, Randomized, Placebo-Controlled Multicenter Study to Evaluate Efficacy, Safety, and Tolerability of JBT-101/Lenabasum in Systemic Lupus Erythematosus, an Autoimmunity Centers of Excellence Study (ALE09). Arthritis rheumatol. 2022;74:735. doi: https://doi.org/10.1002/art.42355. **Exclusion reason:** Ineligible publication type

262. Maida V, Ennis M, Irani S, et al. Adjunctive nabilone in cancer pain and symptom management: a prospective observational study using propensity scoring. J Support Oncol. 2008 Mar;6(3):119-24. PMID: 18402303. **Exclusion reason:** Ineligible population

263. Malik Z, Bayman L, Valestin J, et al. Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial. Dis Esophagus. 2017 Feb 1;30(2):1-8. doi: 10.1111/dote.12455. PMID: 26822791. **Exclusion reason:** Ineligible population

264. Manca A, Valz C, Chiara F, et al. Cannabinoid levels description in a cohort of patients with chronic and neuropathic pain treated with Cannabis decoction: A possible role of TDM. Biomed Pharmacother. 2024;175doi: 10.1016/j.biopha.2024.116686. PMID: 38713939. **Exclusion reason:** Ineligible comparator

265. Markovà J, Essner U, Akmaz B, et al. Sativex(®) as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant Multiple Sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. Int J Neurosci. 2019 Feb;129(2):119-28. doi: 10.1080/00207454.2018.1481066. PMID: 29792372. **Exclusion reason:** Ineligible population

266. Martin-Sanchez E, Furukawa TA, Taylor J, et al. Systematic review and meta-analysis of Cannabis treatment for chronic pain. Pain Med. 2009 Nov;10(8):1353-68. doi: 10.1111/j.1526-4637.2009.00703.x. PMID: 19732371. **Exclusion reason:** Ineligible publication type

PUBLICATION FINAL

267. Matarazzo AP, Elisei LMS, Carvalho FC, et al. Mucoadhesive nanostructured lipid carriers as a Cannabidiol nasal delivery system for the treatment of neuropathic pain. Eur J Pharm Sci. 2021:105698. doi: 10.1016/j.ejps.2020.105698. PMID: 33406408. **Exclusion reason:** Ineligible study design

268. Maurer M, Henn V, Dittrich A, et al. Delta-9-Tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci. 1990;240(1):1-4. doi: 10.1007/bf02190083. PMID: 2175265. **Exclusion reason:** Inadequate duration

269. Maurotti S, Mare R, Pujia R, et al. Hemp seeds in post-arthroplasty rehabilitation: a pilot clinical study and an in vitro investigation. Nutrients. 2021;13(12)doi: 10.3390/nu13124330. PMID: 34959882. **Exclusion reason:** Ineligible intervention

270. Mazza M. Medical Cannabis for the treatment of Fibromyalgia syndrome: a retrospective, open-label case series. J Cannabis Res. 2021;3(1):4. doi: 10.1186/s42238-021-00060-6. PMID: 33597032. **Exclusion reason:** Ineligible comparator

271. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid pharmacologic treatments for chronic pain. Agency for Healthcare Research and Quality (US). 2020 PMID: 32338847. **Exclusion reason:** Systematic review used as source document

272. McDonagh MS, Wagner J, Ahmed AY, et al. Living systematic review on Cannabis and other plant-based treatments for chronic pain - quarterly progress report: May 2021. Agency for Healthcare Research and Quality (US). 2020 12;12:12. PMID: 34228409. **Exclusion reason:** Ineligible publication type

273. McGinty EE, Tormohlen KN, Barry CL, et al. Protocol: mixed-methods study of how implementation of US state Medical Cannabis laws affects treatment of chronic non-cancer pain and adverse opioid outcomes. Implement Sci. 2021;16(1):2. doi: 10.1186/s13012-020-01071-2. PMID: 33413454. **Exclusion reason:** Ineligible publication type

274. McGinty EE, Tormohlen KN, Seewald NJ, et al. Effects of U.S. State Medical Cannabis Laws on Treatment of Chronic Noncancer Pain. Ann Intern Med. 2023;176(7):904-12. doi: 10.7326/M23-0053. PMID: 37399549. **Exclusion reason:** Ineligible study design

275. McMichael BJ, Van Horn RL, Viscusi WK. The impact of Cannabis access laws on opioid prescribing. J Health Econ. 2020 Jan;69:102273. doi: 10.1016/j.jhealeco.2019.102273. PMID: 31865260. **Exclusion reason:** Ineligible intervention

276. McNabb M, Durante KA, Trocchio S, et al. Self-reported Medicinal Cannabis Use as an Alternative to Prescription and Over-the-counter Medication Use Among US Military Veterans. Clin Ther. 2023;45(6):562-77. doi: 10.1016/j.clinthera.2023.04.003. PMID: 37414507. **Exclusion reason:** Ineligible study design

277. McParland AL, Bhatia A, Matelski J, et al. Evaluating the impact of cannabinoids on sleep health and pain in patients with chronic neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. Regional anesthesia and pain medicine. 2022doi: https://dx.doi.org/10.1136/rapm-2021-103431. **Exclusion reason:** Systematic review used as source document

278. Meade E, Hehir S, Rowan N, et al. Mycotherapy: potential of fungal bioactives for the treatment of mental health disorders and morbidities of chronic pain. J Fungi (Basel). 2022;8(3)doi: 10.3390/jof8030290. PMID: 35330292. **Exclusion reason:** Systematic review used as source document

279. Mechtler L, Hart P, Bargnes V, et al. Medical cannabis treatment in patients with trigeminal neuralgia. Neurology. 2019;92(15). **Exclusion reason:** Ineligible publication type

280. Meng H, Johnston B, Englesakis M, et al. Selective Cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. Anesth Analg. 2017 Nov;125(5):1638-52. doi: 10.1213/ANE.0000000000002110. PMID: 28537982. **Exclusion reason:** Ineligible publication type

PREPUBLICATION FINAL

281. Meng H, Page MG, Ajrawat P, et al. Patient-reported outcomes in those consuming Medical Cannabis: a prospective longitudinal observational study in chronic pain patients. Canadian journal of anaesthesia = Journal canadien d'anesthésie. 2021doi: 10.1007/s12630-020-01903-1. PMID: 33469735. **Exclusion reason:** Ineligible population

282. Meuth SG, Henze T, Essner U, et al. Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: consistency of response across subgroups from the SAVANT randomized clinical trial. International Journal of Neuroscience 2020;130(12):1199-205. doi: 10.1080/00207454.2020.1730832. PMID: 32065006. **Exclusion reason:** Ineligible population

283. Mistry M, Simpson P, Morris E, et al. Cannabidiol for the Management of Endometriosis and Chronic Pelvic Pain. J Minim Invasive Gynecol. 2021;25:25. doi: 10.1016/j.jmig.2021.11.017. PMID: 34839061. **Exclusion reason:** Ineligible publication type

284. Mohammed SYM, Leis K, Mercado RE, et al. Effectiveness of Cannabidiol to Manage Chronic Pain: A Systematic Review. Pain Manag Nurs. 2023;10:10. doi: https://dx.doi.org/10.1016/j.pmn.2023.10.002. PMID: 37953193. **Exclusion reason:** Systematic review used as source document

285. Mohiuddin M, Blyth FM, Degenhardt L, et al. General risks of harm with Cannabinoids, Cannabis, and Cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews. Pain. 2021 Jul 01;162(Suppl 1):S80-S96. doi: 10.1097/j.pain.0000000000002000. PMID: 32941319. **Exclusion reason:** Background only

286. Montero-Oleas N, Arevalo-Rodriguez I, Nunez-Gonzalez S, et al. Therapeutic use of Cannabis and Cannabinoids: an evidence mapping and appraisal of systematic reviews. BMC Complement Med Ther. 2020 Jan 15;20(1):12. doi: 10.1186/s12906-019-2803-2. PMID: 32020875. **Exclusion reason:** Systematic review used as source document

287. Moore RA, Fisher E, Finn DP, et al. Cannabinoids, Cannabis, and Cannabis-based medicines for pain management: an overview of systematic reviews. Pain. 2021 Jul 1;162(Suppl 1):S67-s79. doi: 10.1097/j.pain.0000000000001941. PMID: 32804833. **Exclusion reason:** Systematic review used as source document

288. Moreno Torres I, Sanchez AJ, Garcia-Merino A. Evaluation of the tolerability and efficacy of Sativex in Multiple Sclerosis. Expert Rev Neurother. 2014 Nov;14(11):1243-50. doi: 10.1586/14737175.2014.971758. PMID: 25331416. **Exclusion reason:** Ineligible publication type

289. Moreno-Sanz G, Madiedo A, Hernandez P, et al. Sex-dependent prescription patterns and clinical outcomes associated with the use of two oral Cannabis formulations in the multimodal management of chronic pain patients in Colombia. Frontiers in pain research (Lausanne, Switzerland). 2022;3:854795. doi: 10.3389/fpain.2022.854795. PMID: 35399153. **Exclusion reason:** Ineligible comparator

290. Moreno-Sanz G, Madiedo A, Lynskey M, et al. "Flower Power": Controlled Inhalation of THC-Predominant Cannabis Flos Improves Health-Related Quality of Life and Symptoms of Chronic Pain and Anxiety in Eligible UK Patients. Biomedicines. 2022;10(10)doi: 10.3390/biomedicines10102576. **Exclusion reason:** Ineligible study design

291. Mucke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018 Mar 07;3(3):CD012182. doi: 10.1002/14651858.CD012182.pub2. PMID: 29513392. **Exclusion reason:** Systematic review used as source document

292. Muller C, Reggio PH. An Analysis of the Putative CBD Binding Site in the Ionotropic Cannabinoid Receptors. Front Cell Neurosci. 2020;14:615811. doi: 10.3389/fncel.2020.615811. PMID: 33362478. **Exclusion reason:** Ineligible study design

PRE-PUBLICATION FINAL

293. Murff HJ. Review: weak evidence of benefits of Cannabis for chronic neuropathic pain; moderate to weak evidence of adverse effects. Ann Intern Med. 2017 Dec 19;167(12):JC62. doi: 10.7326/ACPJC-2017-167-12-062. PMID: 29255852. **Exclusion reason:** Ineligible publication type

294. Mustard CA, Orchard C, Dobson KG, et al. An observational study of pain severity, cannabis use, and benefit expenditures in work disability. Canadian journal of public health = Revue canadienne de sante publique. 2024;115(1):157-67. doi: https://dx.doi.org/10.17269/s41997-023-00821-1. **Exclusion reason:** Ineligible study design

295. Myers B, Geist T, Hart P, et al. Medical cannabis in the treatment of parkinson's disease. Neurology. 2019;92(15). **Exclusion reason:** Ineligible publication type

296. Naftali T, Mechoulam R, Gabay G, et al. Cannabidiol treatment does not effect active crohn's disease. Gastroenterology. 2013;144(5):S180. **Exclusion reason:** Ineligible publication type

297. Narang S, Gibson D, Wasan AD, et al. Efficacy of Dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008 Mar;9(3):254-64. doi: 10.1016/j.jpain.2007.10.018. PMID: 18088560. **Exclusion reason:** Ineligible study design

298. Neilson LM, Swift C, Swart ECS, et al. Impact of marijuana legalization on opioid utilization in patients diagnosed with pain. J Gen Intern Med. 2021doi: 10.1007/s11606-020-06530-6. PMID: 33575906. **Exclusion reason:** Background only

299. Nguyen T, Li Y, Greene D, et al. Changes in Prescribed Opioid Dosages Among Patients Receiving Medical Cannabis for Chronic Pain, New York State, 2017-2019. JAMA Netw Open. 2023;6(1):e2254573. doi: https://dx.doi.org/10.1001/jamanetworkopen.2022.54573. **Exclusion reason:** Ineligible comparator

300. Nielsen S, Picco L, Murnion B, et al. Opioid-sparing effect of Cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2022doi: 10.1038/s41386-022-01322-4. PMID: 35459926. **Exclusion reason:** Systematic review used as source document

301. Nielsen S, Picco L, Murnion B, et al. Opioid-sparing effect of Cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies. Neuropsychopharmacology. 2022;47(7):1315-30. doi: 10.1038/s41386-022-01322-4. PMID: 35459926. **Exclusion reason:** Systematic review used as source document

302. Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of Medical Cannabis or Cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. BMJ Open. 2021 07 28;11(7):e047717. doi: 10.1136/bmjopen-2020-047717. PMID: 34321302. **Exclusion reason:** Systematic review used as source document

303. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol. 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x. PMID: 21362108. **Exclusion reason:** Ineligible population

304. Nowell WB, Gavigan K, L Silverman S. Cannabis for Rheumatic Disease pain: a review of current literature. Curr Rheumatol Rep. 2022;24(5):119-31. doi: 10.1007/s11926-022-01065-7. PMID: 35486218. **Exclusion reason:** Systematic review used as source document

305. Nugent SM, Kansagara D. The effects of Cannabis among adults with chronic pain. Ann Intern Med. 2018 Apr 03;168(7):525. doi: 10.7326/L17-0732. PMID: 29610910. **Exclusion reason:** Ineligible publication type

PRE-PUBLICATION FINAL

306. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of Cannabis among adults with chronic pain and an overview of general harms: a systematic review. Ann Intern Med. 2017 Sep 05;167(5):319-31. doi: 10.7326/M17-0155. PMID: 28806817. **Exclusion reason:** Systematic review used as source document

307. Nunnari P, Ladiana N, Ceccarelli G, et al. Long-term Cannabis-based oil therapy and pain medications prescribing patterns: an Italian observational study. Eur Rev Med Pharmacol Sci. 2022;26(4):1224-34. doi: 10.26355/eurrev_202202_28114. PMID: 35253178. **Exclusion reason:** Ineligible comparator

308. Nurmikko TJ, Serpell MG, Hoggart B, et al. A multi-centre, double-blind, randomized, controlled trial of oro-mucosal Cannabis based medicine in the treatment of neuropathic pain characterized by Allodynia. Neurology. no: PO6;64(Suppl 1):A374. **Exclusion reason:** Ineligible publication type

309. Nutt DJ, Phillips LD, Barnes MP, et al. A multicriteria decision analysis comparing pharmacotherapy for chronic neuropathic pain, including Cannabinoids and Cannabis-based medical products. Cannabis Cannabinoid Res. 2021 Mar 17;17:17. doi: 10.1089/can.2020.0129. PMID: 33998895. **Exclusion reason:** Ineligible study design

310. O'Connell M, Sandgren M, Frantzen L, et al. Medical Cannabis: effects on opioid and benzodiazepine requirements for pain control. Ann Pharmacother. 2019 Nov;53(11):1081-6. doi: 10.1177/1060028019854221. PMID: 31129977. **Exclusion reason:** Ineligible comparator

311. O'Regan A, Price RL. When cannabis is used for medicinal purposes: A focus on back pain. Cannabis Use, Neurobiology, Psychology, and Treatment. 2023:193-206. **Exclusion reason:** Ineligible study design

312. Okusanya BO, Asaolu IO, Ehiri JE, et al. Medical Cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review. Syst Rev. 2020 Jul 28;9(1):167. doi: 10.1186/s13643-020-01425-3. PMID: 32723354. **Exclusion reason:** Systematic review used as source document

313. Okusanya BO, Lott BE, Ehiri J, et al. Medical Cannabis for the treatment of migraine in adults: a review of the evidence. Frontiers in Neurology. 2022;13doi: 10.3389/fneur.2022.871187. PMID: 35711271. **Exclusion reason:** Systematic review used as source document

314. Pagano C, Ciaglia E, Coppola L, et al. Cannabidiol exerts multitarget immunomodulatory effects on PBMCs from individuals with psoriasis vulgaris. Front. 2024;15:1373435. doi: https://dx.doi.org/10.3389/fimmu.2024.1373435. PMID: 38601151. **Exclusion reason:** Ineligible study design

315. Pankratz T. Impact of telehealth versus traditional visits on pain management patients utilizing medical cannabis during the COVID-19 pandemic. Dissertation Abstracts International Section A: Humanities and Social Sciences. 2023;84(8-A):No-Specified. **Exclusion reason:** Ineligible publication type

316. Parlier-Ahmad AB, Polak K, Wiese A, et al. Alcohol and cannabis use in chronic pain patients with and without opioid medication pain management. Alcoholism: clinical and experimental research. 2023;47:439. doi: 10.1111/acer.15071. PMID: CN-02581285 **Exclusion reason:** Ineligible study design

317. Paulsingh CN, Mohamed MB, Elhaj MS, et al. The efficacy of marijuana use for pain relief in adults with Sickle Cell Disease: a systematic review. Cureus. 2022;14(5):e24962. doi: 10.7759/cureus.24962. PMID: 35706744. **Exclusion reason:** Systematic review used as source document

318. Pellesi L, Licata M, Verri P, et al. Pharmacokinetics and tolerability of oral Cannabis preparations in patients with medication overuse headache (MOH)—a pilot study. Eur J Clin Pharmacol. 2018;74(11):1427-36. doi: 10.1007/s00228-018-2516-3. PMID: 29980818. **Exclusion reason:** Ineligible study design

319. Perras C. Sativex for the management of Multiple Sclerosis symptoms. Issues Emerg Health Technol. 2005 Sep(72):1-4. PMID: 16317825. **Exclusion reason:** Ineligible publication type

PRE-PUBLICATION FINAL

320. Peters EN, Yardley H, Harrison A, et al. A randomized, double-blind, placebo-controlled, repeated-dose pilot study of the safety, tolerability, and preliminary effects of a cannabidiol (CBD)- and cannabigerol (CBG)-based beverage powder to support recovery from delayed onset muscle soreness (DOMS). Journal of the International Society of Sports Nutrition. 2023;20(1):2280113. doi: https://dx.doi.org/10.1080/15502783.2023.2280113. PMID: 37947792. **Exclusion reason:** Ineligible population

321. Petzke F, Tolle T, Fitzcharles MA, et al. Cannabis-based medicines and Medical Cannabis for chronic neuropathic pain. CNS Drugs. 2021;21:21. doi: 10.1007/s40263-021-00879-w. PMID: 34802112. **Exclusion reason:** Systematic review used as source document

322. Pham MN, Hudnall MT, Nadler RB. Marijuana, lower urinary tract symptoms, and pain in the urologic patient. Urology. 2020 05;139:8-13. doi: 10.1016/j.urology.2020.01.029. PMID: 32027882. **Exclusion reason:** Systematic review used as source document

323. Phillips KT, Pedula KL, Choi NG, et al. Chronic health conditions, acute health events, and healthcare utilization among adults over age 50 in Hawai'i who use Cannabis: a matched cohort study. Drug Alcohol Depend. 2022;234:109387. doi: 10.1016/j.drugalcdep.2022.109387. PMID: 35279458. **Exclusion reason:** Ineligible population

324. Phillips TJC, Cherry CL, Cox S, et al. A metanalysis of randomised controlled clinical trials assessing the effectivness of pharmacological interventions for painful HIV-associated sensory neuropathy. European journal of pain supplements. 2010;4(1):141. doi: https://doi.org/10.1016/S1754-3207(10)70503-4. **Exclusion reason:** Systematic review used as source document

325. Philpot LM, Ramar P, Jatoi A, et al. Cannabis in Cancer Survivors Who Report High Impact Chronic Pain: Findings from a 1500+ Patient Survey. American Journal of Hospice and Palliative Medicine. 2022doi: 10.1177/10499091221143098. **Exclusion reason:** Ineligible study design

326. Pichini S, Pacifici R, Busardo FP, et al. The challenge of clinical application of FM2 Cannabis oil produced in Italy for the treatment of neuropathic pain. Eur Rev Med Pharmacol Sci. 2018 Feb;22(4):863-5. doi: 10.26355/eurrev_201802_14363. PMID: 29509231. **Exclusion reason:** Ineligible publication type

327. Pinsger M, Schimetta W, Volc D, et al. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial. Wien Klin Wochenschr. 2006;118(11-12):327-35. doi: 10.1007/s00508-006-0611-4. PMID: 16855921. **Exclusion reason:** Not in English

328. Pinsger M, Schimetta W, Volc D, et al. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain - A randomized controlled trial. Wien Klin Wochenschr. 2006;118(11-12):327-35. doi: 10.1007/s00508-006-0611-4. PMID: 16855921. **Exclusion reason:** Not in English

329. Podda G, Constantinescu CS. Nabiximols in the treatment of spasticity, pain and urinary symptoms due to Multiple Sclerosis. Expert Opin Biol Ther. 2012 Nov;12(11):1517-31. doi: 10.1517/14712598.2012.721765. PMID: 22954177. **Exclusion reason:** Ineligible publication type

330. Poli P, Carnevale S, Scocca A, et al. Promising health benefits of adjuvant Acmella and Zingiber extracts combined with Coenzyme Q10 Phytosomes, supplementation in chronic pain treated with Medical Cannabis: a prospective and open-label clinical study. Evidence-based complementary and alternative medicine : eCAM. 2022;2022:7099161. doi: 10.1155/2022/7099161. PMID: 35733629. **Exclusion reason:** Ineligible comparator

331. Police A, Shankar VK, Pandey P, et al. Novel topical anandamide formulation for alleviating peripheral neuropathic pain. Int J Pharm. 2023;641:123085. doi: https://dx.doi.org/10.1016/j.ijpharm.2023.123085. **Exclusion reason:** Ineligible intervention

PRE-PUBLICATION FINAL

332. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012 May;13(5):438-49. doi: 10.1016/j.jpain.2012.01.003. PMID: 22483680. **Exclusion reason:** Ineligible population

333. Prevete E, Hupli A, Marrinan S, et al. Exploring the use of Kratom (Mitragyna Speciosa) via the YouTube data tool: A novel netnographic analysis. Emerg Trends Drugs Addict Health. 2021 2021/01/01/;1:100007. doi: 10.1016/j.etdah.2021.100007. **Exclusion reason:** Background only

334. Price RL, Charlot KV, Frieler S, et al. The efficacy of Cannabis in reducing back pain: a systematic review. Global Spine J. 2022doi: 10.1177/21925682211065411. PMID: 35128969. **Exclusion reason:** Systematic review used as source document

335. Prieto Gonzalez JM, Vila Silvan C. Safety and tolerability of nabiximols oromucosal spray: a review of real-world experience in observational studies, registries and case reports. Expert Rev Neurother. 2021doi: 10.1080/14737175.2021.1904896. PMID: 33749480. **Exclusion reason:** Systematic review used as source document

336. Prieto Gonzalez JM, Vila Silvan C. Safety and tolerability of nabiximols oromucosal spray: a review of more than 15 years' accumulated evidence from clinical trials. Expert Rev Neurother. 2021 Jun 07;07:07. doi: 10.1080/14737175.2021.1935879. PMID: 34092180. **Exclusion reason:** Systematic review used as source document

337. Prozialeck WC, Lamar PC, Krupp M, 2nd, et al. Kratom use within the context of the evolving Opioid Crisis and the COVID-19 Pandemic in the United States. Front Pharmacol. 2021;12:729220. doi: 10.3389/fphar.2021.729220. PMID: 34512353. **Exclusion reason:** Background only

338. Pud D, Aamar S, Schiff-Keren B, et al. Cannabis oil extracts for chronic pain: what else can be learned from another structured prospective cohort? Pain Reports. 2024;9(2)doi: 10.1097/PR9.0000000000001143. **Exclusion reason:** Ineligible comparator

339. Quintero J-M, Pulido G, Giraldo L-F, et al. A systematic review on Cannabinoids for neuropathic pain administered by routes other than oral or inhalation. Plants (Basel, Switzerland). 2022;11(10)doi: 10.3390/plants11101357. PMID: 35631782. **Exclusion reason:** Systematic review used as source document

340. Rabgay K, Waranuch N, Chaiyakunapruk N, et al. The effects of Cannabis, Cannabinoids, and their administration routes on pain control efficacy and safety: a systematic review and network meta-analysis. J Am Pharm Assoc (2003). 2020 Jan - Feb;60(1):225-34.e6. doi: 10.1016/j.japh.2019.07.015. PMID: 31495691. **Exclusion reason:** Systematic review used as source document

341. Ramphul K, Verma R, Pekyi-Boateng PK, et al. Growing cannabis use among Multiple Sclerosis adults with chronic pain; An analysis from the United States. Mult Scler Relat Disord. 2023;82:105390. doi: https://dx.doi.org/10.1016/j.msard.2023.105390. PMID: 38134607. **Exclusion reason:** Ineligible publication type

342. Rapin L, Gamaoun R, El Hage C, et al. Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic. J Cannabis Res. 2021;3(1)doi: 10.1186/s42238-021-00078-w. PMID: 34162446. **Exclusion reason:** Ineligible population

343. Reddon H, Lake S, Socias ME, et al. Cannabis use to manage opioid cravings among people who use unregulated opioids during a drug toxicity crisis. Int J Drug Policy. 2023;119:104113. doi: 10.1016/j.drugpo.2023.104113. PMID: 37481875. **Exclusion reason:** Ineligible population

344. Reisdorf S. Analgesia: Cannabis for neuropathic pain. MMW Fortschr Med. 2020;162(7):58. doi: 10.1007/s15006-020-0397-8. **Exclusion reason:** Not in English

345. Renslo B, Greis A, Liu CS, et al. Medical Cannabis use reduces opioid prescriptions in patients with Osteoarthritis. Cureus. 2022;14(1):e21564. doi: 10.7759/cureus.21564. PMID: 35228923. **Exclusion reason:** Ineligible comparator

PRE-PUBLICATION FINAL

346. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in Rheumatoid Arthritis. Cochrane Database Syst Rev. 2012 Jan 18;1:CD008921. doi: 10.1002/14651858.CD008921.pub2. PMID: 22258992. **Exclusion reason:** Ineligible publication type

347. Richet E, Ferret L, Gaboriau L, et al. Use of dronabinol in the treatment of resistant neuropathic pain: Feedback from patients followed in a multidisciplinary pain center. Annales Pharmaceutiques Francaises. 2022doi: 10.1016/j.pharma.2022.12.005. **Exclusion reason:** Not in English

348. Riera R, Pacheco RL, Bagattini AM, et al. Efficacy and safety of therapeutic use of Cannabis derivatives and their synthetic analogs: overview of systematic reviews. Phytother Res. 2021;29:29. doi: 10.1002/ptr.7263. PMID: 34841610. **Exclusion reason:** Systematic review used as source document

349. Robinson D, Ritter S, Yassin M. Comparing Sublingual and Inhaled Cannabis Therapies for Low Back Pain: An Observational Open-Label Study. Rambam Maimonides med. 2022;13(4)doi: https://dx.doi.org/10.5041/RMMJ.10485. **Exclusion reason:** Ineligible study design

350. Rogers AH, Bakhshaie J, Buckner JD, et al. Opioid and Cannabis co-use among adults with chronic pain: relations to substance misuse, mental health, and pain experience. J Addict Med. 2019 Jul/Aug;13(4):287-94. doi: 10.1097/ADM.0000000000000493. PMID: 30557213. **Exclusion reason:** Ineligible study design

351. Ross J, Slawek DE, Zhang C, et al. First-year trajectories of Medical Cannabis use among adults taking opioids for chronic pain: an observational cohort study. Pain Med. 2021doi: 10.1093/pm/pnab257. PMID: 34411246. **Exclusion reason:** Background only

352. Rouhollahi E, Macleod BA, Barr AM, et al. Cannabis extract CT-921 has a high efficacy– adverse effect profile in a neuropathic pain model. Drug Des Devel Ther. 2020;14:3351-61. doi: 10.2147/DDDT.S247584. PMID: 32884239 **Exclusion reason:** Ineligible population

353. Russo E. Cannabis and Cannabis based medicine extracts: additional results. J Cannabis Ther. 2004;3(4):153-61. doi: 10.1300/J175v03n04_03. **Exclusion reason:** Ineligible study design

354. Russo M, Naro A, Leo A, et al. Evaluating sativex in neuropathic pain management: a clinical and neurophysiological assessment in multiple sclerosis. Pain Med. 2016 Jun;17(6):1145-54. doi: 10.1093/pm/pnv080. PMID: 26764336. **Exclusion reason:** Ineligible population

355. Safakish R, Ko G, Salimpour V, et al. Medical Cannabis for the management of pain and quality of life in chronic pain patients: a prospective observational study. Pain Med. 2020 Nov 01;21(11):3073-86. doi: 10.1093/pm/pnaa163. PMID: 32556203. **Exclusion reason:** Ineligible study design

356. Safi K, Sobieraj J, Blaszkiewicz M, et al. Tetrahydrocannabinol and Cannabidiol for Pain Treatment-An Update on the Evidence. Biomedicines. 2024;12(2)doi: https://dx.doi.org/10.3390/biomedicines12020307. **Exclusion reason:** Systematic review used as source document

357. Sagy I, Bar-Lev Schleider L, Abu-Shakra M, et al. Safety and efficacy of Medical Cannabis in Fibromyalgia. J Clin Med. 2019 Jun 05;8(6):807. doi: 10.3390/jcm8060807. PMID: 31195754. **Exclusion reason:** Ineligible comparator

358. Sainsbury B, Bloxham J, Pour MH, et al. Efficacy of Cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review with meta-analysis. J Dent Anesth Pain Med. 2021;21(6):479-506. doi: 10.17245/jdapm.2021.21.6.479. PMID: 34909469. **Exclusion reason:** Systematic review used as source document

359. Salmasi V, Nelson LM, Hong J, et al. Association of cannabis and/or opioid with quality of life and healthcare utilization in patients with chronic pain. Frontiers in pain research (Lausanne, Switzerland). 2022;3:1015605. doi: https://dx.doi.org/10.3389/fpain.2022.1015605. **Exclusion reason:** Ineligible study design

PREPUBLICATION FINAL

360. Sanchez-Florez JC, Seija-Butnaru D, Valero EG, et al. Pain management strategies in Rheumatoid Arthritis: a narrative review. J Pain Pall Care Pharmacother. 2021;35(4):291-9. doi: 10.1080/15360288.2021.1973647. PMID: 34623946. **Exclusion reason:** Systematic review used as source document

361. Santos SA, Kontorinis N, Dieterich DT. Management of chronic Hepatitis C virus in patients with HIV. Curr Treat Options Gastroenterol. 2005;8(6):433-41. doi: 10.1007/s11938-005-0029-5. PMID: 16313860. **Exclusion reason:** Ineligible population

362. Schenk M. Chronic neuropathic pain: minimal side effects of therapy with Cannabis. MMW Fortschr Med. 2020;162(3):72. doi: 10.1007/s15006-020-0171-y. **Exclusion reason:** Not in English

363. Schindler E. Sustained reductions in headache burden after the limited administration of low dose psilocybin in migraine and cluster headache: results from two preliminary studies. Neuropsychopharmacology. 2020;45:57-8. doi: 10.1038/s41386-020-00889-0. **Exclusion reason:** Ineligible publication type

364. Schindler EAD, Sewell RA, Gottschalk CH, et al. Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: Results from a randomized, double-blind, placebo-controlled trial. Headache. 2022doi: https://dx.doi.org/10.1111/head.14420. **Exclusion reason:** Ineligible intervention

365. Schloss J, Lacey J, Sinclair J, et al. A phase 2 randomised clinical trial assessing the tolerability of two different ratios of medicinal cannabis in patients with high grade gliomas. Front Oncol. 2021;11:649555. doi: 10.3389/fonc.2021.649555. PMID: 34094937. **Exclusion reason:** Ineligible population

366. Schrader NHB, Duipmans JC, Renken RJ, et al. The C4EB study-Transvamix (10% THC / 5% CBD) to treat chronic pain in epidermolysis bullosa: A protocol for an explorative randomized, placebo controlled, and double blind intervention crossover study. PLoS ONE. 2022;17(12):e0277512. doi: https://dx.doi.org/10.1371/journal.pone.0277512. **Exclusion reason:** Ineligible publication type

367. Schubert EA, Alffenaar JC, Johnstone MT, et al. Medicinal cannabis for patients with chronic non-cancer pain: analysis of safety and concomitant medications. The International journal of pharmacy practice. 2022doi: https://dx.doi.org/10.1093/ijpp/riac073. **Exclusion reason:** Ineligible study design

368. Schulze-Schiappacasse C, Duran J, Bravo-Jeria R, et al. Are Cannabis, Cannabis-Derived Products, and Synthetic Cannabinoids a Therapeutic Tool for Rheumatoid Arthritis? A Friendly Summary of the Body of Evidence. J Clin Rheumatol. 2021doi: 10.1097/RHU.0000000000001745. PMID: 33859125. **Exclusion reason:** Background only

369. Scott JR, Williams DA, Harte SE, et al. Relationship between Nociplastic Pain Involvement and Medication use, Symptom Relief, and Adverse effects Among People using Medical Cannabis for Chronic Pain. The Clinical journal of pain. 2023doi: https://dx.doi.org/10.1097/AJP.0000000000001164. **Exclusion reason:** Ineligible study design

370. Scott JR, Williams DA, Harte SE, et al. Relationship Between Nociplastic Pain Involvement and Medication Use, Symptom Relief, and Adverse Effects Among People Using Medical Cannabis for Chronic Pain. Clin J Pain. 2024;40(1):1-9. doi: https://dx.doi.org/10.1097/AJP.0000000000001164. PMID: 37823303. **Exclusion reason:** Ineligible comparator

PREPUBLICATION FINAL

371. Scuteri D, Guida F, Boccella S, et al. Nabiximols clinical translation to the treatment of pain and agitation in severe dementia (NACTOPAISD): clinical trial protocol. Biomedicine & pharmacotherapy. 2022;153doi: 10.1016/j.biopha.2022.113488. PMID: 36076584. **Exclusion reason:** Ineligible study design

372. Scuteri D, Rombolà L, Hamamura K, et al. Is there a rational basis for Cannabinoids research and development in ocular pain therapy? A systematic review of preclinical evidence. Biomed Pharmacother. 2022;146doi: 10.1016/j.biopha.2021.112505. PMID: 34891121. **Exclusion reason:** Ineligible population

373. Seehusen DA, Kehoe K. Cannabis for treatment of chronic pain. American family physician. 2022;106(2):202-4. PMID: 35977124. **Exclusion reason:** Ineligible publication type

374. Seffah KD, Kumar M, Naveen N, et al. To Weed or Not to Weed: A Systematic Review Exploring the Potential for Cannabis Use in Cardiovascular Disease, Mental Health and Pain Management. Cureus. 2023;15(6):e40606. doi: 10.7759/cureus.40606. PMID: 37476127. **Exclusion reason:** Systematic review used as source document

375. Sena W, Kessomboon P, Pisutthigoson M, et al. Decision-Making Experiences to use Medicinal Cannabis: Perspectives from Patients with Knee Osteoarthritis and Their Care Providers. Journal of Current Science and Technology. 2024;14(1)doi: 10.59796/jcst.V14N1.2024.4. **Exclusion reason:** Ineligible study design

376. Senderovich H, Wagman H, Zhang D, et al. The effectiveness of Cannabis and Cannabis derivatives in treating lower back pain in the aged population: a systematic review. Gerontology. 2021:1-13. doi: 10.1159/000518269. PMID: 34515130. **Exclusion reason:** Systematic review used as source document

377. Senderovich H, Wagman H, Zhang D, et al. The effectiveness of Cannabis and Cannabis derivatives in treating lower back pain in the aged population: a systematic review. Gerontology. 2022;68(6):612-24. doi: 10.1159/000518269. PMID: 34515130. **Exclusion reason:** Systematic review used as source document

378. Serrano A, Galvez R, Paremes E, et al. Off-label pharmacological treatment for neuropathic pain: A Delphi study by the Spanish Pain Society Neuropathic Pain Task Force. Pain practice : the official journal of World Institute of Pain. 2022doi: https://dx.doi.org/10.1111/papr.13176. **Exclusion reason:** Background only

379. Shah J, Fermo O. Review of systemic and syndromic complications of cannabis use: A review. Medicine (United States). 2022;101(49):E32111. doi: 10.1097/MD.0000000000032111. **Exclusion reason:** Ineligible publication type

380. Sharon H, Weizman L, Espaniol J, et al. Cannabis induces changes in functional brain connectivity that correlate with increased vagal tone and clinical analgesia in chronic neuropathic pain. Clinical autonomic research. 2019;29(5):529. doi: https://doi.org/10.1007/s10286-019-00631-x. **Exclusion reason:** Ineligible publication type

381. Shebaby W, Saliba J, Faour WH, et al. In vivo and in vitro anti-inflammatory activity evaluation of Lebanese Cannabis Sativa L. ssp. Indica (Lam.). J Ethnopharmacol. 2020:113743. doi: 10.1016/j.jep.2020.113743. PMID: 33359187. **Exclusion reason:** Ineligible study design

382. Shehata I, Hashim A, Elsaeidy A, et al. Cannabinoids and Their Role in Chronic Pain Treatment: Current Concepts and a Comprehensive Review. Health Psychology Research. 2022;10(4)doi: 10.52965/001c.35848. **Exclusion reason:** Systematic review used as source document

PRE-PUBLICATION FINAL

383. Shkodina AD, Bardhan M, Chopra H, et al. Pharmacological and Non-pharmacological Approaches for the Management of Neuropathic Pain in Multiple Sclerosis. CNS Drugs. 2024;38(3):205-24. doi: https://dx.doi.org/10.1007/s40263-024-01072-5. **Exclusion reason:** Systematic review used as source document

384. Shoshan S, Solt I. Medical Cannabis for Gynecologic pain conditions: a systematic review. Obstetrics and gynecology. 2022;139(5):937-8. doi: 10.1097/AOG.0000000000004777. PMID: 35104069. **Exclusion reason:** Ineligible publication type

385. Shustorovich A, Corroon J, Wallace MS, et al. Biphasic effects of cannabis and cannabinoid therapy on pain severity, anxiety and sleep disturbance: A scoping review. Pain Med. 2024;24:24. doi: https://dx.doi.org/10.1093/pm/pnae004. PMID: 38268491. **Exclusion reason:** Systematic review used as source document

386. Sidhom D, Aboul-Hassan D, Clauw DJ, et al. Chronic pain management in sickle cell disease: A systematic scoping review of controlled trials. Critical reviews in oncology/hematology. 2023;190:104087. doi: 10.1016/j.critrevonc.2023.104087. PMID: 37541536. **Exclusion reason:** Systematic review used as source document

387. Sihota A, Smith BK, Ahmed SA, et al. Consensus-based recommendations for titrating Cannabinoids and tapering opioids for chronic pain control. Int J Clin Pract. 2021;75(8):e13871. doi: 10.1111/ijcp.13871. PMID: 33249713. **Exclusion reason:** Ineligible publication type

388. Singla A, Anstine CV, Huang L, et al. A Cross-Sectional Survey Study of Cannabis Use for Fibromyalgia Symptom Management. Mayo Clin Proc. 2024;99(4):542-50. doi: 10.1016/j.mayocp.2023.12.018. **Exclusion reason:** Ineligible study design

389. Sklenarova M, Sima M, Slanar O. Effects of Cannabidiol in Inflammation: A Review of Pre-clinical and Clinical Findings. Prague medical report. 2023;124(3):216-29. doi: https://dx.doi.org/10.14712/23362936.2023.17. **Exclusion reason:** Systematic review used as source document

390. Smaga S, Gharib A. In adults with chronic low back pain, does the use of inhaled Cannabis reduce overall opioid use? Evid Based Pract. 2017;20(1):E10-E1. doi: 10.1097/01.EBP.0000541620.26384.bf. **Exclusion reason:** Ineligible publication type

391. Socias ME, Choi J, Lake S, et al. Cannabis use is associated with reduced risk of exposure to Fentanyl among people on opioid agonist therapy during a community-wide overdose crisis. Drug Alcohol Depend. 2020;219:108420. doi: 10.1016/j.drugalcdep.2020.108420. PMID: 33342591. **Exclusion reason:** Ineligible population

392. Sotoodeh R, Waldman LE, Vigano A, et al. Predictors of pain reduction among Fibromyalgia patients using Medical Cannabis: a long-term prospective cohort study. Arthritis care & research. 2022doi: 10.1002/acr.24985. PMID: 35876631. **Exclusion reason:** Ineligible comparator

393. Stephens KL, Heineman JT, Forster GL, et al. Cannabinoids and Pain for the Plastic Surgeon: What Is the Evidence? Annals of plastic surgery. 2022doi: 10.1097/SAP.0000000000003128. PMID: 35502947. **Exclusion reason:** Systematic review used as source document

394. Stockings E, Campbell G, Hall WD, et al. Cannabis and Cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018 Oct;159(10):1932-54. doi: 10.1097/j.pain.0000000000001293. PMID: 29847469. **Exclusion reason:** Systematic review used as source document

395. Strand N, D'souza RS, Karri J, et al. Medical Cannabis: A Review from the American Society of Pain and Neuroscience. J Pain Res. 2023;16:4217-28. doi: 10.2147/JPR.S425862. **Exclusion reason:** Systematic review used as source document

396. Strand NH, Maloney J, Kraus M, et al. Cannabis for the Treatment of Fibromyalgia: A Systematic Review. Biomedicines. 2023;11(6)doi: https://dx.doi.org/10.3390/biomedicines11061621. **Exclusion reason:** Systematic review used as source document

PRE-PUBLICATION FINAL

397. Sturgeon JA, Khan J, Hah JM, et al. Clinical profiles of concurrent cannabis use in chronic pain: a CHOIR study. Pain Med. 2020 Nov 01;21(11):3172-9. doi: 10.1093/pm/pnaa060. PMID: 32232476. **Exclusion reason:** Ineligible intervention

398. Sun N, Cunha N, Amar S, et al. Synthetic cannabinoid for the treatment of severe chronic noncancer pain in children and adolescents. Can J Pain. 2022;6(1):225-31. doi: https://dx.doi.org/10.1080/24740527.2022.2132138. **Exclusion reason:** Ineligible study design

399. Svendsen K, Sharkey KA, Altier C. Non-Intoxicating Cannabinoids in Visceral Pain. Cannabis Cannabinoid Res.9(1):3-11. doi: https://dx.doi.org/10.1089/can.2023.0113. PMID: 37883662. **Exclusion reason:** Ineligible publication type

400. Svendsen K, Sharkey KA, Altier C. Non-Intoxicating Cannabinoids in Visceral Pain. Cannabis Cannabinoid Res. 2024;9(1):3-11. doi: https://dx.doi.org/10.1089/can.2023.0113. PMID: 37883662. **Exclusion reason:** Ineligible publication type

401. Svendsen KB, Jensen TS, Bach FW. Does the Cannabinoid Dronabinol reduce central pain in Multiple Sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004 Jul 31;329(7460):253. doi: 10.1136/bmj.38149.566979.AE. PMID: 15258006. **Exclusion reason:** Inadequate duration

402. Swart BB, Reznikoff C, Steen K. Isolated Kratom Use Disorder Treated with Extended-Release Buprenorphine Taper. J Addict Med. 2024;22:22. doi: https://dx.doi.org/10.1097/ADM.0000000000001328. PMID: 38776432. **Exclusion reason:** Ineligible study design

403. Swogger MT, Smith KE, Garcia-Romeu A, et al. Understanding Kratom use: a guide for healthcare providers. Front Pharmacol. 2022;13doi: 10.3389/fphar.2022.801855. PMID: 35308216. **Exclusion reason:** Systematic review used as source document

404. Swogger MT, Walsh Z. Kratom use and mental health: a systematic review. Drug Alcohol Depend. 2018 Feb 1;183:134-40. doi: 10.1016/j.drugalcdep.2017.10.012. PMID: 29248691. **Exclusion reason:** Systematic review used as source document

405. Syed Y, McKeage K, Scott L. Delta-9-Tetrahydrocannabinol/Cannabidiol (Sativex(R)): a review of its use in patients with moderate to severe spasticity due to Multiple Sclerosis. Drugs. 2014;74(5):563-78. doi: 10.1007/s40265-014-0197-5. PMID: 24671907. **Exclusion reason:** Systematic review used as source document

406. Sznitman S, Mabouk C, Said Z, et al. Opioid and healthcare service use in medical cannabis patients with chronic pain: a prospective study. BMJ Support Palliat Care. 2021;14:14. doi: 10.1136/bmjspcare-2020-002661. PMID: 34521640. **Exclusion reason:** Ineligible comparator

407. Sznitman S, Mabouk C, Said Z, et al. Opioid and healthcare service use in medical cannabis patients with chronic pain: a prospective study. BMJ Support Palliat Care. 2023;13(e2):e464-e8. doi: https://dx.doi.org/10.1136/bmjspcare-2020-002661. PMID: 34521640. **Exclusion reason:** Ineligible outcome

408. Sznitman SR, Vulfsons S, Meiri D, et al. Medical Cannabis and cognitive performance in middle to old adults treated for chronic pain. Drug Alcohol Rev. 2020 Sep 22;22:22. doi: 10.1111/dar.13171. PMID: 32964502. **Exclusion reason:** Ineligible study design

409. Sznitman SR, Vulfsons S, Meiri D, et al. Medical Cannabis and cognitive performance in middle to old adults treated for chronic pain. Drug Alcohol Rev. 2021;40(2):272-80. doi: 10.1111/dar.13171. PMID: 32964502. **Exclusion reason:** Ineligible study design

410. Tait M-A, Costa DSJ, Campbell R, et al. Health-related quality of life in patients accessing medicinal cannabis in Australia: The QUEST initiative results of a 3-month follow-up observational study. PLoS ONE. 2023;18(9):e0290549. doi: https://dx.doi.org/10.1371/journal.pone.0290549. **Exclusion reason:** Ineligible study design

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411. Takakuwa KM, Sulak D. A Survey on the effect that Medical Cannabis has on prescription opioid medication usage for the treatment of chronic pain at three medical Cannabis practice sites. Cureus. 2020;12(12):e11848. doi: 10.7759/cureus.11848. PMID: 33409086. **Exclusion reason:** Ineligible study design

412. Tctr. The study of effectiveness of Zingiber Cassumunar Roxb.(Plai) mixed Cannabis Sativa l. leaf oil for chronic pain in elderly randomized controlled trial. https://trialsearch.who.int/Trial2.aspx?TrialID=TCTR20211116004. 2021. **Exclusion reason:** Ineligible publication type

413. Terrie YC. Medical Cannabis for chronic pain. US Pharm. 2020;45(3):24-8. **Exclusion reason:** Ineligible publication type

414. Tervo-Clemmens B, Schmitt W, Wheeler G, et al. Cannabis use and sleep quality in daily life: a daily diary study of adults starting Cannabis for health concerns. medRxiv. 2022 2022-01-01 00:00:00doi: 10.1101/2022.01.19.22269565. **Exclusion reason:** Ineligible intervention

415. Thomas J. Inhaled Cannabis relieves neuropathic pain. Aust J Pharm. 2011;92(1091):88. doi: 10.3316/informit.861962231552691. **Exclusion reason:** Ineligible publication type

416. Thomas PA, Carter GT, Bombardier CH. A scoping review on the effect of Cannabis on pain intensity in people with spinal cord injury. J Spinal Cord Med. 2021:1-12. doi: 10.1080/10790268.2020.1865709. PMID: 33465022. **Exclusion reason:** Systematic review used as source document

417. Thrul J, Nordeck CD, Devkota J, et al. 'I crave not to feel uncomfortable'– investigating craving for opioids and cannabis among individuals with chronic pain. Drugs: Education, Prevention and Policy. 2024doi: 10.1080/09687637.2024.2331572. **Exclusion reason:** Ineligible publication type

418. Tsai SHL, Lin C-R, Shao S-C, et al. Cannabinoid Use for Pain Reduction in Spinal Cord Injuries: A Meta-Analysis of Randomized Controlled Trials. Front Pharmacol. 2022;13:866235. doi: 10.3389/fphar.2022.866235. PMID: 35571093. **Exclusion reason:** Systematic review used as source document

419. Turcotte D, Chateau D, Doupe M, et al. A randomised, double-blinded, placebo-controlled study evaluating the efficacy and safety of nabilone as an adjunctive to gabapentin in managing multiple sclerosisinduced neuropathic pain. Mult Scler. 2011;17(10):S475. doi: https://doi.org/10.1177/1352458511422301. **Exclusion reason:** Ineligible study design

420. Turcotte D, Doupe M, Torabi M, et al. A randomized, double-blinded, placebo-controlled study evaluating efficacy and tolerability of nabilone as an adjunctive to gabapentin in the management of multiple sclerosis-induced neuropathic pain. Mult Scler. 2013;19(11):112. doi: https://doi.org/10.1177/1352458513502429. **Exclusion reason:** Ineligible publication type

421. Turcotte DA, Gomori AJ, Esfahani FE, et al. Randomized, double-blinded, placebo-controlled study evaluating the efficacy and safety of nabilone adjunctive to gabapentin in managing multiple sclerosis-induced neuropathic pain. European journal of pain supplements. 2011;5(1):240. doi: https://doi.org/10.1016/S1754-3207(11)70830-6. **Exclusion reason:** Ineligible publication type

422. Turcotte DA, Namaka MP, Gomori AJ, et al. A randomized, double-blinded, placebo-controlled study evaluating the efficacy and safety of Nabilone as an adjunctive to Gabapentin in managing Multiple Sclerosis-induced neuropathic pain: an interim analysis. Pain Res Manag. 2011;15(2):99. **Exclusion reason:** Ineligible publication type

423. Uberall MA. A review of scientific evidence for THC: CBD oromucosal spray (Nabiximols) in the management of chronic pain. J Pain Res. 2020 Feb 14;13:399-410. doi: 10.2147/JPR.S240011. PMID: 32104061. **Exclusion reason:** Systematic review used as source document

PRE-PUBLICATION FINAL

424. Ueberall MA, Essner U, Mueller-Schwefe GH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry. J Pain Res. 2019 May 20;12:1577-604. doi: 10.2147/JPR.S192174. PMID: 31190969. **Exclusion reason:** Ineligible comparator

425. Ueberall MA, Horlemann J, Schuermann N, et al. Effectiveness and tolerability of Dronabinol use in patients with chronic pain - a retrospective analysis of 12-week open-label real-world data provided by the German Pain e-Registry. Pain Med. 2022 Feb 01;01:01. doi: 10.1093/pm/pnac010. PMID: 35104881. **Exclusion reason:** Ineligible study design

426. Urits I, Adamian L, Fiocchi J, et al. Advances in the understanding and management of chronic pain in Multiple Sclerosis: a comprehensive review. Curr Pain Headache Rep. 2019 Jul 25;23(8):59. doi: 10.1007/s11916-019-0800-2. PMID: 31342191. **Exclusion reason:** Systematic review used as source document

427. Urits I, Charipova K, Gress K, et al. Adverse Effects of Recreational and Medical Cannabis. Psychopharmacol Bull. 2021;51(1):94-109. PMID: 33897066. **Exclusion reason:** Ineligible study design

428. van Amerongen G, Kanhai K, Baakman AC, et al. Effects on spasticity and neuropathic pain of an oral formulation of DELTA9-tetrahydrocannabinol in patients with progressive multiple sclerosis. Clin Ther. 2018 Sep;40(9):1467-82. doi: 10.1016/j.clinthera.2017.01.016. PMID: 28189366. **Exclusion reason:** Ineligible population

429. van Dam CJ, van Velzen M, Kramers C, et al. Cannabis-opioid interaction in the treatment of fibromyalgia pain: an open-label, proof of concept study with randomization between treatment groups: cannabis, oxycodone or cannabis/oxycodone combination-the SPIRAL study. Trials. 2023;24(1):64. doi: https://dx.doi.org/10.1186/s13063-023-07078-6. **Exclusion reason:** Ineligible publication type

430. van der Walt JJN, Parker R. LSD and psilocybin for chronic nociplastic pain: A narrative review of the literature supporting the use of classic psychedelic agents in chronic pain. S Afr Med J. 2023;113(11):1446-70. doi: 10.7196/SAMJ.2023.v113i11.814. **Exclusion reason:** Ineligible publication type

431. Vanegas SO, Zaki A, Dealy CN, et al. The minor phytocannabinoid delta-8-tetrahydrocannabinol attenuates collagen-induced arthritic inflammation and pain-depressed behaviors. J Pharmacol Exp Ther. 2024;04:04. doi: https://dx.doi.org/10.1124/jpet.124.002189. PMID: 38834355. **Exclusion reason:** Ineligible population

432. Vela J, Kjaer Petersen K, Dreyer L, et al. The effect of Cannabidiol on quantitative sensory testing parameters in patients with Hand Osteoarthritis and Psoriatic Arthritis: a randomized double-blind placebo-controlled trial. Ann Rheum Dis. 2022;81:821-2. doi: 10.1136/annrheumdis-2022-eular.1101. **Exclusion reason:** Ineligible publication type

433. Vermersch P, Trojano M. Tetrahydrocannabinol: cannabidiol oromucosal spray for multiple sclerosis-related resistant spasticity in daily practice. Eur Neurol. 2016;76(5-6):216-26. doi: 10.1159/000449413. PMID: 27732980. **Exclusion reason:** Ineligible population

434. Vickery AW, Roth S, Ernenwein T, et al. A large Australian longitudinal cohort registry demonstrates sustained safety and efficacy of oral medicinal cannabis for at least two years. PLoS ONE. 2022;17(11):e0272241. doi: https://dx.doi.org/10.1371/journal.pone.0272241. **Exclusion reason:** Ineligible study design

435. Vicknasingam B, Chooi WT, Rahim AA, et al. Kratom and pain tolerance: a randomized, placebo-controlled, double-blind study. Yale J Biol Med. 2020;93(2):229-38. PMID: 32607084. **Exclusion reason:** Ineligible population

PRE-PUBLICATION FINAL

436. Vila Silvan C, Vaney C, Dykukha I. Systematic reviews of randomized controlled trials of Cannabinoid products in chronic pain conditions and for symptoms associated with Multiple Sclerosis: what do they tell us? Expert Rev Clin Pharmacol. 2022doi: 10.1080/17512433.2022.2088501. PMID: 35679523. **Exclusion reason:** Systematic review used as source document

437. Villanueva MRB, Joshaghani N, Villa N, et al. Efficacy, safety, and regulation of Cannabidiol on chronic pain: a systematic review. Cureus. 2022;14(7):e26913. doi: 10.7759/cureus.26913. PMID: 35860716. **Exclusion reason:** Systematic review used as source document

438. Wade DT, Makela P, Robson P, et al. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler. 2004;10(4):434-41. doi: 10.1191/1352458504ms1082oa. PMID: 15327042. **Exclusion reason:** Ineligible population

439. Wade DT, Robson P, House H, et al. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 2003 Feb;17(1):21-9. doi: 10.1191/0269215503cr581oa. PMID: 12617376. **Exclusion reason:** Ineligible population

440. Walitt B, Klose P, Fitzcharles MA, et al. Cannabinoids for Fibromyalgia. Cochrane Database Syst Rev. 2016 Jul 18;7:CD011694. doi: 10.1002/14651858.CD011694.pub2. PMID: 27428009. **Exclusion reason:** Ineligible publication type

441. Wallace MS, Marcotte TD, Umlauf A, et al. Efficacy of inhaled Cannabis on painful Diabetic Neuropathy. J Pain. 2015 Jul;16(7):616-27. doi: 10.1016/j.jpain.2015.03.008. PMID: 25843054. **Exclusion reason:** Inadequate duration

442. Wang C, Erridge S, Holvey C, et al. Assessment of clinical outcomes in patients with fibromyalgia: Analysis from the UK Medical Cannabis Registry. Brain and behavior. 2023;13(7):e3072. doi: https://dx.doi.org/10.1002/brb3.3072. **Exclusion reason:** Ineligible comparator

443. Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. 2021;374:n1034. doi: 10.1136/bmj.n1034. PMID: 34497047. **Exclusion reason:** Systematic review used as source document

444. Wang T, Collet JP, Shapiro S, et al. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008;178(13):1669-78. doi: 10.1503/cmaj.071178. PMID: 18559804. **Exclusion reason:** Ineligible publication type

445. Wang Y, Jean Jacques J, Li Z, et al. Health outcomes among adults initiating Medical Cannabis for chronic pain: a 3-month prospective study incorporating ecological momentary assessment (EMA). Cannabis. 2021;4(2):69-83. doi: 10.26828/cannabis/2021.02.006. PMID: 34671723. **Exclusion reason:** Ineligible comparator

446. Ware MA, Fitzcharles MA, Joseph L, et al. The effects of Nabilone on sleep in Fibromyalgia: results of a randomized controlled trial. Anesth Analg. 2010 Feb 01;110(2):604-10. doi: 10.1213/ANE.0b013e3181c76f70. PMID: 20007734. **Exclusion reason:** Inadequate duration

447. Ware MA, Wang T, Shapiro S, et al. Smoked Cannabis for chronic neuropathic pain: a randomized controlled trial. Cmaj. 2010 Oct 05;182(14):E694-701. doi: 10.1503/cmaj.091414. PMID: 20805210. **Exclusion reason:** Inadequate duration

PRE-PUBLICATION FINAL

448. Weizman L, Sharon H, Dayan L, et al. Oral Delta-9-Tetrahydrocannabinol (THC) Increases Parasympathetic Activity and Supraspinal Conditioned Pain Modulation in Chronic Neuropathic Pain Male Patients: A Crossover, Double-Blind, Placebo-Controlled Trial. CNS Drugs. 2024;38(5):375-85. doi: 10.1007/s40263-024-01085-0. **Exclusion reason:** Inadequate duration

449. White CM. Pharmacologic and clinical assessment of Kratom. Am J Health-Syst Pharm. 2018 Mar 1;75(5):261-7. doi: 10.2146/ajhp161035. PMID: 29255059. **Exclusion reason:** Background only

450. White CM. Pharmacologic and clinical assessment of Kratom: an update. Am J Health-Syst Pharm. 2019 Nov 13;76(23):1915-25. doi: 10.1093/ajhp/zxz221. PMID: 31626272. **Exclusion reason:** Background only

451. Williams AR, Hill KP. Care of the patient using Cannabis. Ann Intern Med. 2020;173(9):ITC65-ITC80. doi: 10.7326/AITC202011030. PMID: 33137270. **Exclusion reason:** Ineligible publication type

452. Williams AR, Mauro CM, Feng T, et al. Adult Medical Cannabinoid Use and Changes in Prescription Controlled Substance Use. Cannabis Cannabinoid Res. 2022doi: 10.1089/can.2021.0212. PMID: 35486854. **Exclusion reason:** Ineligible comparator

453. Wilsey B, Marcotte T, Deutsch R, et al. Low-dose vaporized Cannabis significantly improves neuropathic pain. J Pain. 2013 Feb;14(2):136-48. doi: 10.1016/j.jpain.2012.10.009. PMID: 23237736. **Exclusion reason:** Inadequate duration

454. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of Cannabis cigarettes in neuropathic pain. J Pain. 2008 Jun;9(6):506-21. doi: 10.1016/j.jpain.2007.12.010. PMID: 18403272. **Exclusion reason:** Inadequate duration

455. Wong SSC, Chan WS, Cheung CW. Analgesic effects of Cannabinoids for chronic non-cancer pain: a systematic review and meta-analysis with meta-regression. J Neuroimmune Pharmacol. 2020 Dec;15(4):801-29. doi: 10.1007/s11481-020-09905-y. PMID: 32172501. **Exclusion reason:** Systematic review used as source document

456. Xantus G, Gyarmathy V. Cannabidiol in acute low back pain-a protocol and rationale of a clinical effectiveness trial. Med Cannabis Cannabinoids. 2020;3(2):134. doi: 10.1159/000511664. PMID: 634190900. **Exclusion reason:** Ineligible publication type

457. Xiao ATY, Turk T, Deol K, et al. Evidence for the use of cannabis-based medicines in osteoarthritis: a scoping review. Clin Rheumatol. 2024doi: 10.1007/s10067-024-07001-7. **Exclusion reason:** Ineligible publication type

458. Yacyshyn B, Hanauer S, Klassen P, et al. Safety, Pharmacokinetics, and efficacy of Olorinab, a peripherally acting, highly selective, full agonist of the Cannabinoid receptor 2, in a Phase 2a study of patients with chronic abdominal pain associated with Crohn's Disease. Crohns Colitis 360. 2021;3(1)doi: 10.1093/crocol/otaa089. **Exclusion reason:** Ineligible intervention

459. Yanes JA, McKinnell ZE, Reid MA, et al. Effects of Cannabinoid administration for pain: a meta-analysis and meta-regression. Exp Clin Psychopharmacol. 2019 Aug;27(4):370-82. doi: 10.1037/pha0000281. PMID: 31120281. **Exclusion reason:** Systematic review used as source document

460. Yassin M, Oron A, Robinson D. Effect of adding Medical Cannabis to Analgesic treatment in patients with low back pain related to Fibromyalgia: an observational cross-over single centre study. Clin Exp Rheumatol. 2019 Jan-Feb;37(Suppl 116):S13-S20. PMID: 30418116. **Exclusion reason:** Ineligible study design

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461. Yimam M, O'Neal A, Horm T, et al. Antinociceptive and Anti-Inflammatory Properties of Cannabidiol Alone and in Combination with Standardized Bioflavonoid Composition. J Med Food. 2021doi: 10.1089/jmf.2020.0178. PMID: 33570460. **Exclusion reason:** Ineligible population

462. Yu JS, Premkumar A, Liu S, et al. Rates of self-directed perioperative Cannabidiol use in patients undergoing total hip or knee arthroplasty. Pain manag. 2021 Jun 09;09:09. doi: 10.2217/pmt-2021-0018. PMID: 34102871. **Exclusion reason:** Ineligible study design

463. Zadikoff C, Wadia PM, Miyasaki J, et al. Cannabinoid, CB1 agonists in cervical dystonia: Failure in a phase IIa randomized controlled trial. Basal Ganglia. 2011 2011/07/01/;1(2):91-5. doi: https://doi.org/10.1016/j.baga.2011.04.002. **Exclusion reason:** Ineligible population

464. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 2003 Nov 8;362(9395):1517-26. doi: 10.1016/s0140-6736(03)14738-1. PMID: 14615106. **Exclusion reason:** Ineligible population

465. Zalai D, Chung SA, Hussain N, et al. Does cannabinoid really improve sleep? Testing the sleep effects of nabilone in chronic pain patients: a placebo-controlled, randomized, pilot study. Psychotherapy and psychosomatics. 2015;84:81. doi: https://doi.org/10.1159/000438780. **Exclusion reason:** Ineligible publication type

466. Zavori L, Xantus G, Matheson C, et al. Cannabidiol in low back pain: scientific rationale for clinical trials in low back pain. Expert Rev Clin Pharmacol. 2021doi: 10.1080/17512433.2021.1917379. PMID: 33861675. **Exclusion reason:** Background only

467. Zeraatkar D, Cooper MA, Agarwal A, et al. Long-term and serious harms of Medical Cannabis and Cannabinoids for chronic pain: a systematic review of non-randomized studies. medRxiv. 2021 2021-01-01 00:00:00doi: 10.1101/2021.05.27.21257921. PMID: 35926992. **Exclusion reason:** Systematic review used as source document

468. Zloczower O, Brill S, Zeitak Y, et al. Risk and benefit of Cannabis prescription for chronic non-cancer pain. J Addict Dis. 2021 Aug 02:1-11. doi: 10.1080/10550887.2021.1956673. PMID: 34338621. **Exclusion reason:** Ineligible study design

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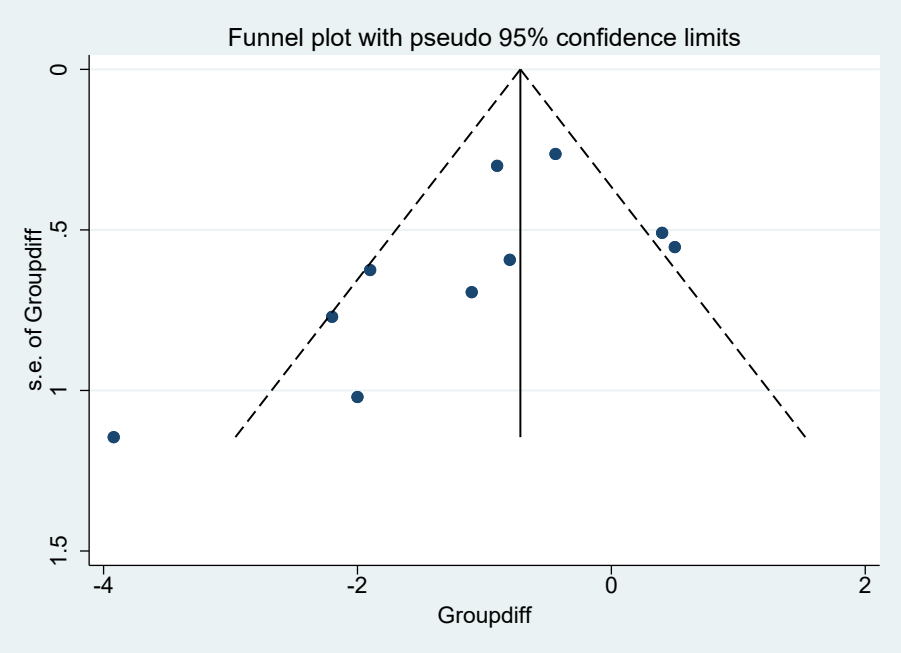
Appendix I. Funnel Plot of High-THC Ratio Studies Included in Meta-Analysis for Pain Severity

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



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

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