Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) ALL 1946 to February 4, 2022

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

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

1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab,hw.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,hw.
8 1 or 2 or 5 or 6 or 7

9 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,hw.
10 8 and 9
11 conference abstract.pt.
12 "journal: conference abstract".pt.
13 "journal: conference review".pt.
14 "http://.www.who.int/trialsearch*".so.
15 "https://clinicaltrials.gov*".so.
16 11 or 12 or 13 or 14 or 15
17 10 not 16

Database: APA PsycInfo 1806 to January Week 4, 2022
1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
8 1 or 2 or 5 or 6 or 7
9 Cannabis/
10 exp Cannabinoids/
11 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab.
12 or/9-11
13 8 and 12
14 limit 13 to english language

Database: Elsevier Embase to January 30, 2022
('cannabis'/exp OR cannabis OR cannabinoid* OR 'cannabinol'/exp OR cannabinol OR 'marijuana'/exp OR marijuana OR 'cannabidiol'/exp OR cannabidiol OR phytocannabinoid* OR 'tetrahydrocannabinol'/exp OR tetrahydrocannabinol OR 'dronabinol'/exp OR dronabinol OR 'nabilone'/exp OR nabilone OR 'sativex'/exp OR sativex OR 'cbd' OR 'thc' OR 'kratom'/exp OR kratom OR 'khat'/exp OR khat OR 'qat'/exp OR qat OR 'psilocybin'/exp OR psilocybin OR 'hemp'/exp OR hemp OR hydroxymitragynine) AND ('chronic pain'/exp OR arthralgia OR 'back pain' OR headache OR 'musculoskeletal pain' OR 'neck pain' OR neuralgia OR 'nociceptive pain' OR 'intractable pain' OR fibromyalgia OR myalgia OR arthritis OR osteoarthrtis) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Database: Elsevier Scopus to February 7, 2022
(TITLE (cannabis OR cannabinoid* OR cannabinol OR marijuana OR cannabidiol OR phytocannabinoid* OR tetrahydrocannabinol OR dronabinol OR nabilone OR sativex OR

"CBD" OR "THC" OR kratom OR khat OR qat OR psilocybin OR hemp OR hydroxymitragynine)) AND (TITLE ("chronic pain" OR arthralgia OR "back pain" OR headache OR "musculoskeletal pain" OR "neck pain" OR neuralgia OR "nociceptive pain" OR "intractable pain" OR fibromyalgia OR myalgia OR arthritis OR osteoarthritis OR "neuropathic pain"))

Appendix B. Methods

Inclusion and Exclusion Criteria

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

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

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

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

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

Table B-1. PICOTS

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

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

Important subgroups to consider in evaluating this evidence are:

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

Below are additional details on the scope of this project:

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

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

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through February 4, 2021. Searches were initially run in September 2020 with ongoing, automated monthly searches to identify newly published studies. Search strategies are available in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and reviewing the two prior AHRQ pain reports[1,2] for studies that met our inclusion criteria. A Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies. As part of living systematic review methods, the

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

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

Data Extraction

After studies were selected for inclusion, data were abstracted into categories that included but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results relevant to each Key Question as outlined in the previous inclusion and exclusion criteria section. Information that was abstracted that was relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. All study data were verified for accuracy and completeness by a second team member. On a quarterly basis, any newly identified studies were abstracted and evidence tables updated. Quarterly reports were published to the Agency for Healthcare Research and Quality (AHRQ) website, and evidence tables 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,[4] and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force.[5] These criteria and methods were used in accordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews developed by AHRQ.[6] Studies were given an overall rating of "low," "medium," or "high" risk of bias. We used DistillerSR® software to conduct these assessments, using dual review by two independent reviewers. Disagreements identified by DistillerSR® were resolved through consensus. Assessments and final ratings were converted to evidence tables, and will be uploaded on a quarterly basis to SRDR+.

Data Synthesis and Analysis

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

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

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were homogeneous enough to provide a meaningful combined estimate.[10] The decision to conduct quantitative synthesis depends on presence of at least two studies, completeness of reported outcomes and a lack of heterogeneity among the reported results. To determine whether meta-analyses were indicated, we considered the risk of bias of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Meta-analyses were conducted using a random effects model based on the profile likelihood method,[11] 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[1,2,7-9] to provide a consistent benchmark for comparing results of pain interventions across reviews. Table B-2 provides thresholds for determining the magnitude of effect. A small effect is defined for pain as a mean between-group difference following treatment of 5 to 10 points on a 0- to 100-point visual analog scale (VAS), 0.5 to 1.0 points on a 0- to 10-point numeric rating scale, or equivalent; for function as a mean difference of 5 to 10 points on the 0- to 100-point Oswestry Disability Index (ODI) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A moderate effect is defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large effects are defined as greater than moderate. We apply similar thresholds to other outcomes measures. Small effects using this system may be below published thresholds for clinically meaningful effects; however, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or function using a treatment with low cost or no serious harms may be important.

Table B-2. Definitions of effect sizes

Effect Size	Definition
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to 10-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 to 10-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)[12]
- If the magnitude of effect is below the threshold for a small effect, the finding is considered to have "No effect"[1]
- If the magnitude of effect is small or greater, and SOE is at least Low, the finding is considered to have a "Potential effect, not statistically significant"
- If the magnitude of effect is small or greater, and SOE is insufficient, the finding is considered to have "failed to demonstrate or exclude a beneficial/detrimental effect."[13]

Grading the Strength of the Body of Evidence

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

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

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

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

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

"reduces/increases;" moderate SOE is described as "probably;" and low SOE is described as "may be."[14]

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

Appendix B References

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Appendix C. Included Studies List

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Appendix D. Results

Appendix D-1. Individual Study Summary Tables

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

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

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

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

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

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

[b] Difference in median differences.

[c] Difference in mean differences.

[d] Mean sprays calculated by systematic review team.

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

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

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

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

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

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

[b] Estimated from graph.

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

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

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

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

Table D-4. Other cannabinoids study primary outcomes

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

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

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

Table D-5. Observational study primary outcomes

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Lee, 2021[b] Moderate Matched cohort NR	A: Chronic opioid users authorized to use medical cannabis in Canada (5,373) B: Controls who did not receive authorization for medical cannabis in Canada (5,373) 20 months Unknown THC concentration; patient-driven choice	NR	NR	NR
Merlin, 2019[b] High Prospective cohort Chronic non-cancer pain (HIV)	A: Daily or weekly use of marijuana (55) B: Monthly or 1-2 times a month use of marijuana (65) C: No use (313) 52 weeks Unknown THC concentration; patient-driven choice	NR	NR	NR
Ueberall, 2022 Moderate Retrospective cohort Peripheral neuropathic pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 16.6 mg THC/15.4 mg CBD/day (337) B: THC oral capsule (Dronabinol), strength NR, mean dose 17.2 mg THC/day (337) 24 weeks Whole plant extracted and synthetic	Pain intensity index (mean relative change [improvement] rates at week 24, 0 to 100 VAS scale): 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)	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

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%) WAE: 10/215 (4.65%) vs. NR (assumed 0)

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

[a] Higher scores indicate better outcomes.

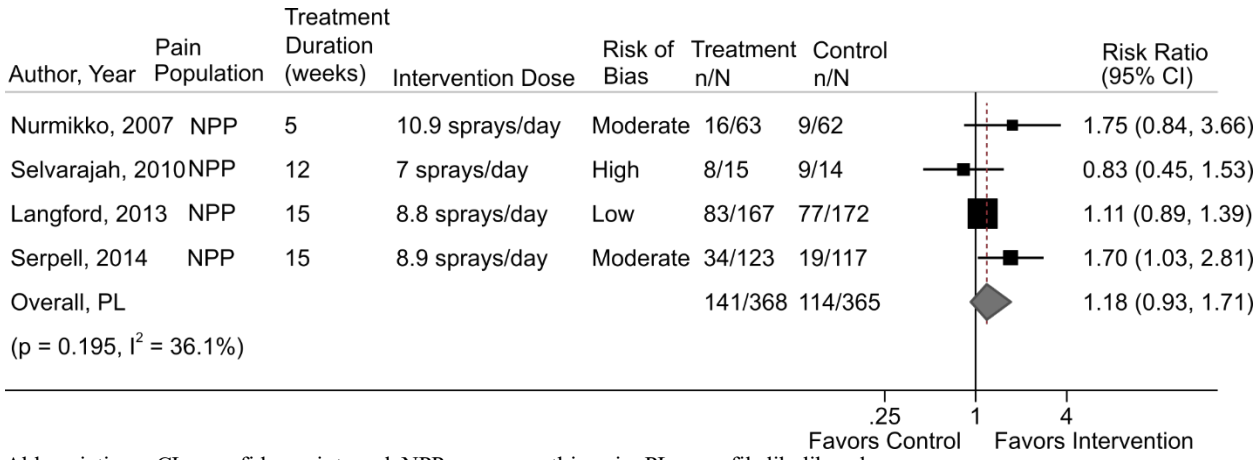
[b] Only included outcome reported was opioid-use.

Appendix D-2. Meta-Analyses

Comparable THC to CBD Ratio Studies

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

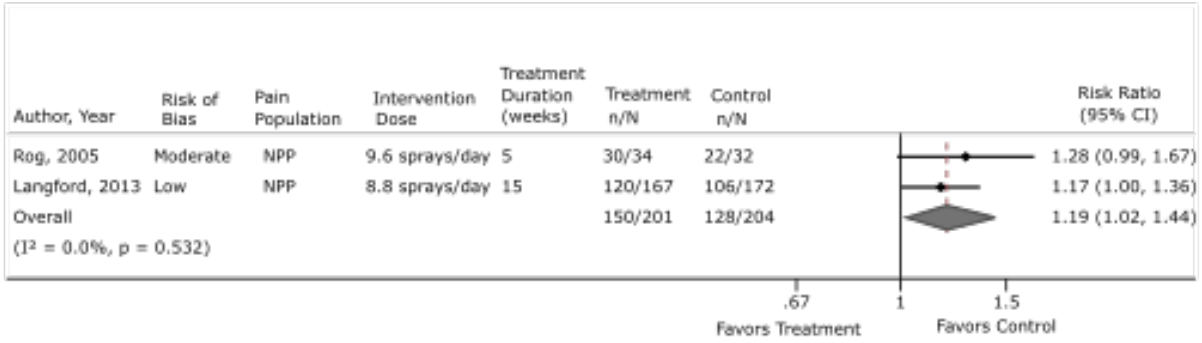
Figure D-1. Proportion of patients with pain response (≥30% improvement) with comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



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

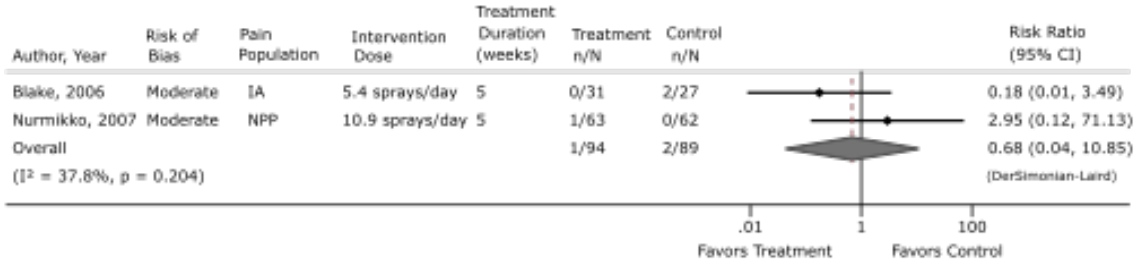
[a] Calculated by review team

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



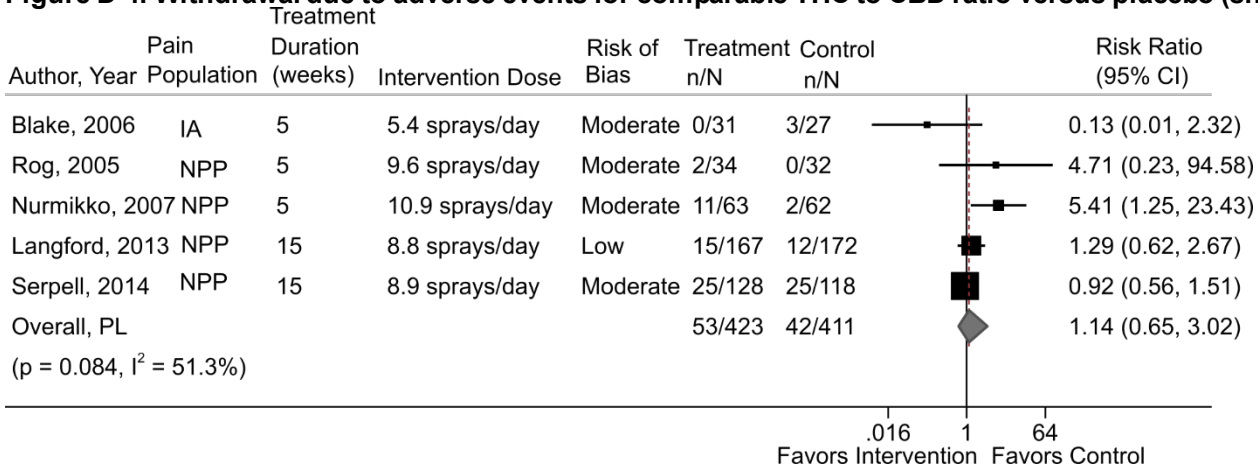
Abbreviations: CI = confidence interval; NPP = neuropathic pain

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



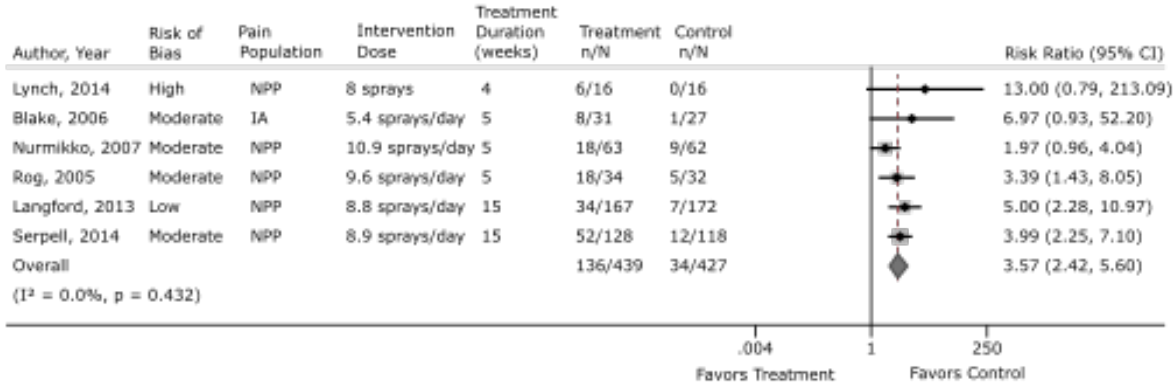
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

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



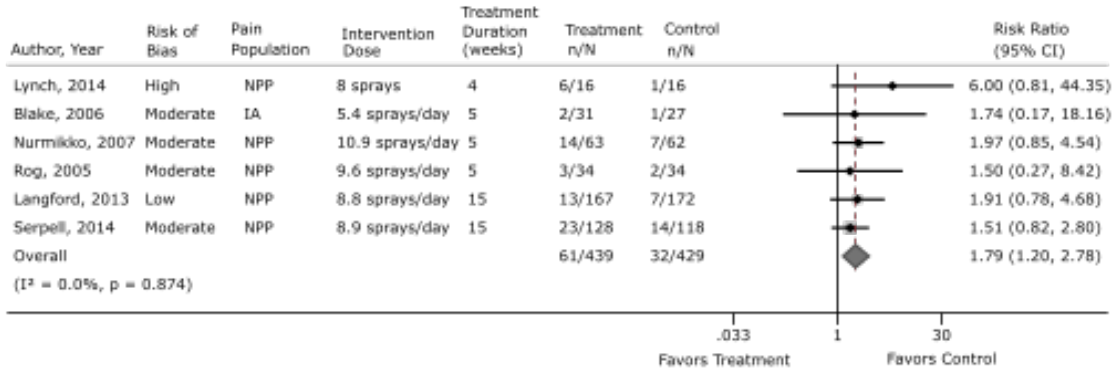
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

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



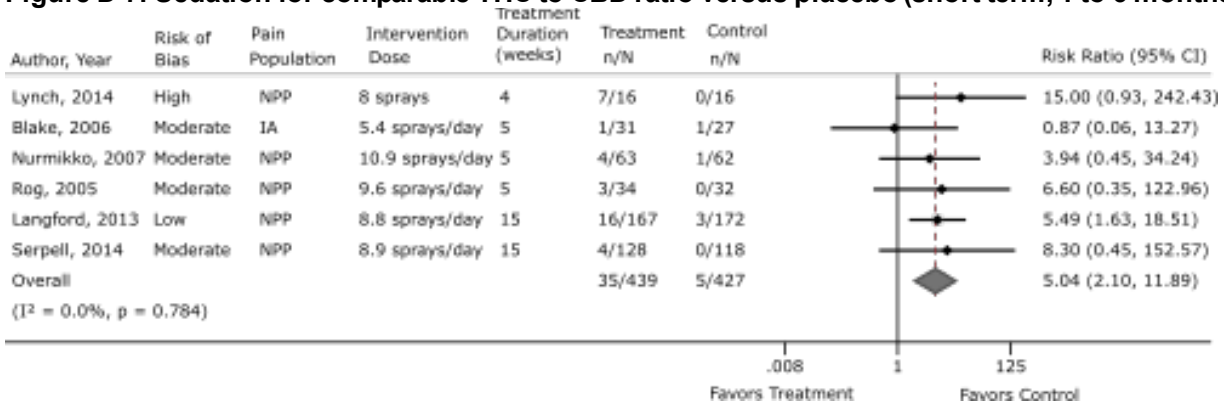
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain

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



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

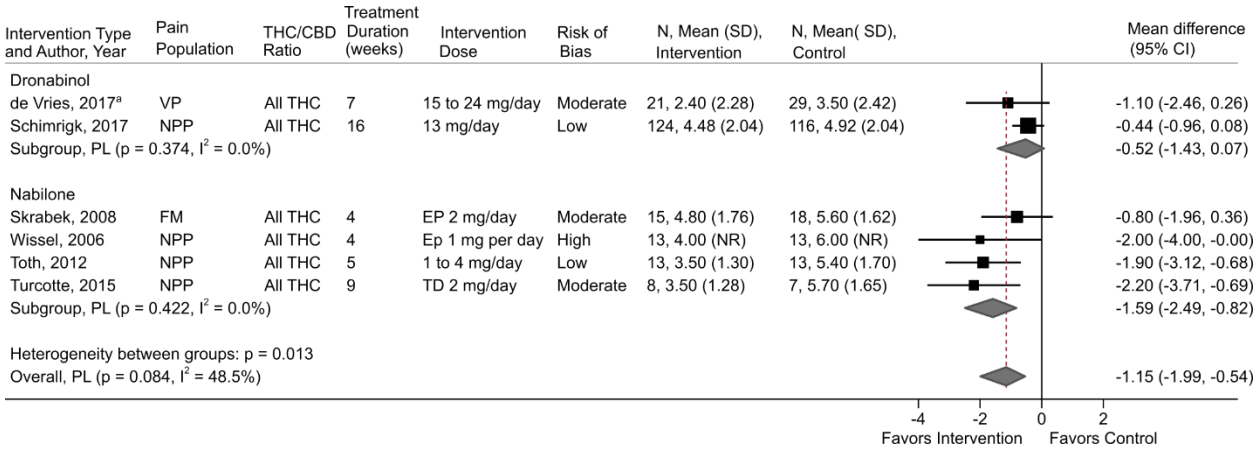
Figure D-7. Sedation for comparable THC to CBD ratio versus placebo (short term, 1 to 6 months followup)



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

High-THC to CBD Ratio Studies

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



Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; 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.

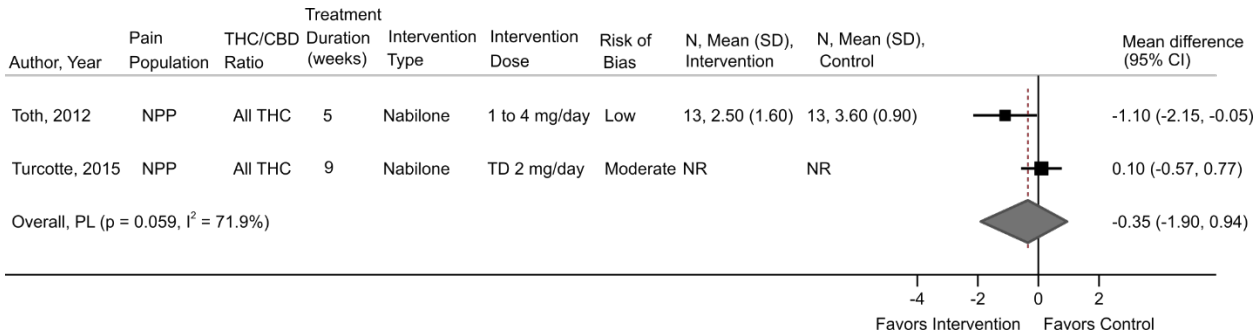
Table D-6. Interaction effect of RCTs assessing synthetic cannabinoids: nabilone versus dronabinol

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

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

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

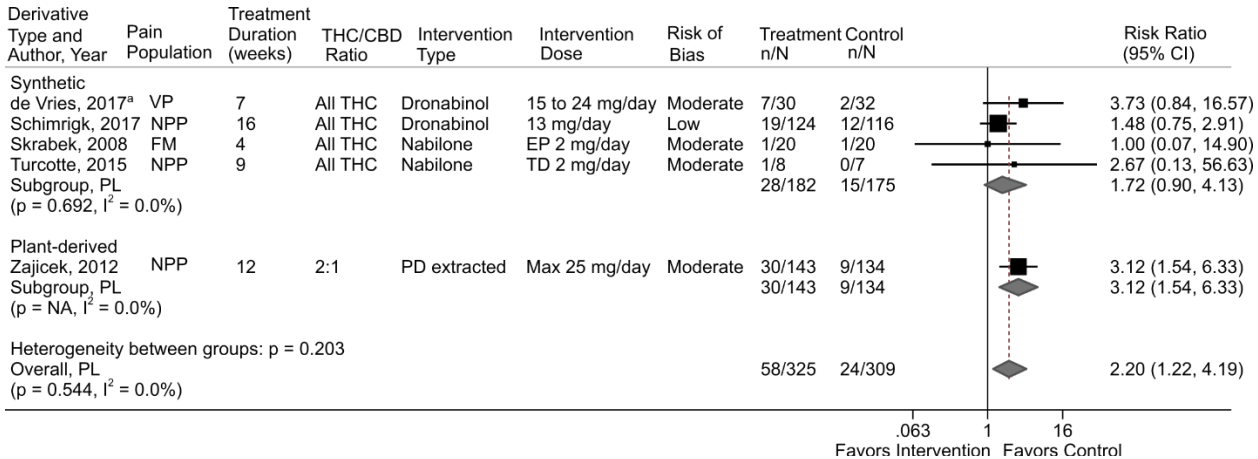
Figure D-9. Overall function for high-THC versus placebo (short term, 1-6 months followup)



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

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

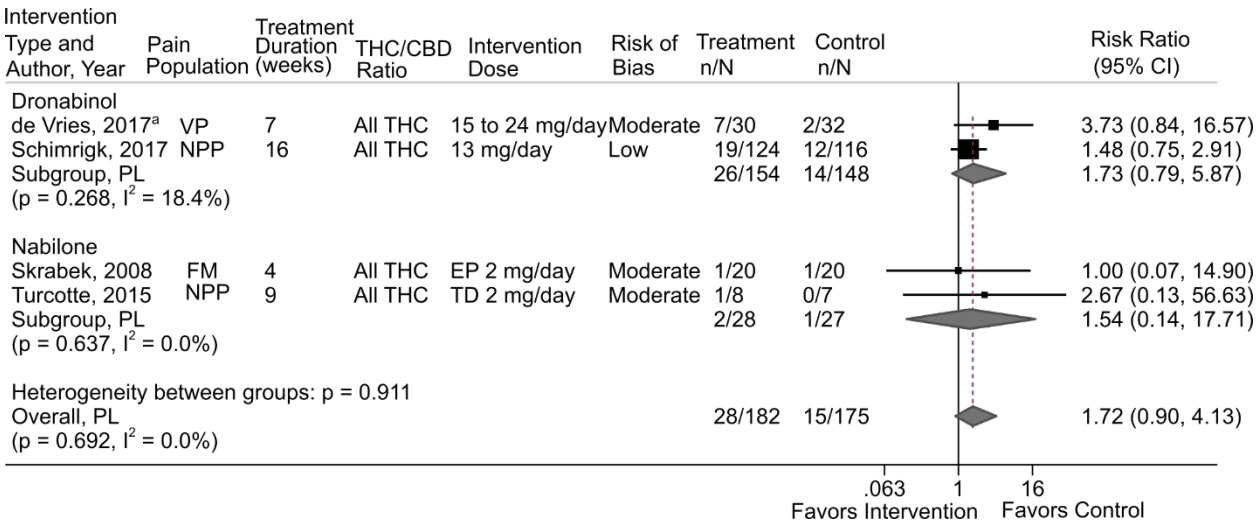
Figure D-10. Withdrawal due to adverse events for high-THC versus placebo (short term, 1 to 6 months followup)



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

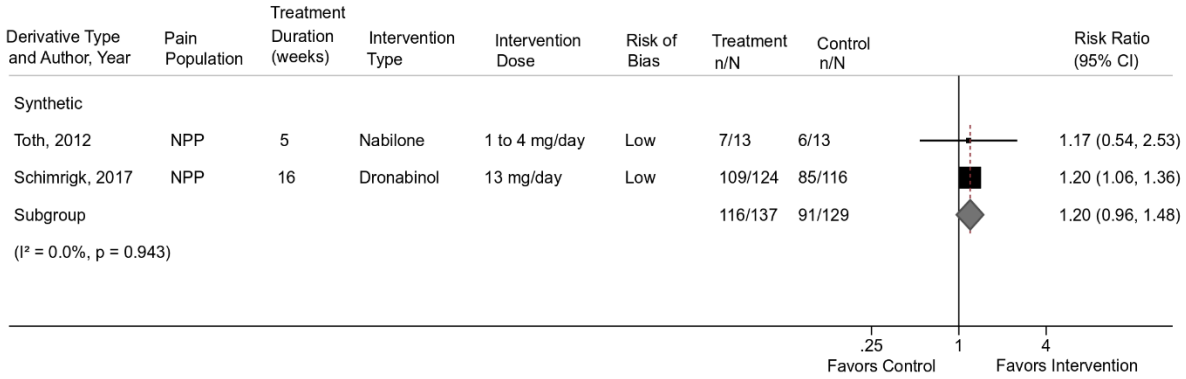
[a] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

Figure D-11. Study withdrawals for adverse events for synthetic high-THC (short term, 1 to 6 months followup)



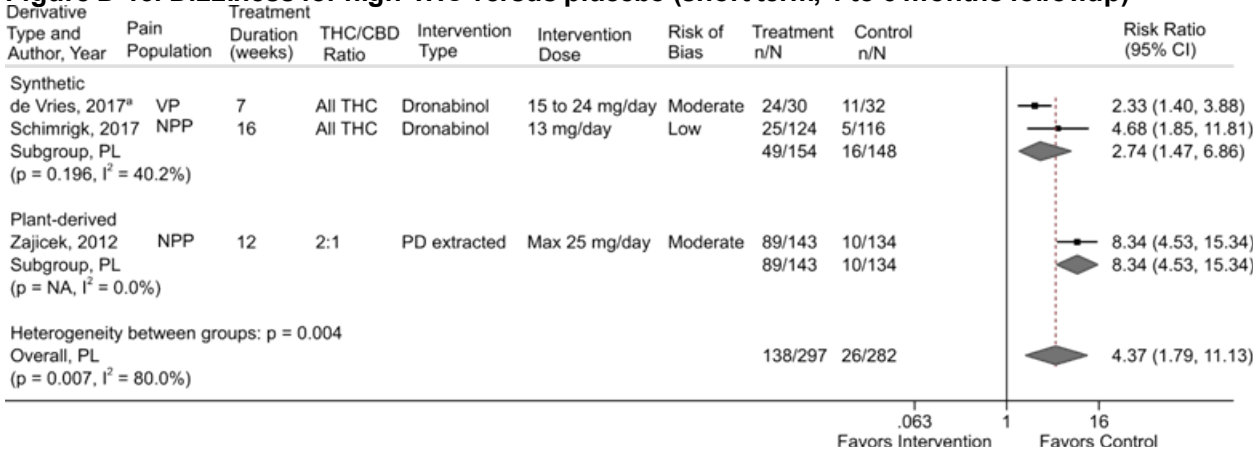
Abbreviations: CI = confidence interval; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol; VP = visceral pain.
[a] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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



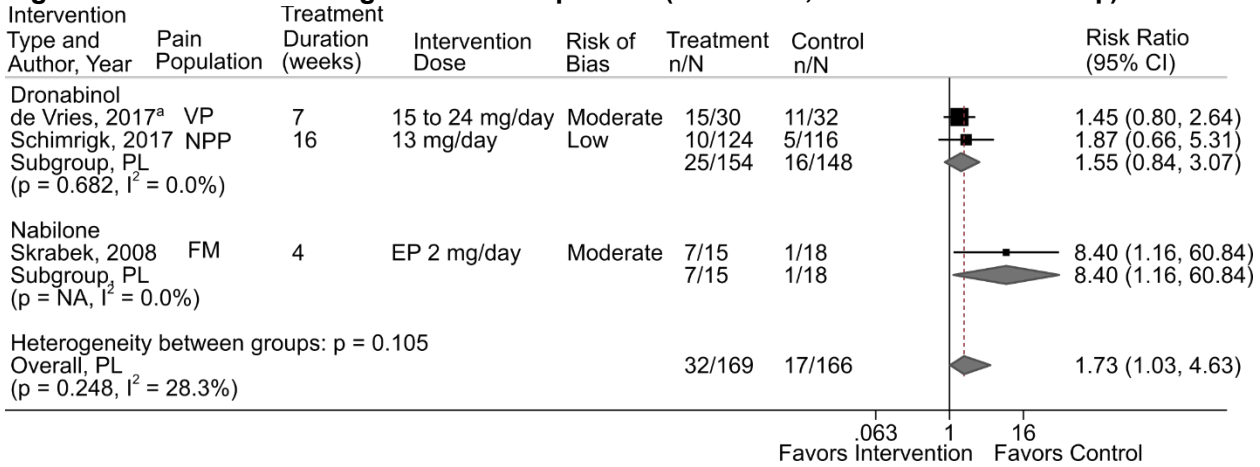
Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol

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



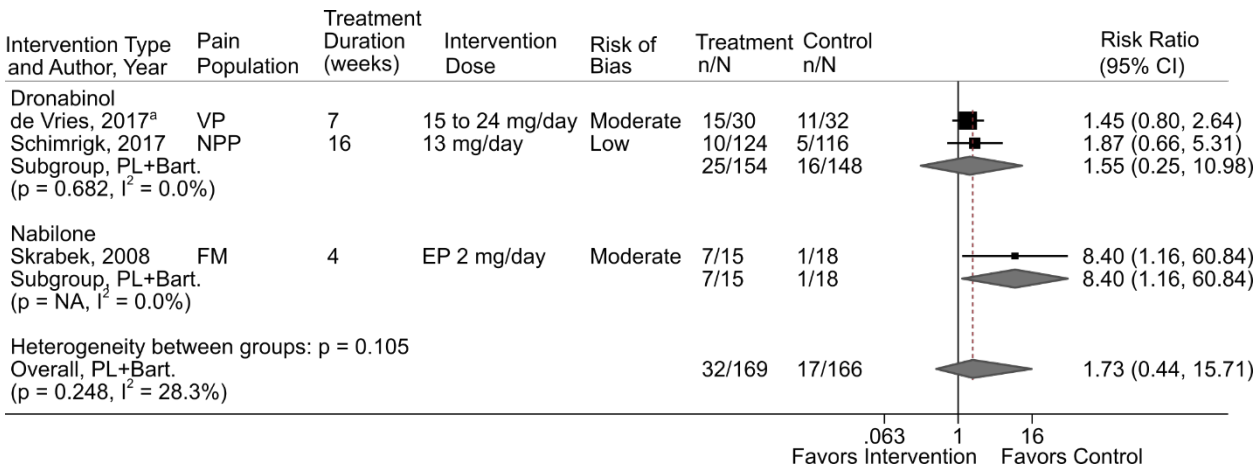
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PD = plant-derived; THC = tetrahydrocannabinol; VP = visceral pain.
[a] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.

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



Abbreviations: CI = confidence interval; 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.

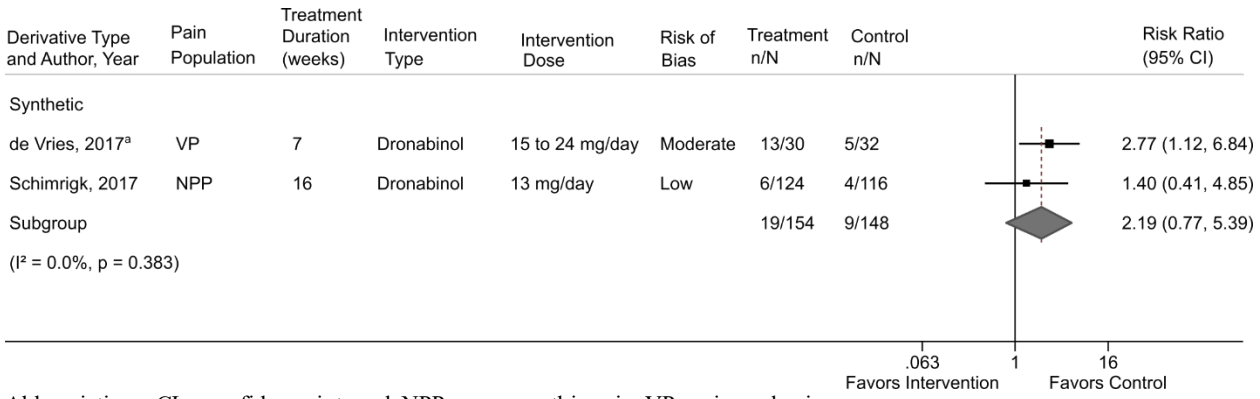
Figure D-15. Sensitivity analysis of sedation for high-THC versus placebo (short term, 1 to 6 months followup)



Abbreviations: Bart = Bartlett's correction; CI = confidence interval; 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; 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 13% vs. 10%, RR 1.14 (0.65 to 3.02); I^2=51%	Low
Comparable THC to CBD Ratio vs. Placebo	SAEs	2 RCTs (N= 183)[2,5]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 1.1% vs. 2.2%, RR 0.68 (0.04 to 10.85; I^2=38%)	Low

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Dizziness	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Large effect with THC:CBD 30% vs. 8%, RR 3.57 (2.42 to 5.60; I^2=0%)	Low
Comparable THC to CBD Ratio vs. Placebo	Nausea	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with THC:CBD 14% vs. 7.5% RR 1.79 (1.19 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)	Strength of Evidence Grade
Synthetic THC vs. Placebo	Pain response (≥30% improvement from baseline)	1 RCT (N=26)[8]	Low	Direct	Unknown	Imprecise	Unknown	Large effect with nabilone 85% vs. 38%, RR 2.20 (CI 1.06 to 4.55)	Insufficient
Synthetic THC vs. Placebo	Pain severity	6 RCTs (N=390)[8-13]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with synthetic THC 0 to 10 scale, MD −1.15 (−1.99 to −0.54; I^2=48%)	Low
Synthetic THC vs. Placebo	Function/disability	2 RCTs (N=41)[8,12] 1 RCT (N=13) not Included in meta-analysis[13]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect (scale 0 to 10) MD : −0.35, −1.9 to 0.94, 0 to 10 scale, I^2=72%	Low
Synthetic THC vs. Placebo	WAEs	4 RCTs (N=357)[9-12]	Moderate	Direct	Consistent	Imprecise	Unknown	Potential moderate effect, not statistically significant 13% vs. 9%, RR 1.72 (0.90 to 4.13; I^2=0%)	Low
Synthetic THC vs. Placebo	SAEs	1 RCT (N=240)[10]	Low	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 10% vs. 6%, RR 1.60 (0.65 to 3.93)	Insufficient
Synthetic THC vs. Placebo	Dizziness	2 RCTs (N=302)[9,10]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 32% vs. 11%, RR 2.74 (1.47 to 6.86; I^2=40%)	Moderate

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Synthetic THC vs. Placebo	Nausea	2 RCTs (N=302)[9,10]	Low	Direct	Consistent	Imprecise	Unknown	Potential large effect with dronabinol, not statistically significant 12% vs. 6%, RR 2.19 (0.77 to 5.39; I^2=0%)	Low
Synthetic THC vs. Placebo	Sedation	3 RCTs (N=335)[9-11]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with dronabinol 19% vs. 10%, RR 1.73 (1.03 to 4.63; I^2=28%)	Low

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

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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Extracted THC vs. Placebo	Pain severity	2 RCTs (N=294)[14,15]	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)[15]	High	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 1.75 (−0.46 to 3.98)	Insufficient
	WAEs	1 RCT (N=277)[14]	Moderate	Direct	Unknown	Imprecise	Unknown	Large increased risk 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Low
	SAEs	1 RCT (N=277)[14]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 4.9% vs. 2.2%, RR 2.19 (0.58 to 8.28)	Insufficient
	Dizziness	1 RCT (N=277)[14]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect 62.2% vs. 7.5%, RR 8.34 (4.53 to 15.34)	Low

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

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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Combined High THC Ratio Studies (Synthetic and Whole-plant extracted)	Pain severity	8 RCTs (N=684)[8-15]	Moderate	Direct	Consistent	Precise	Unknown	Moderate effect MD −1.25 (−2.09 to −0.71; I^2=58%)	Moderate

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

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

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

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

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Topical CBD vs. Placebo	Pain severity (change)	1 RCT (N=29)[17]	High	Direct	Unknown	Imprecise	Unknown	Small effect with CBD cream MD −0.75, P=0.009 by ANCOVA (0 to 10 scale)	Insufficient
Oral Synthetic CBD vs. Placebo	Pain response (≥30% improvement)	1 RCT (N=136)[18]	Moderate	Direct	Unknown	Imprecise	Unknown	No effect with oral synthetic CBD RR 1.01 (0.66 to 1.55)	Insufficient

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

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
CBDV vs. Placebo	Pain Response (≥30% improvement from baseline)	1 RCT (N=31)[19]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect, favors placebo 38% vs. 81%, RR 0.46 (95% CI 0.24 to 0.91)	Insufficient
CBDV vs. Placebo	Pain severity (change)	1 RCT (N=31)[19]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 0.62 (−0.05 to 1.32)	Insufficient

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

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)[20,21]	High	Direct	Inconsistent	Imprecise	Unknown	VAS (0-100): 41.5 vs 43.6 at 3 months[20] 34.1 vs 48.8; mean difference −14.71 (95% CI, −32.71 to 3.29)[21]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Long-term (12 months)	1 cohort (N=1,514)[22]	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[22]	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)[20,21]	High	Direct	Consistent	Imprecise	Unknown	SF-36 Physical Functioning (mean, 0 to 100 scale) 46.5 vs. 43.7 at 6 months[20] 70.0 vs. 69.4; MD 0.56 (95% CI −17.2 to 18.3) at 3 months[21]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	WAEs	1 cohort study, short- and intermediate-term (N=156)[20]	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)[20]	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)[20]	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)[20]	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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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. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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;27:27. PMID: 34510141.

19. 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.

20. 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.

21. 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. 2021doi: 10.1037/pha0000435. PMID: 33764103.

22. 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.

Appendix H. Excluded Studies List

1. 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 Print. doi: 10.1097/MJT.0000000000001236. PMID: 33416237. **Exclusion reason:** Ineligible study design
2. 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:** Used as source document
3. 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
4. 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. PMID: 17296917. **Exclusion reason:** Inadequate duration
5. 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
6. Abuhasira R, Ron A, Sikorin I, et al. Medical cannabis for older patients—treatment protocol and initial results. J Clin Med. 2019;8(11). doi: 10.3390/jcm8111819. PMID: 31683817. **Exclusion reason:** Ineligible population
7. 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:** Used as source document
8. 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. doi: 10.1177/1179573519831997. PMID: 30886530. **Exclusion reason:** Used as source document
9. 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
10. 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
11. 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:** Used as source document
12. 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
13. 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. 2021. doi:

10.1093/sleep/zsab234. **Exclusion reason:** Used as source document

14. Anaya HJM, Ortiz MPT, Valencia DHF, et al. Efficacy of cannabinoids in fibromyalgia: A literature review. Colombian Journal of Anesthesiology. 2021;49(4). doi: 10.5554/22562087.e980. **Exclusion reason:** Inadequate duration

15. 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

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

17. 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

18. Aviram J, Lewitus GM, Vysotski Y, et al. Sex differences in medical cannabis-related adverse effects. Pain. 2021. doi: 10.1097/j.pain.0000000000002463. **Exclusion reason:** Ineligible comparator

19. 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

20. 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:** Used as source document

21. 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:** Used as source document

22. 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. PMID: 25676540. **Exclusion reason:** Ineligible outcome

23. 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

24. 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. PMID: 16553576. **Exclusion reason:** Ineligible publication type

25. 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

26. 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

27. 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

28. Bennici A, Mannucci C, Calapai F, et al. Safety of Medical Cannabis in Neuropathic Chronic Pain Management. Molecules (Basel). 2021;26(20):16. PMID: 34684842. **Exclusion reason:** Used as source document

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

30. 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. PMID: 15561385. **Exclusion reason:** Inadequate duration

31. 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:** Ineligible population

32. 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. 2021. doi: 10.1016/j.jpain.2020.12.001. PMID: 33400996. **Exclusion reason:** Ineligible study design

33. 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. 2021. doi: 10.1016/j.jpain.2021.04.011. PMID: 33992787. **Exclusion reason:** Background only

34. 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

35. 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. PMID: 34921662. **Exclusion reason:** Ineligible comparator

36. 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

37. Busse JW, MacKillop J. Medical cannabis and cannabinoids for chronic pain: Summary of a Rapid Recommendation. Journal of Military, Veteran and Family Health. 2021;7:118-22. doi: 10.3138/jmvfh-2021-0056. **Exclusion reason:** Ineligible publication type

38. 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:** Used as source document

39. 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:** Used as source document

40. 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

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

42. Clermont-Gnamien S, Atlani S, Attal N, et al. The therapeutic use of Δ9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain. Presse

Medicale. 2002;31(39 I):1840-5. PMID: 12496714. **Exclusion reason:** Not in English

43. 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:** Used as source document

44. 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

45. 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

46. Coughlin LN, Ilgen MA, Jannausch M, et al. Progression of cannabis withdrawal symptoms in people using medical cannabis for chronic pain. Addiction (Abingdon, England). 2021. doi: 10.1111/add.15370. PMID: 33400332. **Exclusion reason:** Ineligible study design

47. 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

48. 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 opinion on drug safety. 2020. doi: 10.1080/14740338.2021.1842871. PMID: 33103931. **Exclusion reason:** Used as source document

49. 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

50. 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

51. 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

52. 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

53. Datta S, Ramamurthy PC, Anand U, et al. Wonder or evil?: Multifaceted health hazards and health benefits of Cannabis sativa and its phytochemicals. Saudi Journal of Biological Sciences.28(12):7290-313. PMID: 34867033. **Exclusion reason:** Ineligible publication type

54. 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

55. 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 outcome

56. 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

57. 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

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

59. 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:** Used as source document

60. Eadie L, Lo LA, Christiansen A, et al. Duration of Neurocognitive Impairment With Medical Cannabis Use: A Scoping Review. Frontiers in Psychiatry. 2021;12. doi: 10.3389/fpsyt.2021.638962. PMID: 33790818. **Exclusion reason:** Used as source document

61. 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

62. 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

63. 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

64. 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

65. 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

66. 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:** Used as source document

67. 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. PMID: 10524471. **Exclusion reason:** Background only

68. 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:** Used as source document

69. 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. Clinical and experimental rheumatology. 2021 PMID: 33938797. **Exclusion reason:** Ineligible study design

70. 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

71. 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. PMID: 34800285. **Exclusion reason:** Ineligible publication type

72. 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

73. 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 comparator

74. 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 comparator

75. 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

76. 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. 2020. doi: 10.1093/pm/pnaa318. PMID: 33123730. **Exclusion reason:** Ineligible comparator

77. 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. PMID: 34695720. **Exclusion reason:** Ineligible comparator

78. 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. PMID: 34767730. **Exclusion reason:** Ineligible comparator

79. Grotenhermen F. Treatment of severe chronic pain with cannabis preparations. Arztliche Praxis Neurologie Psychiatrie. 2002(5):28-30. **Exclusion reason:** Not in English

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238. 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:

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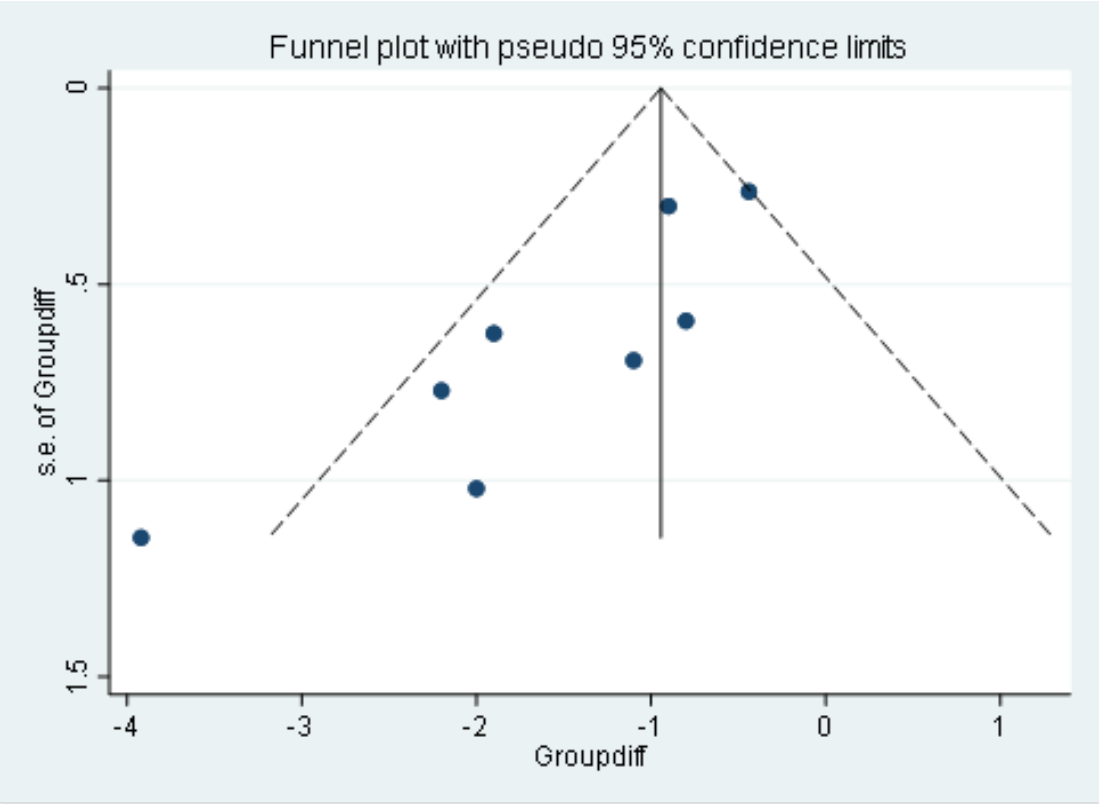
243. Zavori L, Xantus G, Matheson C, et al. Cannabidiol in low back pain: scientific rationale for clinical trials in low back pain. Expert Rev Clin Pharmacol. 2021doi: 10.1080/17512433.2021.1917379. PMID: 33861675. **Exclusion reason:** Background only

244. 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

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

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



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