Appendixes

Appendix A. Literature Search Strategies

Note: The search strategies were edited for this version of the report due to an expansion of the scope. Subacute pain was added. No edits were needed to add adolescents, as there were previously no age restrictions in the 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
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 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"))

Appendix B. Methods

Inclusion and Exclusion Criteria

Table B-1 outlines the inclusion and exclusion criteria related to populations, interventions, comparators, outcomes, timing, and settings (PICOTS), and study designs of interest for each Key Question (KQ). In the winter of 2022, the protocol was amended to include adolescents and subacute pain.[1] These changes were documented on in a revised protocol submitted to PROSPERO,[2] the AHRQ Protocol, and the title, key questions, and inclusion and exclusion criteria were edited to reflect said changes. The changes expanded inclusion criteria to include subacute pain and adolescents.

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

Table B-1. PICOTS

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults or adolescents (including pregnant or breastfeeding women) with noncancer chronic (>12 weeks or pain persisting past the time for normal tissue healing) or subacute pain (pain lasting 4 weeks to 3 months). See categorization of specifically included pain populations below.	**All KQs:** Children; adults with acute pain; patients at end of life or in palliative care (e.g., with late stage cancer-related pain)
Interventions	**KQs 1 and 2:** Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes **KQs 3 and 4 :** Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids **All KQs**: Co-use of other drugs for pain	**All KQs:** Non-plant-based interventions, capsaicin, herbal supplements
Comparators	**All KQs:** Any comparator, or usual care	**All KQs:** No comparison

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, general function [e.g., Short-Form 36 Physical Functioning Scale] or pain-related [e.g., Oswestry Disability Index or Roland-Morris Disability Questionnaire, for low back pain] or disability, including pain interference[a]); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder, serious adverse events as defined by study); secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, healthcare utilization)	**All KQs:** Other outcomes
Time of followup	**All KQs:** short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year)	**All KQs:** studies with <1-month (4 weeks) of treatment or followup after treatment
Setting	**All KQs:** Any nonhospital setting or setting of self-directed care	**All KQs**: Hospital care, hospice care, emergency department care
Study design	**All KQs:** RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits	**All KQs:** Other study designs

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

[a]The degree to which pain directly interferes with patients' ability to participate in their daily activities (challenges in performing daily, social, or work-related tasks due to pain).

Important subgroups to consider in evaluating this evidence are:

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

Below are additional details on the scope of this project:

Study Design: For all Key Questions, we included randomized controlled trials (RCTs) of at least 4 weeks duration. Initially, in the base-year of this living systematic review, we included observational studies for both benefits (to address gaps in evidence where RCTs are not available) and harms. Eligible observational studies must have assessed a mean duration of treatment of at least 4 weeks, and have concurrent controls (e.g., cohort and case-control studies). Those controlling for potential confounders were prioritized. As the evidence grows, and more RCTs become available throughout the project, we will reassess the need to include observational studies, specifically to address benefits. A decision to discontinue including them

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

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

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through January 16, 2023. Searches were initially run in September 2020 with ongoing, automated monthly searches to identify newly published studies. For this 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 last year's 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 randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. All study data were verified for accuracy and completeness by a second team member. On a quarterly basis, any newly identified studies were abstracted and evidence tables updated. Quarterly reports were published to the Agency for Healthcare Research and Quality (AHRQ) website, and evidence tables are updated in AHRQ's Systematic Review Data Repository Plus (SRDR+).

Risk of Bias Assessment of Individual Studies

Predefined criteria were used to assess the risk of bias of individual controlled trials, systematic reviews, and observational studies. RCTs were evaluated using criteria and methods developed by the Cochrane Back Review Group,[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 0- to 100-point visual analog scale (VAS), 0.5 to 1.0 points on a 0- to 10-point numeric rating scale, or equivalent; for function as a mean difference of 5 to 10 points on the 0- to 100-point Oswestry Disability Index (ODI) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A moderate effect is defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large effects are defined as greater than moderate. We apply similar thresholds to other outcomes measures. Small effects using this system may be below published thresholds for clinically meaningful effects; however, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or function using a treatment with low cost or no serious harms may be important.

Table B-2. Definitions of effect sizes

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

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

Findings that were not statistically significant were interpreted as follows:

- In determining the strength of evidence (SOE), the precision of evidence was downgraded two levels if inadequate sample size (optimal information size) *and* the 95% confidence interval includes both potentially meaningful benefit and harm (e.g. for a relative effect, the lower bound is ≤ 0.75 *and* the upper bound is ≥ 1.25)[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 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.

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.

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]. Agency for Healthcare Research and Quality. 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.
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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.

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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.

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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: 14/167 (8.38%) vs. 9/172 (5.23%), RR 1.60 (95% CI 0.71 to 3.60)
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)

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.

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)

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Turcotte, 2015 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), max dose 2 mg/day (8) B: Placebo (7) 9 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): 35 vs. 57[b]	Pain interference (mean [SD NR] 0 to 100 VAS impact scale): 41 vs. 40[b]	SAE: 0/8 (0%) vs. 0/7 (0%), 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)
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: CBD 5 mg capsule (unknown if synthetic or plant-derived), max dose 50 mg/day (27) C: CBD/THC capsule, max dose 50 mg CBD (unknown of synthetic or plant-derived)/25 mg THC (dronabinol)/day (30) D: Placebo (30)	Pain response ≥30% (NRS scale): 12/28 (42.86%) vs. 9/27 (33.34%) vs. 18/30 (60.00%) vs. 17/30 (56/67%), RR (95% CI) A vs. B: 1.29 (0.65 to 2.55) A vs. C: 0.71 (0.43 to 1.20) A vs. D: 0.76 (0.45 to 1.28) B vs. C: 0.56 (0.30 to 1.02) B vs. D: 0.59 (0.32 to 1.09) C vs. D: 1.06 (0.69 to 1.62) Pain severity change from baseline (mean [95% CI] 0 to 10 NRS scale): −1.4 (-2.2 to -0.7) vs. -0.6 (-1.2 to 0.1) vs. -1.9 (-2.7 to -1.2) vs. -1.9 (-2.7 to -1.0)	Pain interference (mean [SD] 0 to 10 Pain Impact on Daily Activities Scale): MD (95% CI) A vs. D: 0.36 (-1.19 to 1.91) B vs. D: 1.24 (-0.32 to 2.81) C vs. D: 0.89 (-0.64 to 2.42)	SAE: 0/28 (0%) vs. 0/27 (0%) vs. 1/30 (3.3%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.96 (0.02 to 47.01) A vs. C: 0.36 (0.02 to 8.40) A vs. D: 1.07 (0.02 to 52.14) B vs. C: 0.37 (0.02 to 8.70) B vs. D: 1.11 (0.02 to 53.97) C vs. D: 3.00 (0.13 to 70.83) WAE: 1/28 (3.57%) vs. 2/27 (7.41%) vs. 4/30 (13.33%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.48 (0.05 to 5.01) A vs. C: 0.27 (0.03 to 2.25) A vs. D: 3.21 (0.14 to 75.62) B vs. C: 0.56 (0.11 to 2.80) B vs. D: 5.54 (0.28 to 110.42) C vs. D: 9.00 (0.51 to 160.18)

Abbreviations: BPI = brief pain inventory; CBD = cannabidiol; CI = confidence interval; CRS = category rating scale; FIQ = fibromyalgia impact questionnaire; MBPI = modified brief pain inventory; MD = mean difference; NR = not reported; NRS = numeric rating scale; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; SE = standard error; THC = tetrahydrocannabinol; RR = relative risk; VAS = visual analog scale; WAE = withdrawal due to due adverse events.
[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.
[b] Estimated from graph.

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Xu, 2020 High RCT (crossover) Neuropathic pain-mixed	A: CBD cream (250 mg/3 oz) up to 4 times daily (15) B: Placebo (14) 4 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 NPS scale): 3.33 (2.02) vs. 5.55 (2.81), MD −2.22 (95% CI −4.07 to −0.37)	NR	SAE: 0/15 (0%) vs. 0/14 (0%), RR 0.94 (95% CI 0.02 to 44.33)

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

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

Table D-4. Other cannabinoids study primary outcomes

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

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

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

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, 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)
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; MD = mean difference; NR = not reported; SAE = serious adverse events; SD = standard deviation; SF−36= short form−36; THC = tetrahydrocannabinol; VAS = visual analog scale; WAE = withdrawal due to due adverse events.

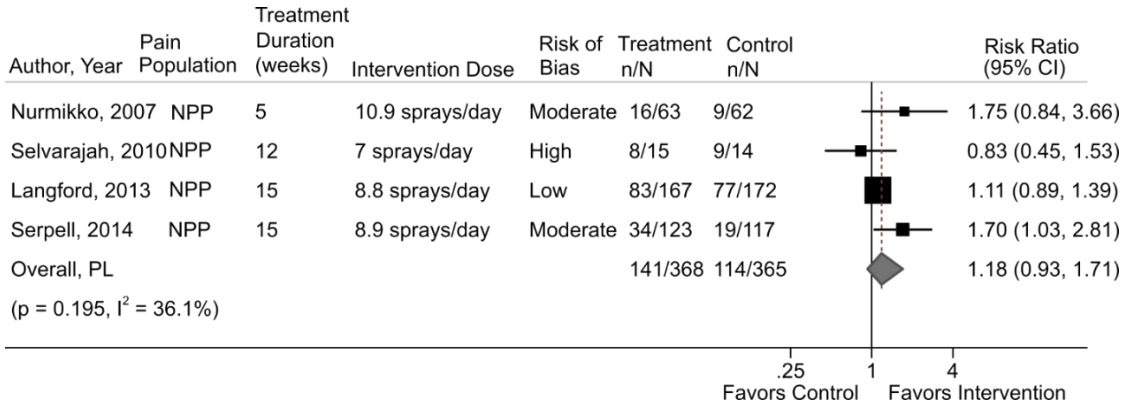
[a] Higher scores indicate better outcomes.

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

Appendix D-2. Meta-Analyses

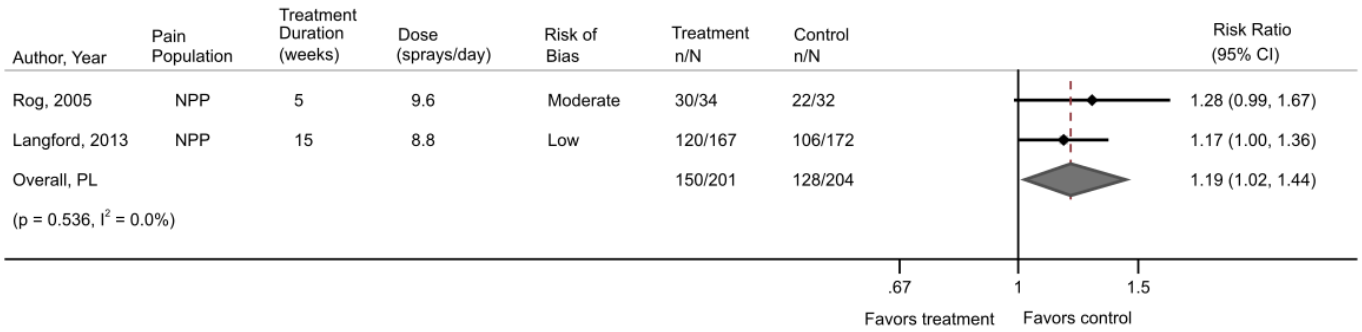
Comparable THC to CBD Ratio Studies

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)



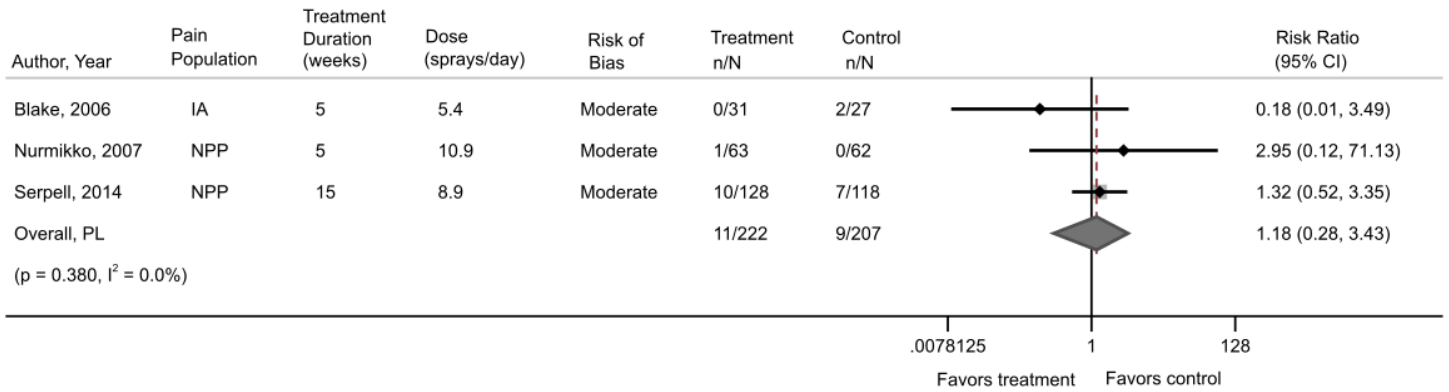
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood

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



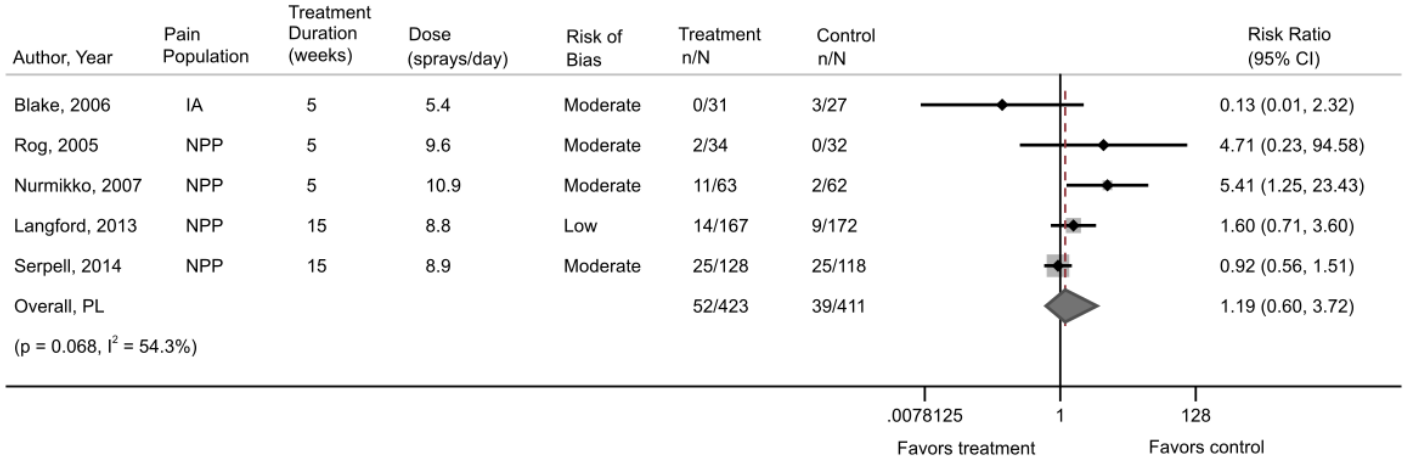
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood.

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



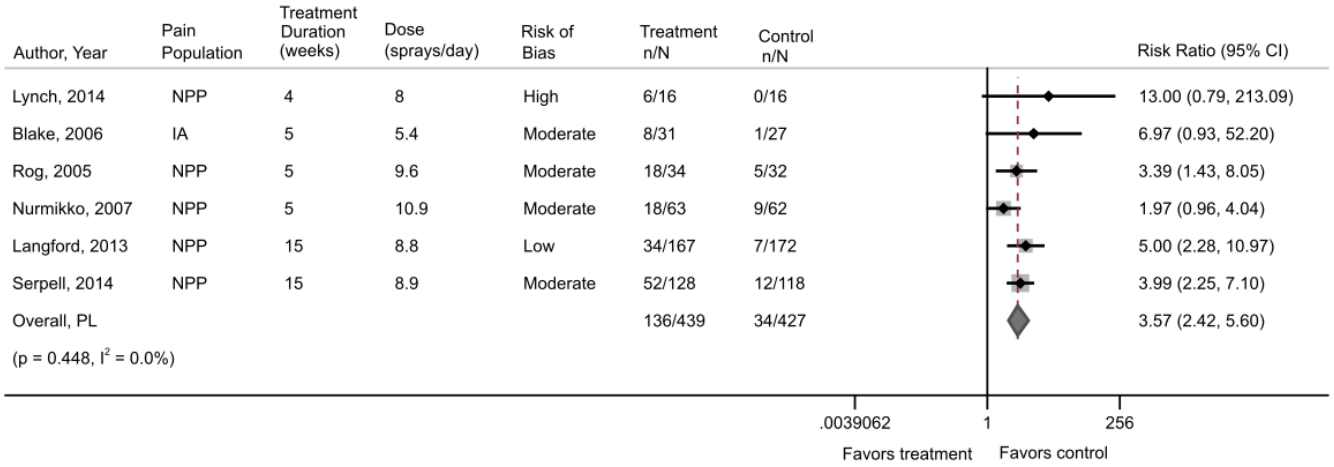
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood.

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



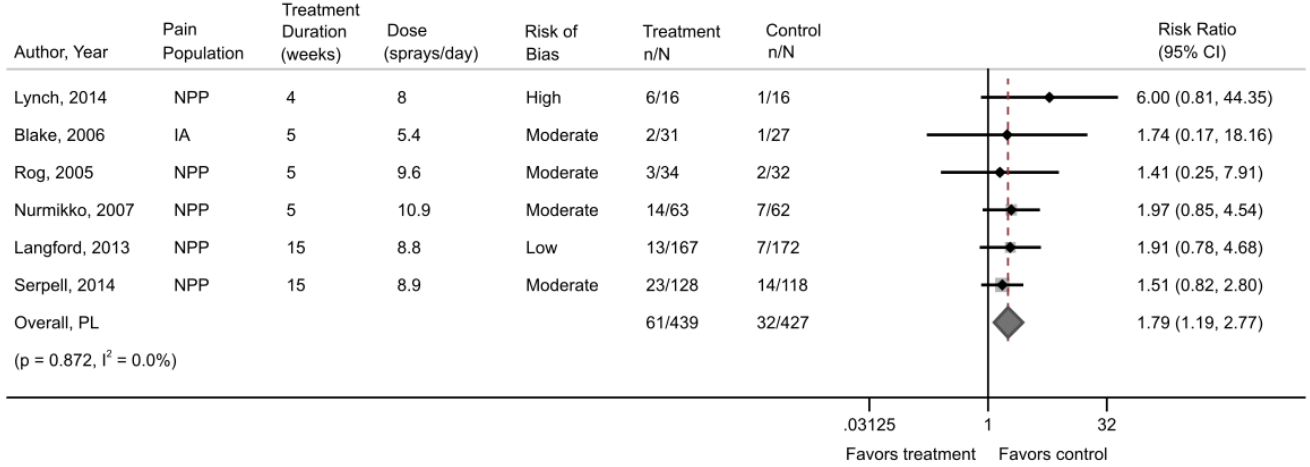
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

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



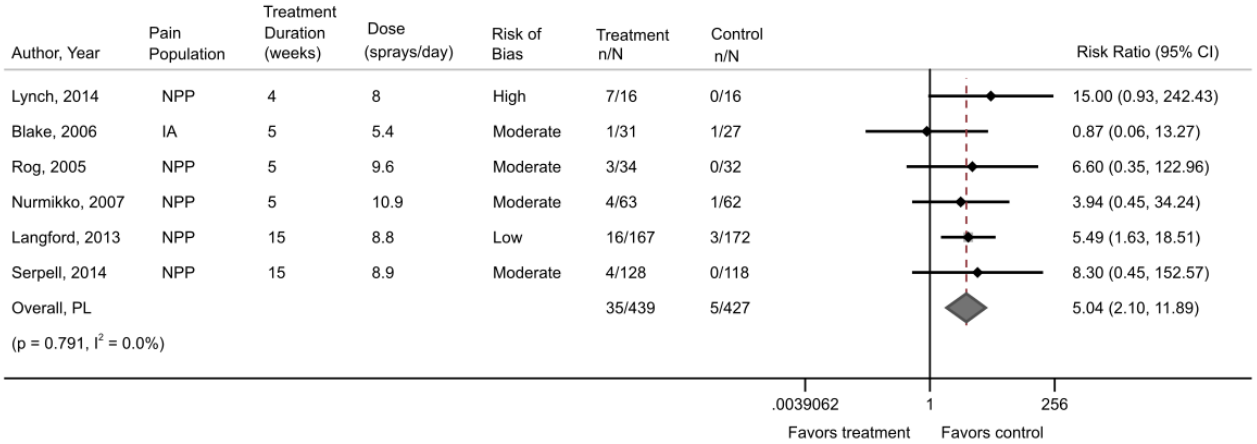
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood.

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.

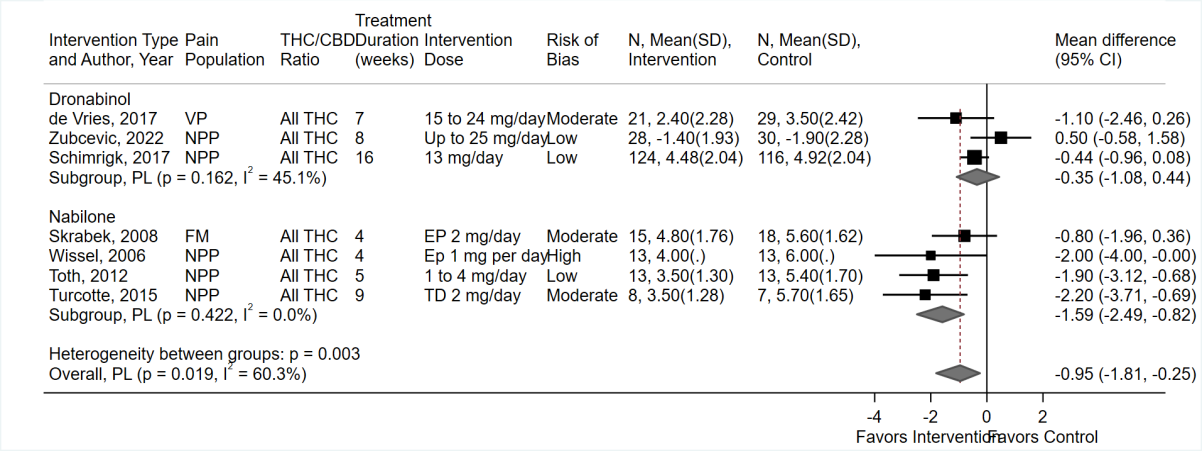
Figure D-7. Sedation for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



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

High-THC to CBD Ratio Studies

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



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

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

Table 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	−1.29	0.510	−2.53	0.053	−2.60 to 0.022

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%
Comparable	Pain response (≥30% improvement)	N=733; k=4	RR 1.18	0.93 to 1.71	0.67 to 2.43	36%
Comparable	Function	N=616; k=6	MD −0.42	−0.73 to −0.16	−0.80 to −0.10	32%
Comparable	Adverse events	N=405; k=2	RR 1.19	1.02 to 1.44	0.74 to 2.03	0%
Comparable	SAEs	N=427; k=3	RR 1.18	0.26 to 3.43	0.02 to 35.25	0%
Comparable	WAEs	N=834; k=5	RR 1.19	0.60 to 3.72	0.25 to 8.29	54%
Comparable	Dizziness	N=866; k=6	RR 3.57	2.42 to 5.60	2.15 to 6.62	0%
Comparable	Nausea	N=866; k=6	RR 1.79	1.19 to 2.77	1.06 to 3.32	0%
Comparable	Sedation	N=866; k=6	RR 5.04	2.10 to 11.89	1.41 to 17.29	0%
High	Pain severity	N=742; k=9	MD −1.12	−1.97 to −0.48	−2.08 to −0.40	65%
High (synthetic)	Pain severity	N=448; k=7	MD −0.95	−1.81 to −0.25	−1.95 to −0.13	60%
High (synthetic - dronabinol)	Pain severity	N=348; k=3	MD −0.35	−1.08 to 0.44	−2.21 to 1.54	45%
High (synthetic - nabilone)	Pain severity	N=100; k=4	MD −1.59	−2.49 to −0.82	−2.21 to −0.39	0%
High (plant-derived)	Pain severity	N=294; k=2	MD −1.97	−5.91 to 1.21	−11.33 to 6.53	85%
High	Function	N=unclear; k=3	MD −0.18	−1.25 to 0.77	−2.23 to 1.78	51%
High	WAEs	N=692; k=6	RR 2.21	1.27 to 4.14	0.96 to 5.58	0%
High (synthetic)	WAEs	N=415; k=5	RR 1.75	0.95 to 4.11	0.50 to 8.88	0%
High (synthetic - dronabinol)	WAEs	N=360; k=3	RR 1.77	0.90 to 5.44	0.25 to 24.91	0%
High (synthetic - nabilone)	WAEs	N=55; k=2	RR 1.54	0.14 to 17.71	0.01 to 280.12	0%
High	Any adverse event	N=266; k=2	RR 1.20	0.96 to 1.48	0.42 to 3.36	0%
High	Dizziness	N=637; k=4	RR 3.57	1.30 to 8.32	0.90 to 11.47	78%
High (synthetic)	Dizziness	N=360; k=3	RR 2.52	1.20 to 4.82	0.42 to 12.00	41%
High	Sedation	N=335; k=3	RR 1.73	1.03 to 4.63	0.44 to 15.71	28%

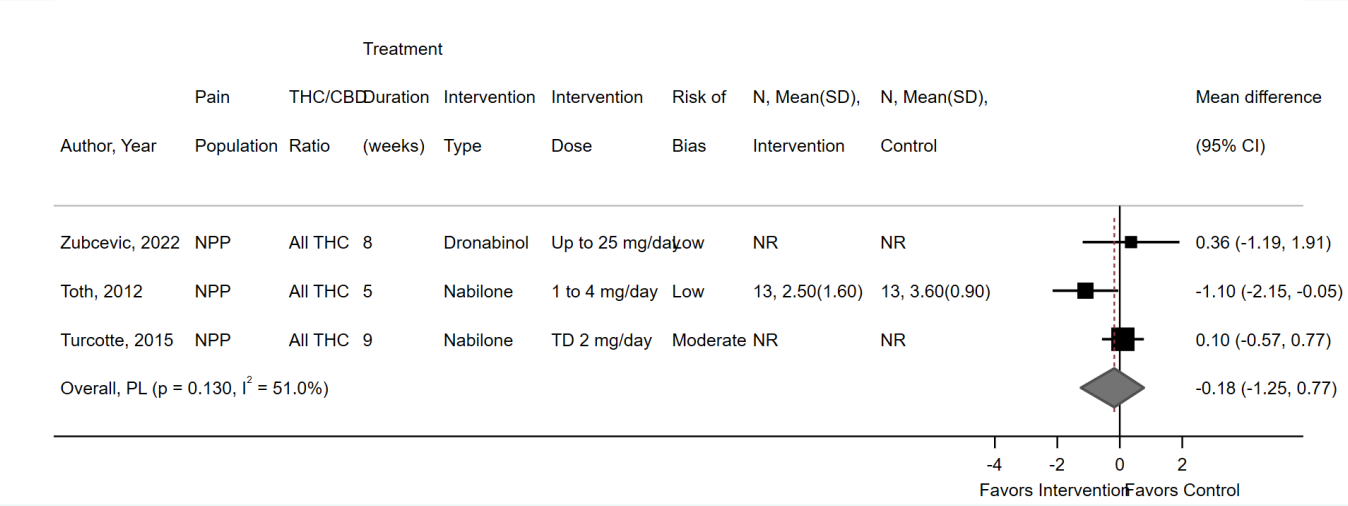
THC to CBD Ratio	Outcome	N; k Studies	Point Estimate	PL 95% CI	BC 95% CI	I-Squared
High (synthetic - dronabinol)	Sedation	N=360; k=3	RR 1.46	0.88 to 2.42	0.59 to 3.66	0%
High	Nausea	N=360; k=3	RR 2.22	0.90 to 5.05	0.40 to 11.80	0%

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

Table D-8. Interaction effect of randomized controlled trials: synthetic versus plant-based interventions

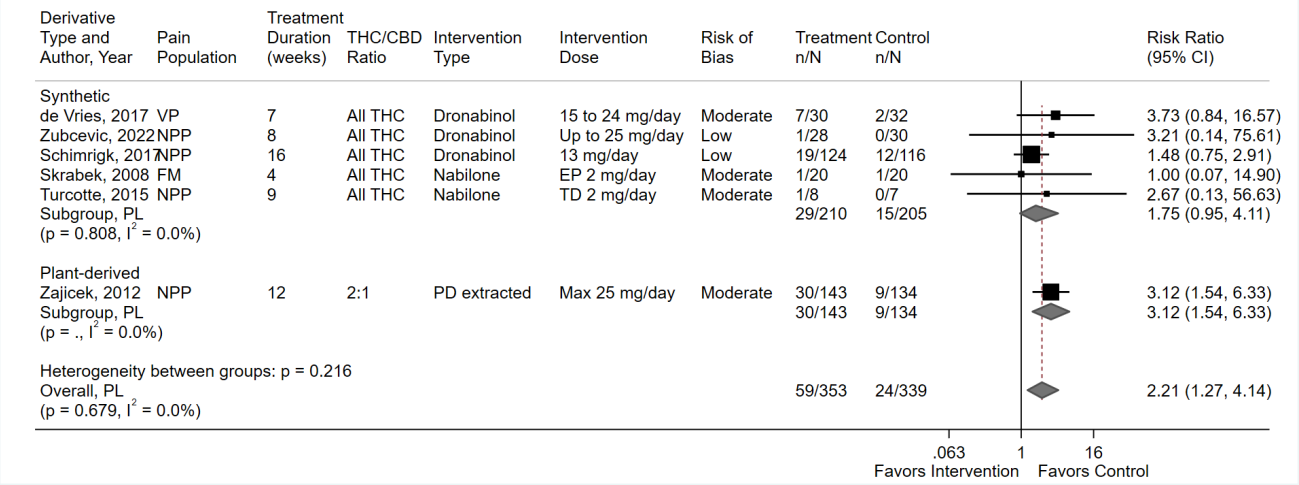
Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−0.986	0.85	−1.16	0.272	−2.87 to 0.90

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



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

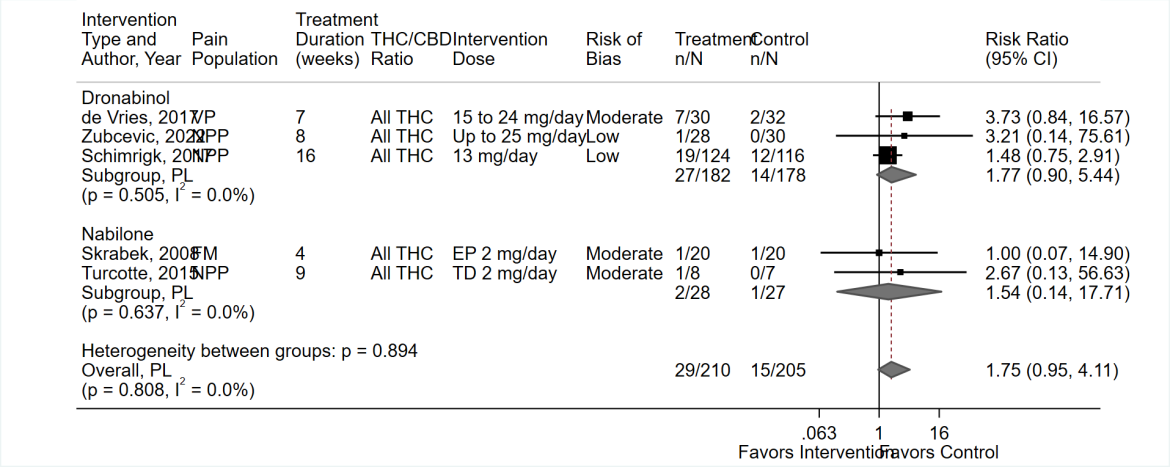
Figure D-10. Study withdrawal due to adverse events for high-THC versus placebo (short term, 1 to 6 months followup)



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

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

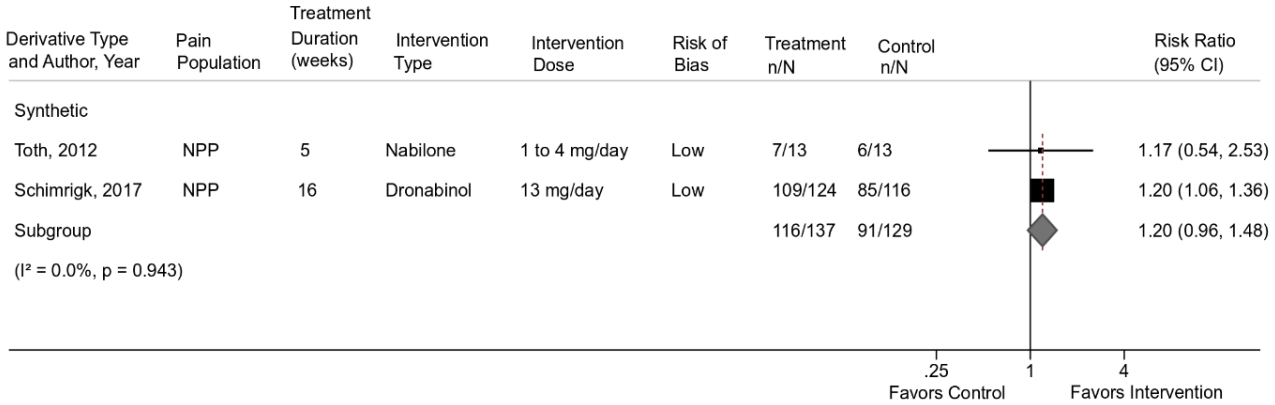
Figure D-11. Study withdrawal due to adverse events for dronabinol or nabilone (short term, 1 to 6 months followup)



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

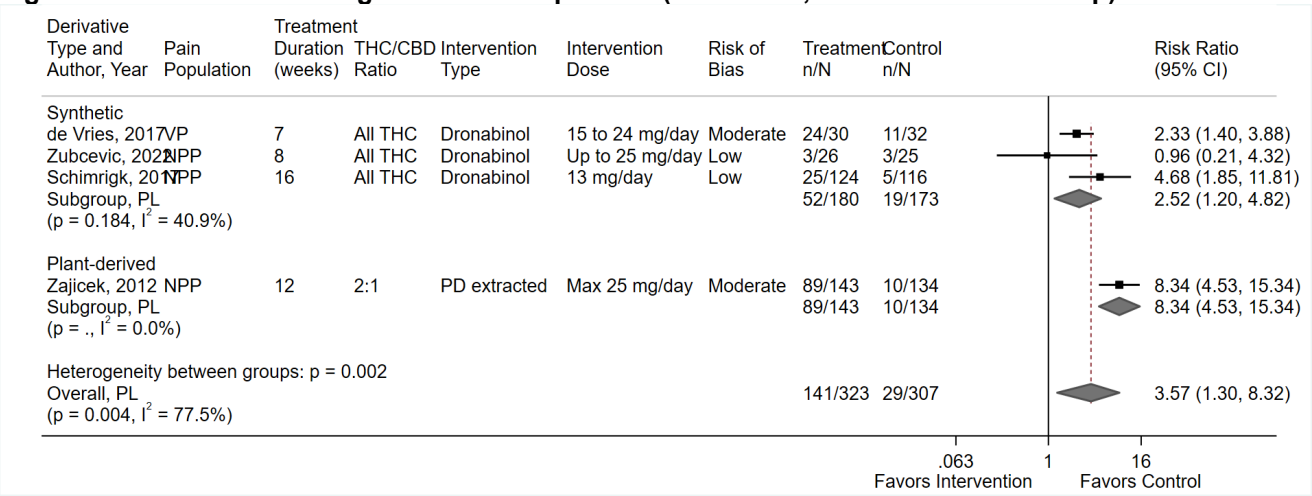
[a]Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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



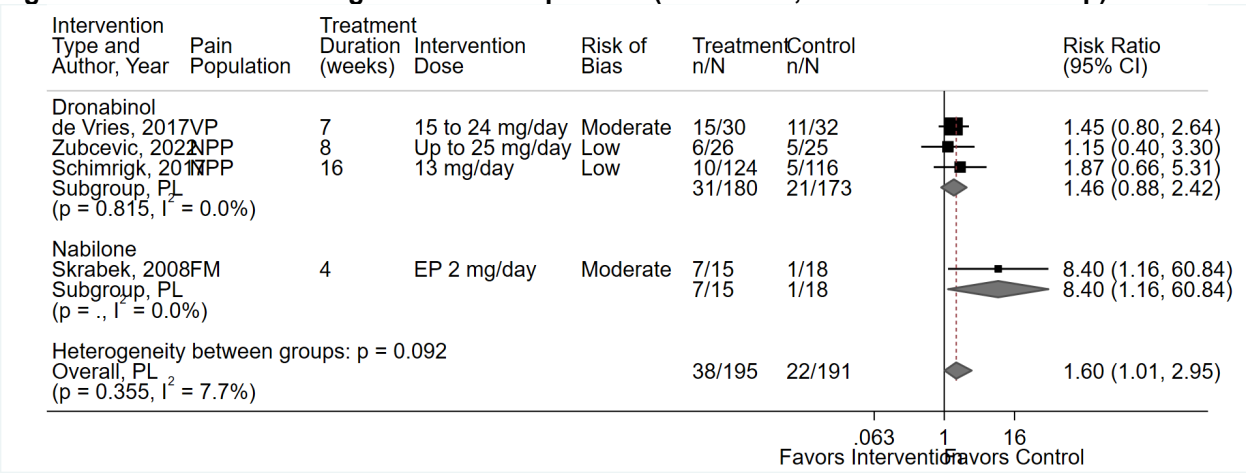
Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol.

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



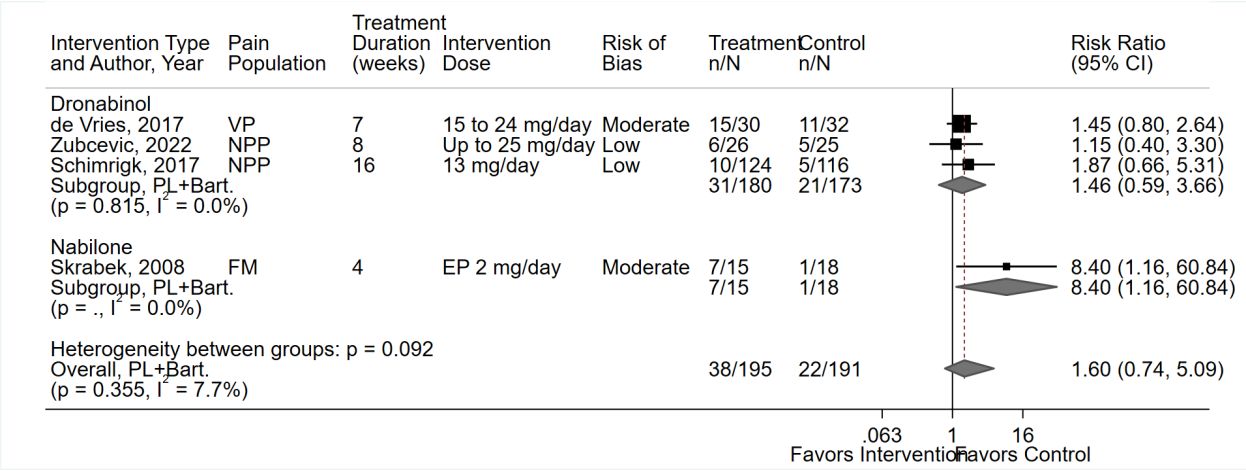
Abbreviations: CBD = cannabidiol; CI = confidence interval; NPP = neuropathic pain; PD = plant-derived; THC = tetrahydrocannabinol; VP = visceral pain.
[a] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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



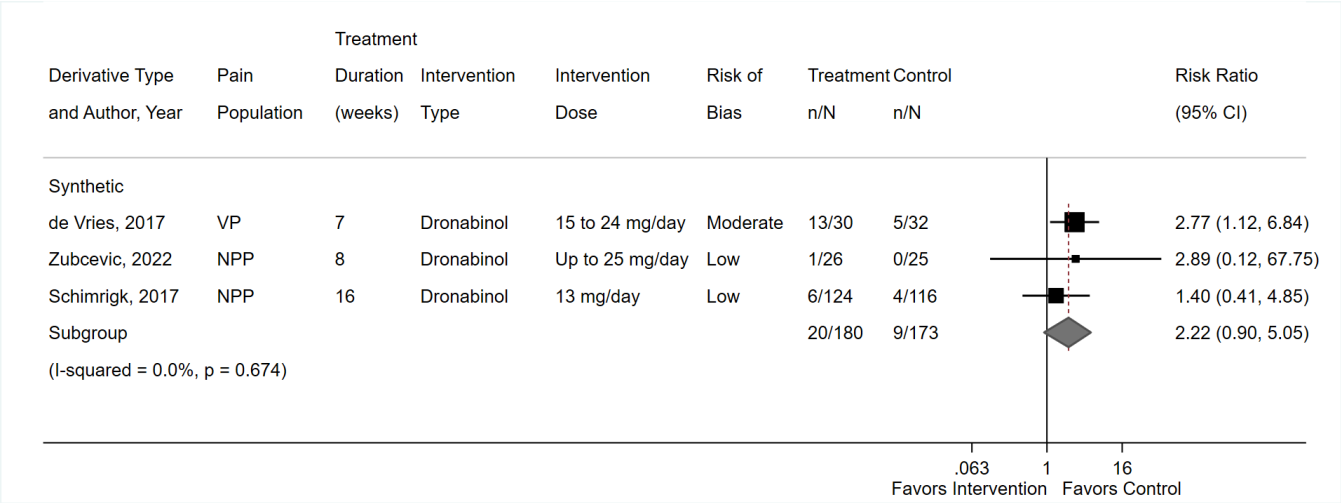
Abbreviations: CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL= profile likelihood; VP = visceral pain.
[a] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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



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

Figure D-16. Nausea for high-THC versus placebo (short term, 1 to 6 months followup)



Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol; VP = visceral pain.
[a] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

Appendix E. Evidence Tables

Shown in associated Excel files.

Appendix F. Risk of Bias Assessment

Shown in associated Excel files.

Appendix G. Details on Strength of Evidence

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Pain response (≥30% improvement from baseline)	4 RCTs (N=733)[1-4]	Moderate	Direct	Consistent	Imprecise	Unknown	Potential small effect, not statistically significant, with THC:CBD 38% versus 31%, RR 1.18 (0.93 to 1.71); 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	Small benefit with THC:CBD, MD −0.42, 95% CI –0.73 to −0.16, I^2=32% (scale 0 to 10)	Moderate
Comparable THC to CBD Ratio vs. Placebo	WAEs	5 RCTs (N=834)[1,2,4,5,7]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 12.3% vs. 9.5%, RR 1.19 (0.60 to 3.72); I^2=54%	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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Dizziness	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Large effect with THC:CBD 30% vs. 8%, RR 3.57 (2.42 to 5.60; I^2=0%)	Low
Comparable THC to CBD Ratio vs. Placebo	Nausea	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with THC:CBD 14% vs. 7.5% RR 1.79 (1.19 to 2.77; I^2=0%)	Low
Comparable THC to CBD Ratio vs. Placebo	Sedation	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Large effect with THC:CBD RR 5.04 (2.10 to 11.89; I^2=0%)	Low

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

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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Synthetic THC vs. Placebo	Pain response (≥30% improvement from baseline)	2 RCTs (N=84)[8,9]	Low	Direct	Very serious inconsistency	Imprecise	Unknown	Unable to assess, due to inconsistency from two trials (one trial of nabilone, 85% vs. 38%, RR 2.20 [1.06 to 4.55] and one trial of dronabinol, 43% vs. 57%, RR 0.76 [0.45 to 1.28])	Insufficient (previously low)
Synthetic THC vs. Placebo	Pain severity	7 RCTs (N=448)[8-14]	Moderate	Direct	Consistent	Imprecise	Unknown	Small effect with synthetic THC 0 to 10 scale, MD −0.95 (−1.81 to −0.25; I^2=60%)	Low
Synthetic THC vs. Placebo	Function/disability	3 RCTs (N=unclear)[8,9,13] 1 RCT (N=13) not Included in meta-analysis[14]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect (scale 0 to 10) MD: −0.18, −1.25 to 0.77, I^2=51%)	Low
Synthetic THC vs. Placebo	WAEs	5 RCTs (N=415)[9-13]	Moderate	Direct	Consistent	Imprecise	Unknown	Potential moderate effect, not statistically significant 14% vs. 7%, RR 1.75 (0.95 to 4.11; I^2=0%)	Low
Synthetic THC vs. Placebo	SAEs	1 RCT (N=240)[11]	Low	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 10% vs. 6%, RR 1.60 (0.65 to 3.93)	Insufficient
Synthetic THC vs. Placebo	Dizziness	3 RCTs (N=360)[9-11]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 29% vs. 11%, RR 2.52 (1.20 to 4.82; I^2=41%)	Moderate

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

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

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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Extracted THC vs. Placebo	Pain severity	2 RCTs (N=294)[15,16]	Moderate	Direct	Inconsistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD −1.97 (−5.91 to 1.21; I^2=72%)	Insufficient
	Function/disability	1 RCT (N=18)[16]	High	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 1.75 (−0.46 to 3.98)	Insufficient
	WAEs	1 RCT (N=277)[15]	Moderate	Direct	Unknown	Imprecise	Unknown	Large increased risk 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Low
	SAEs	1 RCT (N=277)[15]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 4.9% vs. 2.2%, RR 2.19 (0.58 to 8.28)	Insufficient
	Dizziness	1 RCT (N=277)[15]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect 62.2% vs. 7.5%, RR 8.34 (4.53 to 15.34)	Low

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

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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Combined High THC Ratio Studies (Synthetic and Whole-plant extracted)	Pain severity	9 RCTs (N=742)[8-16]	Moderate	Direct	Consistent	Precise	Unknown	Moderate effect MD −1.12 (−1.97 to −0.48; I^2=65%)	Moderate

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

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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Whole plant cannabis (standardized to 12% THC) vs. Usual Care	Pain Severity change	1 (N=431, 302 contribute to pain outcome)[17]	High	Direct	Unknown	Imprecise	Unknown	Moderate effect 0 to 10 scale, Adjusted MD at 12 months: −1.10 (−1.56 to −0.72)	Insufficient
	WAE	1 (N=431)[17]	High	Direct	Unknown	Imprecise	Unknown	Large effect with cannabis 4.7% vs. 0%, RR 21.10 (1.24 to 357.80)	Insufficient
	SAE	1 (N=431)[17]	High	Direct	Unknown	Imprecise	Unknown	No effect 13% vs. 19%, OR 0.64 (0.38 to 1.04)	Insufficient
	Dizziness	1 (N=431)[17]	High	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 12.6% vs. 9.7%, RR 1.29 (0.75 to 2.21)	Insufficient
	Nausea	1 (N=431)[17]	High	Direct	Unknown	Imprecise	Unknown	Moderate effect 16.7% vs. 9.7%, RR 1.72 (1.04 to 2.85)	Insufficient
	Sedation	1 (N=431)[17]	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.5% vs. 4.63%, RR 2.91 (1.46 to 5.83)	Insufficient
	Cognitive Disorder	1 (N=431)[17]	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Insufficient

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

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Topical, Plant-Extracted CBD vs. Placebo	Pain severity (change)	1 RCT (N=29)[18]	High	Direct	Unknown	Imprecise	Unknown	Small effect with CBD cream MD −0.75, P=0.009 by ANCOVA (0 to 10 scale)	Insufficient
Oral Synthetic CBD vs. Placebo	Pain response (≥30% improvement)	1 RCT (N=136)[19]	Moderate	Direct	Unknown	Imprecise	Unknown	No effect with oral synthetic CBD RR 1.01 (0.66 to 1.55)	Insufficient
Oral CBD or THC/CBD (Unknown If Synthetic or Plant-extracted vs. Placebo[a]	Pain severity (change)	1 RCT (N=87)[9]	Low	Unclear	Unknown	Imprecise	Unknown	Potential increase in pain for CBD (MD 1.14 [0.11 to 2.19]) and no difference but imprecise for THC/CBD (MD -0.12 [-1.13 to 0.89])	Insufficient
	Pain response (≥30% improvement)	1 RCT (N=87)[9]	Low	Unclear	Unknown	Imprecise	Unknown	Imprecise estimates for CBD (RR 0.59 [0.32 to 1.09]) and THC/CBD (RR 1.06 [0.69 to 1.62])	Insufficient
	Function/disability	1 RCT (N=87)[9]	Low	Unclear	Unknown	Imprecise	Unknown	Imprecise estimates for CBD (MD 1.24 [-0.32 to 2.81]) and THC CBD (MD 0.89 [-0.64 to 2.42])	Insufficient

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

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

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
CBDV vs. Placebo	Pain Response (≥30% improvement from baseline)	1 RCT (N=31)[20]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect, favors placebo 38% vs. 81%, RR 0.46 (95% CI 0.24 to 0.91)	Insufficient
CBDV vs. Placebo	Pain severity (change)	1 RCT (N=31)[20]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 0.62 (−0.05 to 1.32)	Insufficient

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

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Unknown THC to CBD Ratio vs. Usual Care	Pain response (≥30% improvement from baseline)	No studies	NA	NA	NA	NA	NA	NA	No evidence
Unknown THC to CBD Ratio vs. Usual Care	Pain severity (change) Short-term (3 months)	2 cohort studies: short- to intermediate-term (N=202)[21,22]	High	Direct	Inconsistent	Imprecise	Unknown	VAS (0-100): 41.5 vs 43.6 at 3 months[21] 34.1 vs 48.8; mean difference −14.71 (95% CI, −32.71 to 3.29)[22]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Long-term (12 months)	1 cohort (N=1,514)[23]	High	Direct	Unknown	Precise	Unknown	Adjusted mean; BPI, 0-10 scale) 5.2 vs. 4.9; Beta: 0.37 (95% CI −0.23 to 1.10), p=0.20[23]	Insufficient

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	Function or Disability (SF-36 Physical Function)	2 cohorts = short to medium-term (N=202)[21,22]	High	Direct	Consistent	Imprecise	Unknown	SF-36 Physical Functioning (mean, 0 to 100 scale) 46.5 vs. 43.7 at 6 months[21] 70.0 vs. 69.4; MD 0.56 (95% CI −17.2 to 18.3) at 3 months[22]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	WAEs	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	6 months: 23% (12/52) vs. 9% (5/55), RR 2.54 (95% CI 0.95 to 6.71)	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	SAEs	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	None in any group	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + gabapentin vs Gabapentin Alone)	Dizziness	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	3 months: 33% (17/52) vs. 29% (16/55), RR 1.12 (95% CI 0.64 to 1.98) 6 months: 39% (20/52) vs. 33% (18/55), RR 1.17 (95% CI 0.70 to 0.91)	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + gabapentin vs. Gabapentin Alone)	Nausea	No studies	NA	NA	NA	NA	NA	NA	No evidence

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)	Sedation	1 cohort study, short- and intermediate-term (N=156)[21]	Moderate	Direct	Unknown	Imprecise	Unknown	3 months: 54% (28/52) vs. 33% (18/55) RR 1.65 (95% CI 1.04 to 2.59) 6 months: 60% (31/52) vs. 36% (20/55) RR 1.64 (95% CI 1.08 to 2.48)	Insufficient

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

Appendix G References

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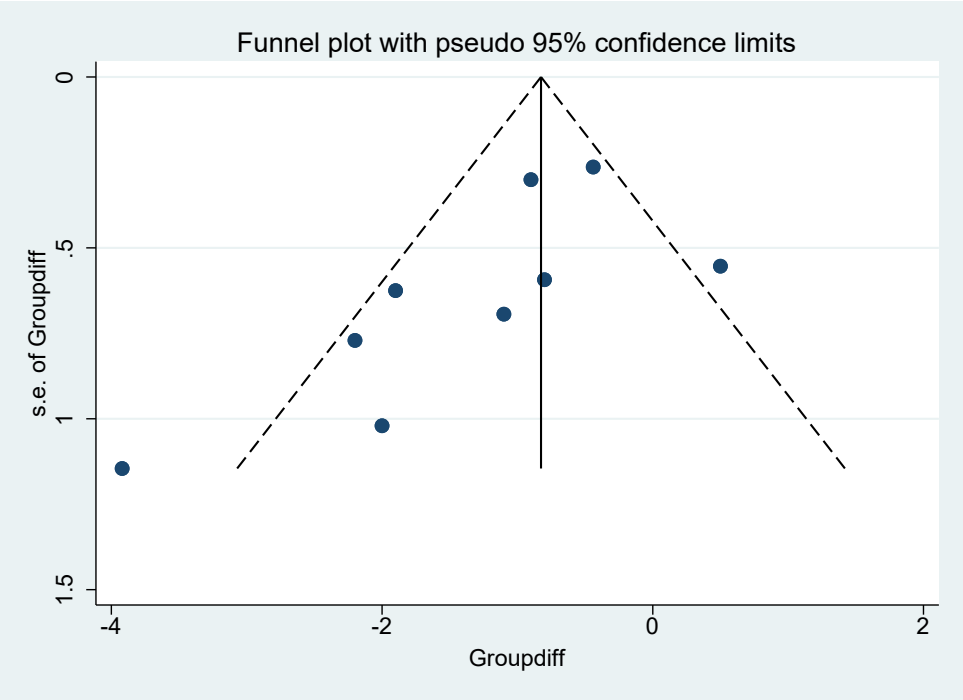
Appendix I. Funnel Plot of High-THC Ratio Studies Included in Meta-Analysis for Pain Severity

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



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