

# Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2022 Update— Surveillance Report 1

Literature Update Period: April 2022 Through Early July 2022

## Overview

This is the first surveillance report since the annual update of a living systematic review on cannabis and other plant-based treatments for chronic pain.

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

The purpose of this surveillance report is to describe new studies identified since the last search (April 2022) and provide a synthesis of the accumulated evidence. Surveillance update reports are planned on a quarterly basis, and the systematic review will be updated annually. The systematic review is available on the Agency for Healthcare Research and Quality (AHRQ) website (<https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review>). Table 1 provides a summary of the version history.

**Table 1. Version history**

Search End Date	Report (Publication Date)
July 2021	<a href="#">Systematic Review</a> (Oct. 27, 2021)
August 2021	<a href="#">Surveillance Report 1</a> (Oct. 27, 2021)
October 2021	<a href="#">Surveillance Report 2</a> (Jan. 28, 2022)
Mid-January 2022	<a href="#">Surveillance Report 3</a> (May 2022)
March 2022	<a href="#">Surveillance Report 4</a> (August 2022)
April 2022	<a href="#">Systematic Review</a> (August 2022)
Early July 2022	Surveillance Report 1 (September 2022)

## Main Points

The Key Questions (KQs) for this review focus on the benefits (KQ1) and harms (KQ2) of cannabinoids for treating chronic pain, as well as the benefits (KQ3) and harms (KQ4) of other PBCs, such as kratom, for treating chronic pain. Studies of cannabis-related products were grouped based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio using the following categories: high THC to CBD ratio, comparable THC to CBD ratio, and low THC to CBD ratio. One new study<sup>1</sup> comparing nabiximols (plant-extracted comparable THC to CBD ratio) with long-acting opioids for chronic peripheral neuropathic back pain was identified for inclusion during this surveillance period.



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

- Comparable THC to CBD ratio oral spray is probably associated with small improvements in pain severity and function. There may be a large increased risk of dizziness and sedation, and a moderate increased risk of nausea.
- Synthetic THC (high THC to CBD ratio) may be associated with moderate improvement in pain severity but with increased risk of sedation and potential increased risk of nausea. Synthetic THC is probably associated with a large increased risk of dizziness.
- Extracted whole-plant high THC to CBD ratio products may be associated with large increases in risk of withdrawal due to adverse events and dizziness.
- Evidence on whole-plant cannabis, low THC to CBD ratio products (topical or oral CBD), and other cannabinoids (cannabidivarin), and comparisons with other active interventions or between different cannabis-related products (*one new observational study*) was insufficient to draw conclusions.
- Other key adverse event outcomes (i.e., psychosis, cannabis use disorder, cognitive deficits) and outcomes on the impact on opioid use were not reported.
- No evidence on other plant-based compounds, such as kratom, met criteria for this review.

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

**Table 2. Assessment of systematic review conclusions**

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

Key Question <sup>a</sup>	Conclusions From Systematic Review	Findings From Surveillance to Date	Assessment
KQ1 and KQ2. Low THC to CBD Ratio Benefits and Harms	Insufficient evidence (2 RCTs)	No new studies	No change in conclusions
KQ1 and KQ2. Whole-Plant Cannabis and Other Cannabinoids Benefits and Harms	Insufficient evidence (2 RCTs)	No new studies	No change in conclusions
KQ1 and KQ2. Comparable THC to CBD Ratio Vs. Synthetic THC Benefits and Harms	Insufficient evidence (1 observational study)	No new studies	No change in conclusions
KQ1 and KQ2. Comparable THC to CBD Ratio Vs. LAOs	No studies	<b>1 moderate risk of bias observational study of plant-extracted comparable THC to CBD as add-on therapy to current underlying systemic analgesia vs. LAOs (n=1,310)</b>	Insufficient evidence
KQ3 and KQ4. Kratom or Other Plant-Based Substances Benefits and Harms	Insufficient evidence (0 RCTs)	No new studies	No change in conclusions

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

<sup>a</sup> For Key Question wording, see the Background section below.

## Summary of Findings Tables

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

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

THC to CBD Ratio Product	Pain Response Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD - Oromucosal Spray	Potential effect (4) <sup>a</sup> [+]	Small effect (7) [++]	Small effect (6) [++]
High THC – Synthetic, Oral	Moderate effect (1) [+]	Moderate effect (6) [+]	No effect (3) [+]
High THC – Extracted From Whole Plant, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Topical CBD	No evidence	Insufficient (1)	No evidence
Low THC – Oral CBD	No evidence	Insufficient (1)	Insufficient (1)
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence

THC to CBD Ratio Product	Pain Response Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Whole-Plant Cannabis (12% THC) <sup>b</sup>	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.

<sup>a</sup> Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.

<sup>b</sup> Comparison was “usual care.”

Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased benefit; SOE: [+] = low, [++] = moderate, [+++] = high.

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

THC to CBD Ratio Product	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Comparable THC/CBD – Oromucosal Spray	Insufficient (5)	No effect (3) [+]	Large effect (6) [+]	Moderate effect (6) [+]	Large effect (6) [+]
High THC – Synthetic, Oral	Potential effect <sup>a</sup> (4) [+]	Insufficient (1)	Large effect (2) [++]	Potential effect <sup>a</sup> (2) [+]	Moderate effect (3) [+]
High THC – Extracted From Whole Plant, Oral	Large effect (1) [+]	Insufficient (1)	Large effect (1) [+]	No evidence	No evidence
Low THC – Topical CBD	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Oral CBD	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC) <sup>b</sup>	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

<sup>a</sup> Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.

<sup>b</sup> Comparison was “usual care.”

Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: [+] = low, [++] = moderate, [+++] = high.

## Background

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

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

The term *cannabinoid* refers to a group of closely related compounds that are active in cannabis, with the two main cannabinoid compounds being THC and CBD. THC has demonstrated analgesic properties,<sup>12,13</sup> although its psychoactive effects and abuse potential may limit its suitability as an analgesic. CBD may also have some analgesic or anti-inflammatory properties and is thought to be less intoxicating and not addictive.<sup>14,15</sup> While not derived from plants, two synthetic cannabinoid products, dronabinol (synthetic THC) and nabilone (a THC analog), have also been studied for treating chronic pain. Other PBCs with effects similar to opioids or cannabis, such as kratom, have been considered to treat chronic pain. These may also have serious harms, including dependence, addiction, and physiological withdrawal potential.<sup>16</sup>

Four KQs guide the review:

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

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

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

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

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

## Methods

In brief, we searched Ovid<sup>®</sup> MEDLINE<sup>®</sup>, PsycINFO<sup>®</sup>, Embase<sup>®</sup>, the Cochrane Library, and SCOPUS<sup>®</sup> databases monthly through July 8, 2022, for studies of patients with chronic pain with at least 4 weeks of treatment or followup. We selected studies of cannabis, kratom, and similar PBCs compared with a placebo, no treatment, each other, or another treatment. Pain is the primary outcome for this review; details on the search strategies are in [Appendix A](#). Briefly, we included randomized controlled trials (RCTs) and observational studies with a concurrent control group with a minimum of 4 weeks' followup assessing cannabis and other plant-based interventions in adults with noncancer chronic pain. The full inclusion and exclusion criteria for all primary and secondary outcomes for this report are in [Appendix B](#).

We followed the methods guidance in the AHRQ Methods Guide,<sup>17</sup> and abstracted key information and conducted risk-of-bias assessments using the Cochrane Back Pain Group's version of the Cochrane guidance for randomized trials<sup>18</sup> and criteria developed by the U.S. Preventive Services Task Force<sup>19</sup> for observational studies for each included study. Our methods included categorizing studies based on the duration of followup as short-, intermediate-, and long-term. Studies that assessed the cannabinoids THC and/or CBD were grouped based on their THC to CBD ratios and categorized as high THC to CBD ratio, comparable THC to CBD ratio, and low THC to CBD ratio (Table 5). We also grouped studies by whether the product was a whole-plant product (cannabis), cannabinoids extracted or purified from a whole plant, or synthetic. When studies were similar enough to provide a meaningful combined estimate, we conducted meta-analyses using the profile likelihood random effects model and assessed between-study heterogeneity using Cochran's Q statistic chi square and the I<sup>2</sup> test for

inconsistency. Magnitude of benefit was categorized into no effect or small, moderate, and large effects. (See [Appendix B](#), Table B-2.)

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

Intervention Category (Definition)	Source	Possible Derivatives	Example Products	U.S. Availability
<b>High THC</b> (THC to CBD ratio equals $\geq 2:1$ ratio)	Synthetic	Synthetic THC (100% THC or analog)	Dronabinol (Marinol®) or nabilone (Cesamet®)	Available via prescription*
	Synthetic	Purified from whole-plant with close to 100% THC	Purified dronabinol (Namisol®)	Not available in the U.S.
	Plant-based	Commercially marketed product extracted from whole-plant with known high ratio of THC/CBD	THC/CBD extracts with high THC/CBD ratio	Unknown – may be available at dispensaries where allowed
	Plant-based	Whole-plant with known high concentration of THC	Whole-plant cannabis with known high THC concentration	Unknown – may be available at dispensaries where allowed
<b>Comparable THC to CBD</b> (THC to CBD ratio is $< 2:1$ and $> 1:2$ )	Plant-based	Extracted from whole-plant with comparable ratio of THC/CBD	Nabiximols (Sativex®)	Not available in the U.S.
	Plant-based	Extracted from whole-plant with comparable ratio of THC/CBD	Oral tinctures with similar ratio of THC/CBD	Unknown – may be available at dispensaries where allowed
	Plant-based	Whole-plant with known comparable ratio of THC/CBD	Whole-plant with known comparable ratio of THC/CBD	Unknown – may be available at dispensaries where allowed
<b>Low THC</b> (THC to CBD ratio equals $\leq 1:2$ )	Plant-based	Extracted from whole plant with low ratio of THC/CBD	CBD topical or oral	Unknown – may be available at dispensaries where allowed
<b>Whole-Plant Cannabis Products</b> (THC to CBD ratio categorized based on information provided [potentially unknown])	Plant-based	Whole-plant products	Cannabis flowers, resins, buds, leaves, hashish	Unknown – may be available at dispensaries where allowed.
<b>Other Cannabinoids</b> (Cannabinoids other than THC or CBD)	Plant-based	Extracted from whole-plant	Cannabidivarin (CBDV) extracted oil (oral)	Unknown – may be available at dispensaries where allowed

Abbreviations: CBD = cannabidiol; THC = tetrahydrocannabinol.

\* These products are approved by the Food and Drug Administration for non-pain indications (anorexia related to HIV infection, nausea related to chemotherapy).

A more detailed discussion of methods can be found in the [protocol](#) and in [Appendix B](#).

# Results to Date

## Results Overview

Across all of the monthly literature searches to date, 3,419 citations were screened, from which we included 30 studies.<sup>1,20-48</sup>

One new moderate risk of bias retrospective cohort study (n=1,310) met inclusion criteria for this update period. [Appendix C](#) contains a list of included studies, and a literature flow diagram can be found in [Appendix D](#). [Appendix E](#) contains summary tables of individual study data for all included studies and the results of synthesis (i.e., forest plots). [Appendix F](#) contains detailed evidence tables of included studies, and [Appendix G](#) contains risk-of-bias assessments.

[Appendix H](#) contains details on strength-of-evidence ratings. A list of studies excluded after reviewing the full manuscripts can be found in [Appendix I](#) along with reasons for their exclusion. [Appendix J](#) provides a funnel plot of high THC ratio studies included in the meta-analysis for pain severity.

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

**Table 6. Characteristics of included randomized controlled trials to date**

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
<b>THC to CBD Ratio</b>	Comparable (Study Count)	High (Study Count)	High (Study Count)	Low (Study Count)	NA - other cannabinoids
<b>Source</b>	Plant-extracted	Plant-extracted	Synthetic Nabilone Dronabinol Dronabinol/Namisol <sup>®a</sup>	Plant-extracted	Plant-extracted
<b>N Studies</b>	7	2	9	2 (1 topical, 1 oral)	1
<b>Comparator (Study Count)</b>	Placebo (7)	Placebo (2)	Placebo (6); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1)	Placebo (2)	Placebo
<b>Route of Administration, Formulation</b>	Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl	Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)  Oral capsule, 2.5 mg THC/0.8 – 1.8 mg CBD extract (1)	Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Namisol <sup>®a</sup> 3 mg oral tablet (1)	Topical oil, 83 mg CBD/fluid ounce (k =1),  Oral tablet, 10 mg CBD (1)	Oral oil, 50 mg/ml CBDV
<b>Dosing Regimen</b>	108 to 130 mg THC daily (max 22 mg in 3 hours). Final mean dose 23 mg THC/21 mg CBD daily.	Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily  Capsule: 2.5 - 12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily	Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84  Dronabinol capsules: 2.5 -15 mg daily, titrated. Final dose 12.7 mg/day Namisol <sup>®a</sup> tablet: 3 - 8 mg 3 times daily, titrated. Final dose NR	Topical oil: applied locally 1-4 times/day (volume/dose, final dose NR)  Oral tablet: 10 mg daily, titrated (max 3 times daily). Final dose NR	400 mg CBDV daily. Final dose NR

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
<b>Risk of Bias</b>	29% high, 57% moderate, 14% low	50% moderate, 50% low	22% high, 44% moderate, 33% low	50% high (topical), 50% moderate (oral)	100% moderate
<b>Total Randomized</b>	882	297	534	165	34
<b>Age, Mean Years</b>	53	52	50	65	50
<b>Female, %</b>	66%	89%	61%	41%	3%
<b>Non-White,<sup>b</sup> %</b>	1.6% (2)	1% (1)	5.4% (3)	NR	NR
<b>Primary Pain Type (n Studies)</b>	NPP (6); inflammatory arthritis (1)	NPP (1); fibromyalgia (1)	NPP (6); fibromyalgia (1); headache (1); visceral pain (1)	NPP (1 topical); OA (1 oral)	NPP (1)
<b>Baseline Pain Score, Mean (Range)<sup>c</sup></b>	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.46 (4 to 8.1) <sup>d</sup>	5.38 (4.67 to 6.14)	6.28 (6.12 to 6.44)
<b>Study Duration</b>	4 to 15 weeks	8 to 12 weeks	4 to 47 weeks	4 weeks (topical) and 12 weeks (oral)	4 weeks

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

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

<sup>b</sup> (n) = number of studies reporting this characteristic at baseline.

<sup>c</sup> Scores were standardized to a 0 to 10 scale.

<sup>d</sup> Weighted mean includes median scores for 1 study (6 vs. 6).

**Table 7. Characteristics of included observational studies to date**

Characteristic	THC/CBD <sup>a</sup>	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
<b>THC to CBD Ratio</b>	Unclear	High	High	Comparable vs. high	Comparable
<b>Source</b>	Any cannabis product (patient's choice)	Plant-based	Synthetic (nabilone)	Plant-based vs. synthetic	Plant-based
<b>N Studies</b>	5	1	1	1	1
<b>Comparator (Study Count)</b>	No cannabis use (3); usual care (1); no medical cannabis authorization (1)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)	Active comparator; oral mucosal spray vs. dronabinol	Active comparator; oral mucosal spray vs. long-acting opioids, both as add-on therapy to current underlying systemic analgesia
<b>Route of Administration, Formulation</b>	Unreported (any available allowed, patient's choice)	Whole-plant cannabis, "certified 12.5% THC" (CBD NR) route determined by patient: smoking 27%, oral 8%, vaporization 4%, combination 61%	Nabilone 0.5 mg oral capsule	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Dronabinol oral capsule (strength NR)	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Oral long-acting opioids (dose varied)



Characteristic	THC/CBD <sup>a</sup>	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
<b>Dosing Regimen</b>	None specified. Final dose NR	None specified; titrated to max dose 5 g/day. Final median dose 2.5 g/day	None specified; final mean dose 3 mg/day	None specified; final mean dose 16.6/15.4 mg THC/CBD/day vs. 17.2 mg THC/day	None specified; based on individual patient needs; final mean dose 16.7/15.5 mg THC/CBD/day vs. MME 69.4 mg/day
<b>ROB</b>	60% high, 40% moderate	100% high	100% moderate	100% moderate	100% moderate
<b>N Total</b>	12,508	431	156	674	1,310
<b>Age, Mean Years</b>	53	49	61	46	51
<b>Female, %</b>	55%	57%	59%	57%	57%
<b>% Non-White (Study Count)</b>	54% (1); NR (4)	NR	NR	NR	NR
<b>Primary Pain Type(s)</b>	Mixed musculoskeletal, chronic non- cancer pain	Chronic non- cancer pain	NPP	Peripheral NPP	Peripheral neuropathic back pain
<b>Baseline Pain Score, Mean (Range)<sup>b</sup></b>	5.35 (4.56 to 8.00)	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)	4.4 (4.39 to 4.41)	4.32 (4.31 to 4.33)
<b>Study Duration, Weeks (Range)</b>	12 to 208	52	26	24	24

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

<sup>a</sup> Patients could choose any medicinal product they preferred in these studies.

<sup>b</sup> Scores were standardized to a 0 to 10 scale.

## KQs 1 and 2: Benefits and Harms of Cannabis

### Head-to-Head Comparisons of Cannabis-Based Products Versus Long-Acting Opioids

One new retrospective cohort study using a propensity matched analysis of patients with peripheral neuropathic back pain experiencing inadequate pain relief after recommended first- or second-line treatments (n=1,310) compared nabiximols oromucosal spray (plant-based extracted comparable THC to CBD ratio) versus long-acting opioids (LAOs) as add-on therapies.<sup>1</sup> Mean age was 51 years, 57 percent of patients were female, and mean pain intensity at baseline was 43.2 on a pain intensity index [PIX], 0 to 100 scale. Mean daily doses were 16.7mg THC/15.5mg CBD for nabiximols and 69.4 mg morphine milligram equivalents for LAOs.

At 24 weeks there was a small improvement in pain intensity in the nabiximols group compared with the LAO group (PIX 0 to 100 scale mean difference 9.90, 95% confidence interval (CI) 8.05 to 11.75). The nabiximols group also showed statistically significant improvements compared with LAOs in function (Modified Pain Disability Index, 0 to 100 scale, least squares mean difference -22.55, 95% CI -25.22 to -19.88), quality of life (Marburg Questionnaire on Habitual Well-being, least squares mean difference 51.99%, 95% CI 49.00 to 54.98) and depression/anxiety outcomes. There was little change between groups in opioid use at 24 weeks. Fewer patients withdrew from the study due to treatment-related adverse events in the nabiximols group than the LAO group (7.9% vs. 29.3%; relative risk 0.27, 95% CI 0.20 to 0.36).

The study was rated moderate risk of bias; methodological limitations included unclear enrollment procedures and unclear blinding of data analysts to interventions.

## **Conclusion**

One new study comparing comparable THC to CBD ratio products with LAOs as add-on therapies was identified for this surveillance report, but it was insufficient to determine effects on outcomes due to observational design and methodological limitations. Therefore, overall findings are unchanged from the full systematic review. Only short-term evidence is available for cannabis-related interventions containing THC and/or CBD to treat primarily neuropathic chronic pain. Improvement in pain was small to moderate with high and comparable THC to CBD ratio products. Compared with placebo, these interventions resulted in greater risk of common adverse events (dizziness, nausea, sedation) and study withdrawal due to adverse events. Evidence for other interventions, including kratom, was insufficient or not found. Additional studies are needed to improve confidence in these findings and to provide evidence on longer term followup, other outcomes, and other interventions, including whole-plant cannabis.

## **Next Reports**

The next surveillance report update is scheduled for winter 2022.

## References

1. Ueberall MA, Vila Silvan C, Essner U, et al. Effectiveness, Safety, and Tolerability of Nabiximols Oromucosal Spray vs Typical Oral Long-Acting Opioid Analgesics in Patients with Severe Neuropathic Back Pain: Analysis of 6-Month Real-World Data from the German Pain e-Registry. *Pain Med.* 2022b;23(4):745-60. doi: 10.1093/pm/pnab263. PMID: 34480564.
2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain— United States, 2016. *Jama.* 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464. PMID: 26977696.
3. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. *MMWR Recomm Rep.* 2016 Mar 18;65(1):1-49. doi: 10.15585/mmwr.r6501e1. PMID: 26987082.
4. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. . *MMWR Morb Mortal Wkly Rep.* 2018;67(36):1001-6. doi: 10.15585/mmwr.mm6736a2. PMID: 30212442.
5. Institute of Medicine (US) Committee on Advancing Pain Research C, and Education. *Relieving pain in America: a blueprint for transforming prevention, care, education, and research.* Washington, DC: National Academies Press; National Academy of Sciences; 2011.
6. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *The Clinical Journal of Pain.* 2008 Jul-Aug;24(6):469-78. doi: 10.1097/AJP.0b013e31816b2f26. PMID: 18574357.
7. Eriksen J, Sjogren P, Bruera E, et al. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain.* 2006 Nov;125(1):172-9. doi: 10.1016/j.pain.2006.06.009. PMID: 16842922.
8. Chou R, Hartung D, Turner J, et al. *Opioid treatments for chronic pain.* Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER229. PMID: 32338848.
9. McDonagh MS, Selph SS, Buckley DI, et al. *Nonopioid pharmacologic treatments for chronic pain.* Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER228. PMID: 32338847.
10. Skelly AC, Chou R, Dettori JR, et al. *Noninvasive nonpharmacological treatment for chronic pain: a systematic review update.* Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER227. PMID: 32338846.
11. Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain.* 2018 Oct;159(10):1932-54. doi: 10.1097/j.pain.0000000000001293. PMID: 29847469.
12. Elikkottil J, Gupta P, Gupta K. The analgesic potential of cannabinoids. *J Opioid Manag.* 2009 Nov-Dec;5(6):341-57. doi: 10.5055/jom.2009.0034. PMID: 20073408.
13. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *Jama.* 2015 Jun 23-30;313(24):2456-73. doi: 10.1001/jama.2015.6358. PMID: 26103030.
14. Vučković S, Srebro D, Vujović KS, et al. Cannabinoids and pain: new insights from old molecules. *Front Pharmacol.* 2018 Nov 13;9:1259. doi: 10.3389/fphar.2018.01259. PMID: 30542280.
15. Morales P, Hurst DP, Reggio PH. Molecular targets of the phytocannabinoids: a complex picture. *Phytocannabinoids.* 2017:103-31.
16. White CM. Pharmacologic and clinical assessment of kratom: An update. *Am J Health-Syst Pharm.* 2019 Nov 13;76(23):1915-25. doi: 10.1093/ajhp/zxz221. PMID: 31626272.
17. *Methods guide for effectiveness and comparative effectiveness reviews.* Rockville, MD: Agency for Healthcare Research and Quality; 2018. <https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide>. Accessed June 1, 2019.
18. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011 Oct 18;343:d5928. doi: 10.1136/bmj.d5928. PMID: 22008217.

19. Berger ML, Mamdani M, Atkins D, et al. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report--part I. *Value Health*. 2009 Nov-Dec;12(8):1044-52. doi: 10.1111/j.1524-4733.2009.00600.x. PMID: 19793072.
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. 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.
22. 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.
23. 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.
24. Eibach L, Scheffel S, Cardebring M, et al. Cannabidiol 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.
25. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008 Jan 26;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80. PMID: 18182416.
26. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol*. 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.
27. 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.
28. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007 Dec 15;133(1-3):210-20. PMID: 17997224.
29. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. *J Headache Pain*. 2012 Nov;13(8):677-84. doi: 10.1007/s10194-012-0490-1. PMID: 23070400.
30. Rintala DH, Fiess RN, Tan G, et al. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. *Am J Phys Med Rehabil*. 2010 Oct;89(10):840-8. doi: 10.1097/PHM.0b013e3181f1c4ec. PMID: 20855984.
31. 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.
32. 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.
33. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care*. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.
34. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain*. 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.
35. 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.

36. 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.
37. 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.
38. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *PLoS ONE*. 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795. PMID: 29145417.
39. 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.
40. 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.
41. 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.
42. 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.
43. Gruber SA, Smith RT, Dahlgren MK, et al. No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. *Exp Clin Psychopharmacol*. 2021;29(2):147-56. doi: 10.1037/pha0000435. PMID: 33764103.
44. 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.
45. Lee C, Lin M, Martins KJB, et al. Opioid use in medical cannabis authorization adult patients from 2013 to 2018: Alberta, Canada. *BMC Public Health*. 2021;21(1):843. doi: 10.1186/s12889-021-10867-w. PMID: 33933061.
46. Merlin JS, Long D, Becker WC, et al. Marijuana Use Is Not Associated With Changes in Opioid Prescriptions or Pain Severity Among People Living With HIV and Chronic Pain. *J Acquir Immune Defic Syndr*. 2019 06 01;81(2):231-7. doi: 10.1097/QAI.0000000000001998. PMID: 30865181.
47. Vela J, Dreyer L, Petersen KK, et al. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. *Pain*. 2021 Jun 1;163(6):1206-14. PMID: 34510141.
48. Ueberall MA, Essner U, Silván CV, et al. Comparison of the Effectiveness and Tolerability of Nabiximols (THC:CBD) Oromucosal Spray versus Oral Dronabinol (THC) as Add-on Treatment for Severe Neuropathic Pain in Real-World Clinical Practice: Retrospective Analysis of the German Pain e-Registry. *J Pain Res*. 2022a;15:267-86. doi: 10.2147/JPR.S340968. PMID: 35140513.

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The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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# Afterword

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

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

This and future quarterly surveillance reports will provide up-to-date information following the last full systematic review about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov). They will be considered in the next version of the report.

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# Appendix A. Literature Search Strategies

## Database: Ovid MEDLINE(R) ALL 1946 to July 8, 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 cannabiniol 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 June 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,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 cannabiniol 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 July Week 2, 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 cannabiniol 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 July 17, 2022**

('cannabis'/exp OR cannabis OR cannabinoid\* OR 'cannabiniol'/exp OR cannabiniol 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 osteoarthritis) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

## **Database: Elsevier Scopus to July 18, 2022**

( TITLE ( cannabis OR cannabinoid\* OR cannabitol 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	<b>All KQs:</b> 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.	<b>All KQs:</b> 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	<b>KQs 1 and 2:</b> Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes <b>KQs 3 and 4:</b> Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids <b>All KQs:</b> Co-use of other drugs for pain	<b>All KQs:</b> Non-plant-based interventions, capsaicin, herbal supplements
Comparators	<b>All KQs:</b> Any comparator or usual care	<b>All KQs:</b> No comparison
Outcomes	<b>All KQs:</b> 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)	<b>All KQs:</b> Other outcomes
Time of followup	<b>All KQs:</b> short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year)	<b>All KQs:</b> Studies with <1-month (4 weeks) of treatment or followup after treatment
Setting	<b>All KQs:</b> Any nonhospital setting or setting of self-directed care	<b>All KQs:</b> Hospital care, hospice care, emergency department care
Study design	<b>All KQs:</b> RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits	<b>All KQs:</b> Other study designs

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

Important subgroups to consider in evaluating this evidence are:

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

Below are additional details on the scope of this project:

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

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

## Data Extraction

After studies were selected for inclusion, data were abstracted into categories that included but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results relevant to each Key Question as outlined in the previous inclusion and exclusion criteria section. Information that was abstracted that was relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. All study data were verified for accuracy and completeness by a second team member. On a quarterly basis, any newly identified

studies were abstracted and evidence tables updated. Quarterly surveillance reports were published to the Agency for Healthcare Research and Quality (AHRQ) website, and evidence tables will be updated in AHRQ's Systematic Review Data Repository Plus (SRDR+).

## Risk of Bias Assessment of Individual Studies

Predefined criteria were used to assess the risk of bias of individual controlled trials, systematic reviews, and observational studies. RCTs were evaluated using criteria and methods developed by the Cochrane Back Review Group,<sup>1</sup> and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force.<sup>2</sup> 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.<sup>3</sup> Studies were given an overall rating of “low,” “medium,” or “high” risk of bias. We used DistillerSR<sup>®</sup> software to conduct these assessments, using dual review by two independent reviewers. Disagreements identified by DistillerSR<sup>®</sup> were resolved through consensus. Assessments and final ratings were converted to evidence tables, and are uploaded on a quarterly basis to SRDR+.

## Data Synthesis and Analysis

We constructed evidence tables showing study characteristics (as discussed above), results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. Data were qualitatively summarized in tables, using ranges and descriptive analysis and interpretation of the results. Studies identified in prior AHRQ chronic pain reports<sup>4,5</sup> 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  $\geq 12$  months).<sup>4-8</sup>

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.<sup>9</sup> The decision to conduct quantitative synthesis depends on the presence of at least two studies, completeness of reported outcomes, and a lack of heterogeneity among the reported results. To determine whether meta-analyses were indicated, we considered the risk of bias of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. We used a random effects model based on the profile likelihood method<sup>10</sup> to combine interventions with comparable THC to CBD ratios and high-THC trials. The primary analysis for high-THC trials was stratified by the type of derivative used in the intervention (synthetic vs. whole-plant extracts), and statistical heterogeneity was assessed using the  $I^2$  method. Publication bias (small sample size bias) is assessed using funnel plots when there are eight or more studies in meta-analyses. To evaluate subgroup effects, we summarized within-study analyses of subgroup differences and performed study-level analyses on key demographic and clinical factors. Sensitivity analyses were conducted by excluding studies rated as high risk of bias, excluding a trial of Namisol<sup>®11</sup> (purified plant-extracted dronabinol) that was grouped with synthetic dronabinol, and by repeating analyses using a random effects model based on the profile likelihood method with the Bartlett's correction to reduce potential deviation from the null distribution when the number of studies is small.<sup>12</sup> All meta-analyses were conducted using command *metan* and *admetan* in Stata/SE 16.1 (StataCorp, College Station, TX).

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<sup>4-8</sup>

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	<ul style="list-style-type: none"> <li>• 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</li> <li>• SMD 0.2 to 0.5</li> <li>• RR/OR 1.2 to 1.4</li> </ul>
Moderate effect	<ul style="list-style-type: none"> <li>• MD &gt;1 to 2 points on a 0 to 10-point scale, &gt;10 to 20 points on a 0 to 100-point scale</li> <li>• SMD &gt;0.5 to 0.8</li> <li>• RR/OR 1.5 to 1.9</li> </ul>
Large effect	<ul style="list-style-type: none"> <li>• MD &gt;2 points on a 0 to 10-point scale, &gt;20 points on a 0 to 100-point scale</li> <li>• SMD &gt;0.8</li> <li>• RR/OR <math>\geq 2.0</math></li> </ul>

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

Findings that were not statistically significant were interpreted as follows:

- In determining the strength of evidence (SOE), the precision of evidence was downgraded two levels if inadequate sample size (optimal information size) *and* the 95% confidence interval includes both potentially meaningful benefit and harm (e.g., for a relative effect, the lower bound is  $\leq 0.75$  *and* the upper bound is  $\geq 1.25$ ).<sup>13</sup>
- If the magnitude of effect is below the threshold for a small effect, the finding is considered to have “No effect.”<sup>4</sup>
- 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.”<sup>14</sup>

## Grading the Strength of the Body of Evidence

We assessed the strength of evidence for all primary comparisons and outcomes listed in Table B-1. Regardless of whether evidence is synthesized quantitatively or qualitatively, the strength of evidence for each Key Question/body of evidence is initially assessed by one researcher for each clinical outcome by using the approach described in the AHRQ Methods



Guide.<sup>3</sup> To ensure consistency and validity of the evaluation, the strength of evidence is reviewed by the entire team of investigators prior to assigning a final grade on the following factors:

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

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

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

Plain-language statements are used in the Main Points and the Results to Date sections to convey the SOE. High SOE is described as "is associated with" or simply "reduces/increases;" moderate SOE is described as "probably;" and low SOE is described as "may be."<sup>15</sup>

## **Peer Review and Public Commentary**

Peer reviewers are invited to provide written comments on the annual draft report/systematic reviews based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

## Assessing Applicability

Applicability is assessed in accordance with the AHRQ Methods Guide,<sup>16</sup> which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies. For example, exclusion of chronic pain patients with psychiatric comorbidities reduces applicability to clinical practice since many patients with chronic pain have such comorbidities and may respond more poorly to treatment. Similarly, trials that use active run-in periods evaluate highly selected populations who tolerated and responded well to the study intervention, rather than the general population of chronic pain patients being considered for the intervention. Factors that may affect applicability which we have identified a priori include eligibility criteria and patient factors (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical and psychiatric comorbidities, event rates and symptom severity in treatment and control groups), intervention factors (e.g., dose and duration of therapy, intensity and frequency of monitoring, level of adherence, use of co-interventions), comparisons (e.g., type and dosing of comparison), outcomes (e.g., use of unvalidated or nonstandardized outcomes, measurement of short-term or surrogate outcomes), settings (e.g., primary care vs. specialty setting, country), and study design features (e.g., use of run-in periods) relevant to applicability. We use this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

## Appendix B References

1. Furlan AD, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine*. 2009 Aug 15;34(18):1929-41. doi: 10.1097/BRS.0b013e3181b1c99f. PMID: 19680101.
2. U.S. Preventive Services Task Force. *Methods and processes*. 2019. <https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes>.
3. *Methods guide for effectiveness and comparative effectiveness reviews*. Rockville, MD: Agency for Healthcare Research and Quality; 2018. <https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide>. Accessed June 1, 2019.
4. Chou R, Hartung D, Turner J, et al. *Opioid treatments for chronic pain*. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER229. PMID: 32338848.
5. McDonagh MS, Selph SS, Buckley DI, et al. *Nonopioid pharmacologic treatments for chronic pain*. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER228. PMID: 32338847.
6. Skelly AC, Chou R, Dettori JR, et al. *Noninvasive nonpharmacological treatment for chronic pain: a systematic review update*. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/AHRQEPCCER227. PMID: 32338846.
7. Chou R, Deyo R, Friedly J, et al. *Noninvasive treatments for low back pain*: Agency for Healthcare Research and Quality (US), Rockville (MD); 2016. PMID: 26985522.

8. Skelly AC, Chou R, Dettori JR, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review: Agency for Healthcare Research and Quality (US), Rockville (MD); 2018. doi: 10.23970/AHRQEPCCER209. PMID: 30179389.
9. Morton SC, Murad MH, O'Connor E, et al. Quantitative synthesis—an update: Agency for Healthcare Research and Quality (US), Rockville (MD); 2018. PMID: 30125065.
10. Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. *Statistics in medicine*. 1996 Mar 30;15(6):619-29. doi: 10.1002/(SICI)1097-0258(19960330)15:6<619::AID-SIM188>3.0.CO;2-A. PMID: 8731004.
11. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. *Clin Gastroenterol Hepatol*. 2017 Jul;15(7):1079-86.e4. doi: 10.1016/j.cgh.2016.09.147. PMID: 27720917.
12. Huizenga HM, Visser I, Dolan CV. Testing overall and moderator effects in random effects meta-regression. *The British journal of mathematical and statistical psychology*. 2011 Feb;64(Pt 1):1-19. doi: 10.1348/000711010x522687. PMID: 21506942.
13. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol*. 2011 Dec;64(12):1283-93. doi: 10.1016/j.jclinepi.2011.01.012. PMID: 21839614.
14. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012 Feb;141(2 Suppl):53s-70s. doi: 10.1378/chest.11-2288. PMID: 22315256.
15. Gerrity M, Fiordalisi C, Pillay J, et al. AHRQ methods for effective health care. Roadmap for Narratively Describing Effects of Interventions in Systematic Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020. doi: 10.23970/AHRQEPCWHITEPAPERNARRATIVELY. PMID: 33180401.
16. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.

## Appendix C. Included Studies List

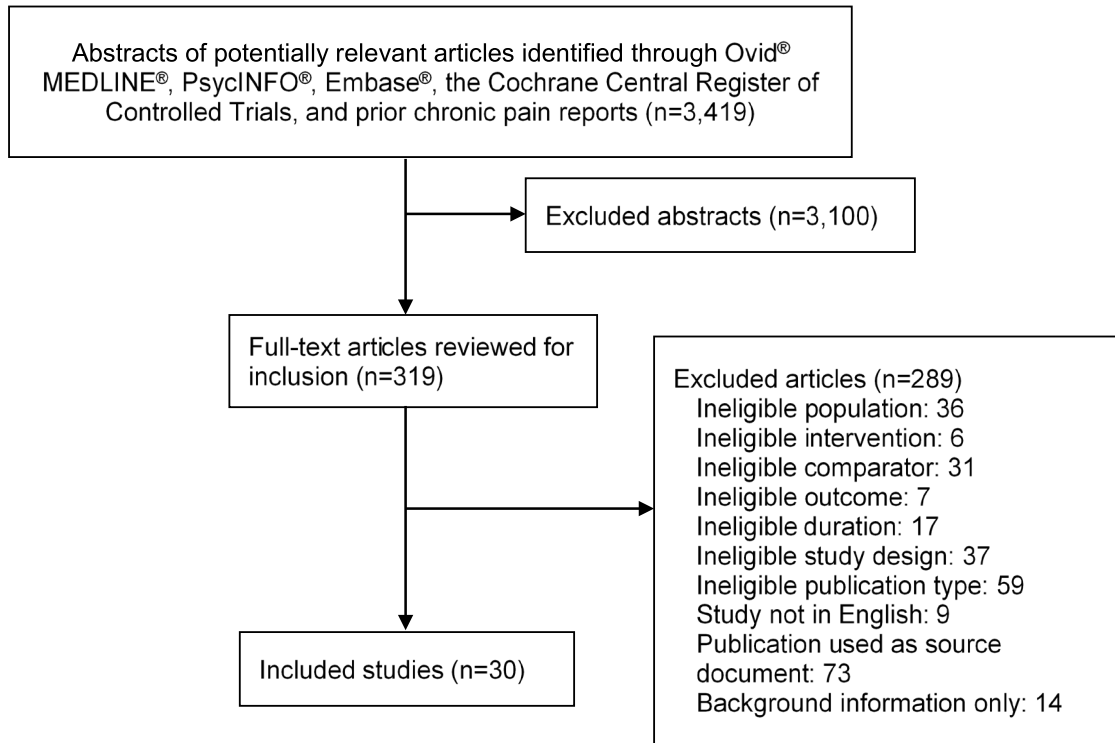
1. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. *Pain Pract.* 2011 Jul-Aug;11(4):353-68. doi: 10.1111/j.1533-2500.2010.00427.x. PMID: 21087411.
2. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford).* 2006 Jan;45(1):50-2. PMID: 16282192.
3. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health.* 2018 Jul;3(7):e341-e50. doi: 10.1016/s2468-2667(18)30110-5. PMID: 29976328.
4. Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a thc-rich cannabis oil in people with fibromyalgia: a randomized, double-blind, placebo-controlled clinical trial. *Pain Med.* 2020;21(10):2212-8. doi: 10.1093/pm/pnaa303. PMID: 33118602.
5. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. *Clin Gastroenterol Hepatol.* 2017 Jul;15(7):1079-86.e4. doi: 10.1016/j.cgh.2016.09.147. PMID: 27720917.
6. Eibach L, Scheffel S, Cardebring M, et al. Cannabidiol for HIV-associated neuropathic pain: a randomized, blinded, controlled clinical trial. *Clin Pharmacol Ther.* 2020 Aug 08;109(4):1055-62. doi: 10.1002/cpt.2016. PMID: 32770831.
7. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ.* 2008 Jan 26;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80. PMID: 18182416.
8. Gruber SA, Smith RT, Dahlgren MK, et al. No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. *Exp Clin Psychopharmacol.* 2021. doi: 10.1037/pha0000435. PMID: 33764103.
9. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol.* 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.
10. Lee C, Lin M, Martins KJB, et al. Opioid use in medical cannabis authorization adult patients from 2013 to 2018: Alberta, Canada. *BMC Public Health.* 2021;21(1):843. doi: 10.1186/s12889-021-10867-w. PMID: 33933061.
11. 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.
12. Merlin JS, Long D, Becker WC, et al. Marijuana Use Is Not Associated With Changes in opioid prescriptions or pain severity among people living with HIV and chronic pain. *J Acquir Immune Defic Syndr.* 2019 06 01;81(2):231-7. doi: 10.1097/QAI.0000000000001998. PMID: 30865181.
13. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain.* 2007 Dec 15;133(1-3):210-20. PMID: 17997224.
14. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. *J Headache Pain.* 2012 Nov;13(8):677-

84. doi: 10.1007/s10194-012-0490-1. PMID: 23070400.
15. Rintala DH, Fiess RN, Tan G, et al. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. *Am J Phys Med Rehabil.* 2010 Oct;89(10):840-8. doi: 10.1097/PHM.0b013e3181f1c4ec. PMID: 20855984.
  16. 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.
  17. 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.
  18. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care.* 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.
  19. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain.* 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.
  20. 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.
  21. 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.
  22. 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.
  23. Ueberall MA, Essner U, Silván CV, et al. Comparison of the effectiveness and tolerability of nabiximols (thc:cbd) oromucosal spray versus oral dronabinol (thc) as add-on treatment for severe neuropathic pain in real-world clinical practice: retrospective analysis of the German Pain e-registry. *J Pain Res.* 2022a;15:267-86. doi: 10.2147/JPR.S340968. PMID: 35140513
  24. Ueberall MA, Vila Silvan C, Essner U, et al. Effectiveness, Safety, and Tolerability of Nabiximols Oromucosal Spray vs Typical Oral Long-Acting Opioid Analgesics in Patients with Severe Neuropathic Back Pain: Analysis of 6-Month Real-World Data from the German Pain e-Registry. *Pain Med.* 2022b;23(4):745-60. doi: 10.1093/pm/pnab263. PMID: 34480564.
  25. 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.
  26. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *PLoS ONE.* 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795. PMID: 29145417.
  27. 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.
  28. 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.
  29. 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.
  30. 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.

# Appendix D. Literature Flow Diagram

Figure D-1. Literature flow diagram



**Note:** Numbers in parenthesis indicate all records identified up to July 2022.

# Appendix E. Results

## Individual Study Summary Tables

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



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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Blake, 2006 Moderate RCT Inflammatory arthritis- rheumatoid arthritis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 5.4 sprays/day (31) B: Placebo (27) 5 weeks Whole plant extracted	Pain severity (mean [SD NR] 0 to 10 NRS scale): 3.1 vs. 4.1, MD -1.04 <sup>b</sup> (95% CI -1.9 to -0.18)	SAE: 0/31 (0%) vs. 2/27 (7.41%), RR 0.18 (95% CI 0.01 to 3.49) WAE: 0/31 (0%) vs. 3/27 (11.11%), RR 0.13 (95% CI 0.01 to 2.32)	Function (mean [SD NR] 0 to 10 28-Joint Disease Activity Score scale): 5 vs. 5.9, MD -0.76 <sup>c</sup> (95% CI -1.23 to -0.28)
Langford, 2013 Low RCT Neuropathic pain- multiple sclerosis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.8 sprays/day (167) B: Placebo (172) 15 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 83/167 (49.75%) vs. 77/172 (44.77%), RR 1.11 (95% CI 0.89 to 1.39)  Pain severity (mean [SD] 0 to 10 NRS scale): 4.54 (2.24) vs. 4.73 (2.26), MD -0.19 (SE 0.24) (95% CI -0.67 to 0.29)	WAE: 14/167 (8.38%) vs. 9/172 (5.23%), RR 1.60 (95% CI 0.71 to 3.60)	Pain interference (0 to 10 BPI-SF scale): Treatment difference -0.12, p=0.56  Function (0 to 100 SF-36 Physical Functioning scale): Treatment difference -0.45, p=0.785
Lynch, 2014 High RCT (crossover) Neuropathic pain- chemotherapy induced	A: THC/CBD oromucosal spray (dose NR), mean dose 8 sprays/day (8) B: Placebo (8) 4 weeks Whole plant extracted	Pain severity (mean, 0 to 10 NRS-PI scale): 6 (95% CI 6.98 to 5.02) vs. 6.38 (95% CI 5.67 to 7.09)	SAE: 0/8 (0%) vs. 0/8 (0%), RR 1.00 (95% CI 0.02 to 45.13) WAE: 0/8 (0%) vs. 0/8 (0%), RR 1.00 (95% CI 0.02 to 45.13)	Function (mean [SD] 0 to 100 SF-36 Physical Functioning scale): 35.5 (9.19) vs. 46.5 (8.5), MD -11 (4.43) (95% CI -20.49 to -1.51)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Nurmikko, 2007 Moderate RCT Neuropathic pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 10.9 sprays/day (63) B: Placebo (62) 5 weeks Whole plant extracted	Pain response $\geq 30\%$ (NRS scale): 16/73 (25.4%) vs. 9/62 (14.52%), RR 1.75 (95% CI 0.84 to 3.66)  Pain severity (mean [SD NR] 0 to 10 NRS scale): 5.82 vs. 6.68, treatment difference $-0.96$ (95% CI $-1.59$ to $-0.32$ )	SAE: 1/63 (1.6%) vs. 0/62 (0%), RR 2.95 (95% CI 0.12 to 71.13) WAE: 11/63 (17.46%) vs. 2/62 (3.23%), RR 5.41 (95% CI 1.25 to 23.43)	Function (0 to 70 Pain Disability Index scale): MD $-5.85$ (95% CI $-9.62$ to $-2.09$ )
Rog, 2005 Moderate RCT Neuropathic pain- multiple sclerosis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 9.6 sprays/day (34) B: Placebo (32) 5 weeks Whole plant extracted	Pain severity (mean [95% CI] 0 to 10 NRS scale): 3.85 (3.13 to 4.58) vs. 4.96 (4.19 to 5.72), treatment difference $-1.25$ (95% CI $-2.11$ to $-0.39$ )	SAE: 0/34 (0%) vs. 0/32 (0%), RR 0.94 (95% CI 0.02 to 46.16) WAE: 2/34 (5.88%) vs. 0/32 (0%), RR 4.71 (95% CI 0.23 to 94.58)	NR
Selvarajah, 2010 High RCT Neuropathic pain- diabetic neuropathy	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 7 sprays/day <sup>d</sup> (15) B: Placebo (14) 12 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 100 NPS scale): 51.6 (21.9) vs. 51.9 (24.1), MD $-0.3$ (SE 8.54) (95% CI $-17.83$ to 17.23)	NR	Function (mean [SD] 0 to 100 SF-36 Physical Functioning scale): 30.5 (16.6) vs. 36.5 (27.9), MD 6 (SE 8.5) (95% CI $-11.35$ to 23.35)
Serpell, 2014 Moderate RCT Neuropathic pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.9 sprays/day (128) B: Placebo (118) 15 weeks Whole plant extracted	Pain response $\geq 30\%$ (NRS scale): 34/123 (27.64%) vs. 19/117 (16.24%), RR 1.7 (95% CI 1.03 to 2.91)  Pain severity (mean [SE NR] 0 to 10 NRS scale): Mean reduction $-0.34$ (0.23) (95% CI $-0.79$ to 0.11)	SAE: 10/128 (7.81%) vs. 7/118 (6%), RR 1.32 (95% CI 0.52 to 3.35) WAE: 25/128 (19.53%) vs. 25/118 (21.19%), RR 0.92 (95% CI 0.56 to 1.51)	Pain interference (0 to 10 BPI-SF scale): Treatment difference $-0.32$ (SE 0.241) (95% CI $-0.8$ to 0.15)

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

<sup>a</sup> Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

<sup>b</sup> Difference in median differences.

<sup>c</sup> Difference in mean differences.

<sup>d</sup> Mean sprays calculated by systematic review team.

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Chaves, 2020 Low RCT Fibromyalgia	A: 1.2 mg THC/0.02 mg CBD sublingual drops, mean 3.6 drops/day (8) B: Placebo (9) 8 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 FIQ scale): 3.75 (2.49) vs. 7.67 (1.84), MD -3.92 (1.05) (95% CI -6.17 to -1.68)	WAE: 0/8 (0%) vs. 0/9 (0%), RR 1.11 (95% CI 0.02 to 50.43)	Function (mean [SD] 0 to 10 FIQ scale): 5.83 (2.02) vs. 4.07 (2.25), MD 1.76 (1.04) (95% CI -0.46 to 3.98)
de Vries, 2017 Moderate RCT Visceral pain- chronic pancreatitis and postsurgical abdominal pain	A: THC oral tablet (Dronabinol), range 15 to 24 mg/day (30) B: Placebo (32) 7 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 2.4 (2.28) vs. 3.5 (2.42), MD -1.1 (SE 0.68) (95% CI -2.46 to 0.26)	WAE: 7/30 (23.33%) vs. 2/32 (6.25%), RR 3.73 (95% CI 0.84 to 16.57)	NR
Frank, 2008 Moderate RCT (crossover) Neuropathic pain	A: THC oral capsule (Nabilone), max dose 2 mg/day (48) B: Dihydrocodeine 30 mg, max dose 240 mg/day (48) 6 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): Treatment effect 5.7 (95% CI 0.5 to 10.9)	SAE: 0/48 (0%) vs. 0/48 (0%), RR 1.00 (95% CI 0.02 to 49.39) WAE: 2/48 (4%) vs. 6/48 (12.5%), RR 0.33 (95% CI 0.07 to 1.57)	Function (mean [SD NR] 0 to 100 SF-36 Physical Functioning scale): Treatment effect 10.8 (95% CI 2.3 to 19.2)

<b>Author, Year Risk of Bias Study Design Pain Condition</b>	<b>Comparison (n) Followup Duration Derivative</b>	<b>Primary Pain Outcomes (Response, Severity)</b>	<b>Serious Adverse Events and Withdrawals Due to Adverse Events<sup>a</sup></b>	<b>Other Primary Outcomes (Function/Disability, Pain Interference)</b>
Pini, 2012 Low RCT (crossover) Headache- medication overuse headache	A: THC 0.5 mg oral capsule (Nabilone) daily (26) B: Ibuprofen 400 mg/day (26) 8 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 5.55 (2.5) vs. 6.75 (2.4), MD -1.2 (0.68) (95% CI -2.57 to 0.17)	WAE: 1/30 (3.33%) vs. 1/30 (3.33%), RR 1.00 (95% CI 0.07 to 15.26)	NR
Rintala, 2010 High RCT (crossover) Neuropathic pain- spinal cord injury	A: THC 5 mg oral capsule (Dronabinol), max dose 20 mg/day (7) B: Diphenhydramine 25 mg, max dose 75 mg/day (5) 47 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 BPI scale): 5.8 vs. 5.8	SAE: 1/7 (14.29%) vs. 1/5 (20%), RR 0.71 (95% CI 0.06 to 8.91) WAE: 1/7 (14.29%) vs. 0/5 (0%), RR 2.25 (95% CI 0.11 to 46.13)	NR
Schimrigk, 2017 Low RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg oral capsule (Dronabinol), mean dose 13 mg/day (124) B: Placebo (116) 16 weeks Synthetic	Pain severity (mean [SD] 0 to 10 NRS scale): 4.48 (2.04) vs. 4.92 (2.04), MD NR, p=0.676	SAE: 12/124 (9.68%) vs. 7/116 (6.03%), RR 1.53 (95% CI 0.63 to 3.76) WAE: 19/124 (15.32%) vs. 12/116 (10.34%), RR 1.48 (95% CI 0.75 to 2.91)	NR
Skrabek, 2008 Moderate RCT Fibromyalgia	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 2 mg/day (15) B: Placebo (18) 4 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 VAS scale): 4.8 vs. 5.6, MD -1.43, p<0.05	SAE: 0/15 (0%) vs. 0/18 (0%), RR 1.19 (95% CI 0.02 to 56.54) WAE: 1/20 (5%) vs. 1/20 (5%), RR 1.00 (95% CI 0.07 to 14.90)	NR
Toth, 2012 Low RCT Neuropathic pain- diabetic neuropathy	A: THC 0.5 mg oral capsule (Nabilone), max dose 4 mg/day (13) B: Placebo (13) 5 weeks Synthetic	Pain response ≥30% (NRS scale): 11/13 (84.62%) vs. 5/13 (38.46%), RR 2.2 (95% CI 1.06 to 4.55)  Pain severity (mean [SD] 0 to 10 NRS scale): 3.5 (1.3) vs. 5.4 (1.7), MD -1.9 (0.59) (95% CI -3.13 to -0.68)	NR	Pain interference (mean [SD] 0 to 10 MBPI scale): 2.5 (1.6) vs. 3.6 (0.9), MD -1.1 (0.51) (95% CI -2.15 to -0.05)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Turcotte, 2015 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), max dose 2 mg/day (8) B: Placebo (7) 9 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): 35 vs. 57 <sup>b</sup>	SAE: 0/8 (0%) vs. 0/7 (0%), RR 0.89 (95% CI 0.02 to 39.84) WAE: 1/8 (12.5%) vs. 0/7 (0%), RR 2.67 (95% CI 0.13 to 56.63)	Pain interference (mean [SD NR] 0 to 100 VAS impact scale): 41 vs. 40 <sup>b</sup>
Wissel, 2006 High RCT (crossover) Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 1 mg/day (13) B: Placebo (13) 4 weeks Synthetic	Pain severity (median [SD NR] 11 Point Box Test): 4 vs. 6, p<0.05	WAE: 2/13 (15.38%) vs. 0/13 (0%), RR 5.00 (95% CI 0.26 to 95.02)	NR
Zajicek, 2012 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg capsule, max dose 25 mg/day (143) B: Placebo (134) 12 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 CRS scale): 4.1 (2.9) vs. 4.7 (3.0), MD -0.6 (95% CI -1.3 to 0.1)	SAE: 7/143 (4.9%) vs. 3/134 (2.24%), RR 2.19 (95% CI 0.58 to 8.28) WAE: 30/143 (20.98%) vs. 9/134 (6.72%), RR 3.12 (95% CI 1.54 to 6.33)	NR

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

<sup>a</sup> Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

<sup>b</sup> Estimated from graph.

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

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Vela, 2021 Moderate RCT Musculoskeletal - hand osteoarthritis and psoriatic arthritis	A: CBD oral tablet (20 to 30 mg/day) (68) B: Placebo (61) 12 weeks Synthetic CBD	Pain response $\geq 30\%$ (VAS 0 to 100 scale): 27/68 (39.7%) vs. 24/61 (39.3%), RR 1.01 (95% CI 0.66 to 1.55)  Pain severity (0 to 100 VAS scale): mean NR, MD 0.23 (95% CI -9.41 to 9.9)	SAE: 2/58 (3.4%) vs. 2/61 (3.3%), RR 1.05 (95% CI 0.15 to 7.22) WAE: 0/70 (0%) vs. 2/66 (3%), RR 0.19 (95% CI 0.01 to 3.86)	Function/disability (0 to 3 HAQ-DI scale): mean NR, MD 0.03 (95% CI -0.11 to 0.18)
Xu, 2020 High RCT (crossover) Neuropathic pain- mixed	A: CBD cream (250 mg/3 oz) up to 4 times daily (15) B: Placebo (14) 4 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 NPS scale): 3.33 (2.02) vs. 5.55 (2.81), MD -2.22 (95% CI -4.07 to -0.37)	SAE: 0/15 (0%) vs. 0/14 (0%)	NR

Abbreviations: CBD = cannabidiol; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire Disability Index; MD = mean difference; NPS = neuropathic pain scale; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; THC = tetrahydrocannabinol.

<sup>a</sup> Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

**Table E-4. Other cannabinoids study primary outcomes**

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Eibach, 2020 Moderate RCT (crossover) Neuropathic pain- HIV associated	A: CBDV oral solution (50 mg/mL) 400 mg/day (16) B: Placebo (16) 4 weeks Whole plant extracted	Pain response $\geq 30\%$ (NRS scale): 6/16 (37.5%) vs. 13/16 (81.25%), RR NR  Pain severity (mean [SD] 0 to 10 NRS scale): 2.74 (1.47) vs. 3.67 (2.62), MD -0.62 (95% CI -0.27 to 1.51)	SAE: 1/16 (6.25%) vs. 0/16 (0%), RR 3.00 (95% CI 0.13 to 68.57) WAE: 1/16 (6.25%) vs. 0/16 (0%), RR 3.00 (95% CI 0.13 to 68.57)	Pain interference (0 to 10 BPI-SF scale): MD -0.35 (95% CI -1.36 to 0.43)

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

<sup>a</sup> Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

**Table E-5. Observational study primary outcomes**

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Bestard, 2011 Moderate Prospective cohort Neuropathic pain- mixed	A: THC oral capsule (Nabilone), mean dose 3.05 mg/day (49) B: Gabapentin, mean dose 2,295.5 mg/day (52) C: Gabapentin + THC capsule, mean dose NR + 3.02 mg/day (55) 6 months Synthetic	Pain intensity (mean [SD] 0 to 100 VAS scale): 28.0 (10.5) vs. 33.8 (11.6) vs. 33.1 (20.2), MD -5.8 (95% CI -10.18 to -1.42) for A vs. B, -5.1 (95% CI -11.48 to 1.28) for A vs. C	SAE: 0/49 (0%) vs. 0/52 (0%) vs. 0/55 (0%) WAE: 5/49 (10%) vs. 12/52 (23%) vs. 5/55 (9%), RR 0.44 (95% CI 0.17 to 1.16 for A vs. B, RR 1.12 (95% CI 0.34 to 3.65) for A vs. C, RR 2.54 (95% CI 0.96 to 6.71) for B vs. C	Pain interference (mean [SD] 0 to 10 BPI scale): 4.5 (2.3) vs. 4.6 (2.2) vs. 4.5 (2.2), MD -0.1 (95% CI -0.99 to 0.79) for A vs. B, MD 0.00 (95% CI -0.88 to 0.88) for A vs. C  Function (mean [SD] 0 to 100 SF-36 scale <sup>a</sup> ): 48.3 (27.2) vs. 46.5 (25.1) vs. 43.7 (26.4), MD 1.80 (95% CI -8.53 to 12.13) for A vs. B, MD 4.60 (95% CI - 5.83 to 15.03) for A vs. C
Campbell, 2018 Moderate	A: Self-reported frequent cannabis use of ≥20 days/mo B: No cannabis use  Overall N Baseline: 1,514 4-year followup: 1,217 Groups unclear 4 years Unclear THC concentration; patient- driven choice	A vs. B (reference) Pain intensity (Adjusted mean [SE]; BPI, 0-10 scale): 5.2 (0.14) vs. 4.9 (0.03); Beta: 0.37 (95% CI, -0.23 to 1.10), p=0.20	A vs. B Pain Interference (Adjusted mean [SE]; BPI pain interference, 0 to 10 scale): 5.2 (0.19) vs. 5.4 (0.04); Beta: -0.63 (95% CI, -1.46 to 0.19), p=0.13	NR
Gruber, 2021 High Prospective cohort Mixed (primarily musculoskeletal)	A: THC/CBD: Medicinal cannabis program, mean dose THC 13.3 mg/day, CBD 28.9 mg/day (37) B: Usual care, dose NA (9) 12 weeks Mixed cannabis products	Pain intensity (mean [SD] 0 to 100 VAS scale): 34.07 (22.36) vs. 48.78 (30.42); MD -14.71 (95% CI, -32.71 to 3.29)	NR	A vs. B Function (mean [SD], 0 to 10 PDI scale): 18.13 (12.26) vs. 19.22 (12.73); MD -1.09 (95% CI -10.33 to 8.16)  SF-36 Function (mean [SD], 0 to 100 scale <sup>a</sup> ): 70.00 (22.87) vs. 69.44 (26.98); MD 0.56 (95% CI -17.17 to 18.29)

<b>Author, Year Risk of Bias Study Design Pain Condition</b>	<b>Comparison (n) Followup Duration Derivative</b>	<b>Primary Pain Outcomes (Response, Severity)</b>	<b>Serious Adverse Events and Withdrawals Due to Adverse Events<sup>a</sup></b>	<b>Other Primary Outcomes (Function/Disability, Pain Interference)</b>
Lee, 2021 <sup>b</sup> 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 <sup>b</sup> High Prospective cohort Chronic non-cancer pain (HIV)	A: Daily or weekly use of marijuana (55) B: Monthly or 1-2 times a month use of marijuana (65) C: No use (313) 52 weeks Unknown THC concentration; patient-driven choice	NR	NR	NR
Ueberall, 2022a Moderate Retrospective cohort Peripheral neuropathic pain	A: Nabiximols as an add-on treatment; 16.6 (SD 6.5) mg THC/15.4 (SD 4.1) mg CBD/day (337) B: Dronabinol as an add-on treatment; 17.2 (SD 7.6) mg THC/day (337) 24 weeks Whole plant extracted vs. synthetic	A vs. B Pain intensity index (VAS 0-100 scale) mean relative change (improvement) rates at week 24 83.4% vs. 75.9%, p<0.001 Pain intensity index (VAS 0-100 scale, converted to 0-10) mean difference: 3.50 (95% CI 1.6 to 5.4)	NR	A vs. B Pain-related disabilities (VAS 0-100 scale) mean relative change (improvement) rates at week 24 76.0% vs. 68.3%, p<0.001



Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Serious Adverse Events and Withdrawals Due to Adverse Events <sup>a</sup>	Other Primary Outcomes (Function/Disability, Pain Interference)
Ueberall, 2022b Moderate Retrospective cohort Peripheral neuropathic back pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 16.7 mg THC/15.5 mg CBD/day (655) B: Long-acting opioid, MME 69.4 mg/day 24 weeks Whole plant extracted and long-acting opioid	Pain intensity index (mean relative change from baseline at week 24, 0 to 100 VAS scale): -72.3% (SD 30.5) vs. -49.2% (SD 39.9)  Pain intensity index (VAS 0-100 scale, converted to 0-10) mean difference: 9.90 (95% CI 8.05 to 11.75)	Pain-related disabilities (mean relative change [improvement] rates at week 24, 0 to 100 VAS scale): -66.1 (28.7) vs. -42.9 (34.5), p<0.001	WAE: 7.9% vs. 29.3%, RR 0.27 (95% CI 0.20 to 0.36)
Vigil, 2017 <sup>b</sup> High Preliminary historical cohort Mixed musculoskeletal pain	A: THC/CBD: Participation in New Mexico Medical Cannabis Program (37) B: Not participating in medical marijuana program and not using cannabis (29) 21 months Unknown THC concentration	NR	NR	NR
Ware, 2015 High Prospective cohort Chronic non-cancer pain	A: THC 12.5 +/- 1.5% herbal cannabis, median dose 2.5 g/day (215) B: Usual care (216) 13 months Whole plant non- extracted	NR	SAE: 28/215 (13%) vs. 42/216 (19.4%), RR 0.67 (95% CI 0.43 to 1.04) WAE: 10/215 (4.65%) vs. NR (assumed 0)	NR

Abbreviations: BPI = brief pain inventory; CBD = cannabidiol; CI = confidence interval; MD = mean difference; NA = not applicable; NR = not reported; PDI = Pain Disability Index; SAE = serious adverse events; SD = standard deviation; SF-36= short form-36; THC = tetrahydrocannabinol; VAS = visual analog scale; WAE = withdrawal due to due adverse events.

<sup>a</sup> Higher scores indicate better outcomes.

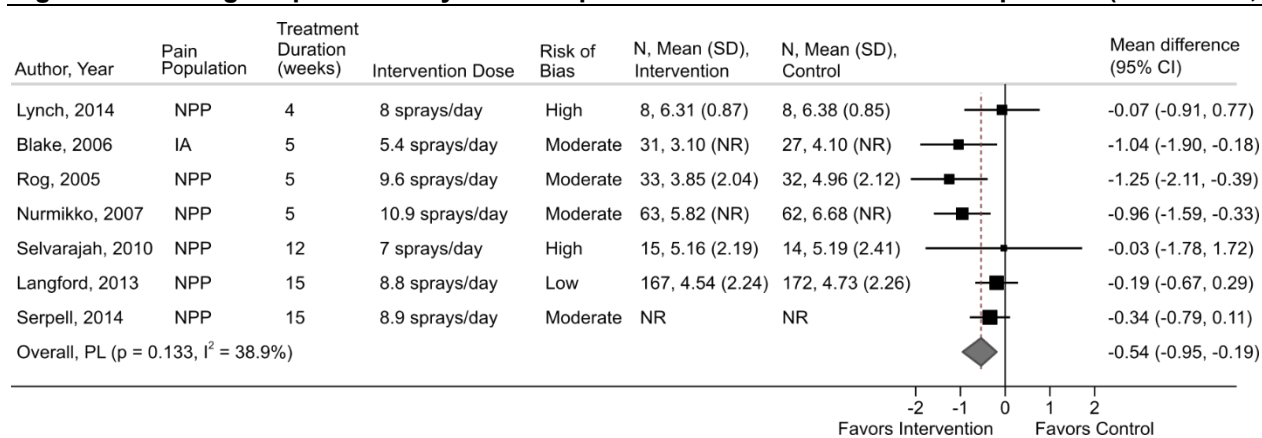
<sup>b</sup> Only included outcome reported was opioid-use.

# Meta-Analysis Results

## Comparable THC to CBD Ratio Studies

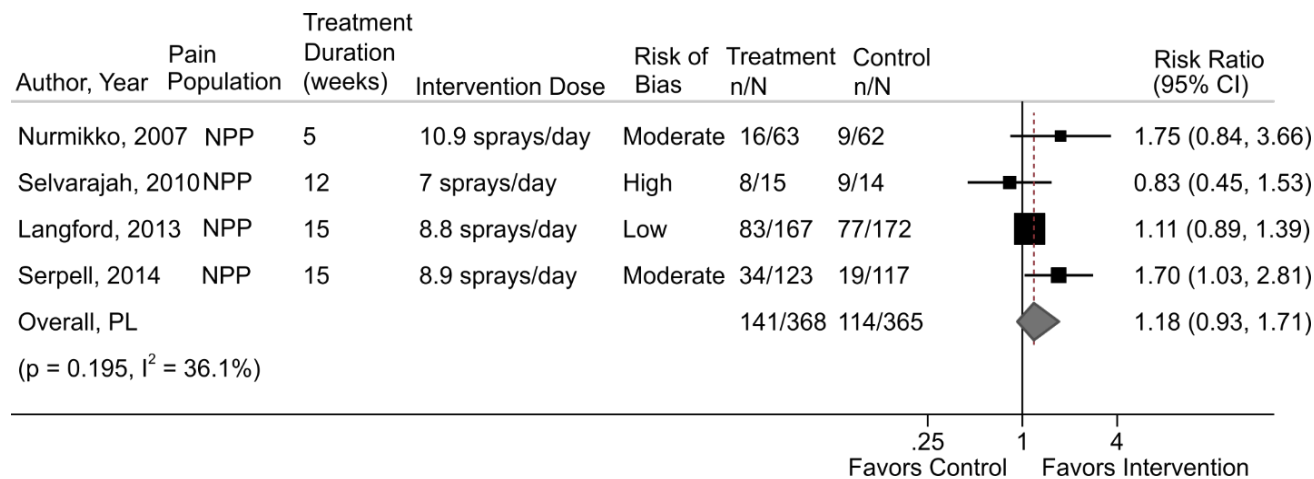
Pooled results and the forest plot for the sensitivity analysis conducted for improvement in pain severity are available upon request by emailing [wagnerje@ohsu.edu](mailto:wagnerje@ohsu.edu).

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



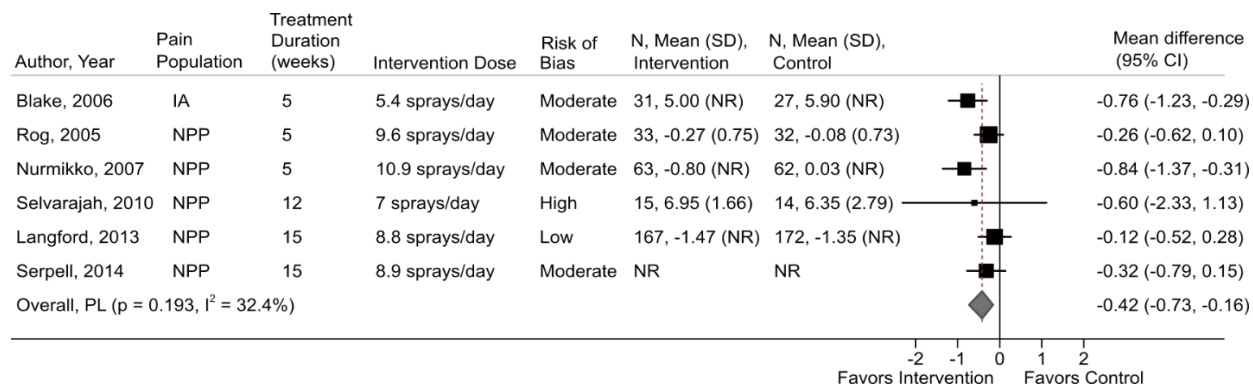
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation.

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



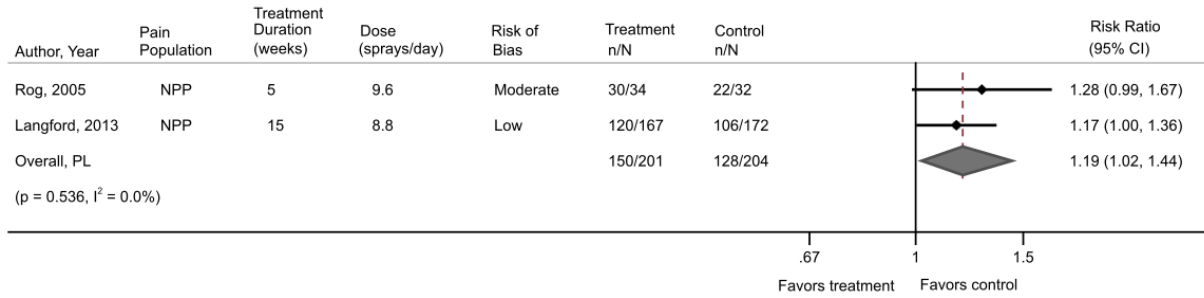
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood.

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



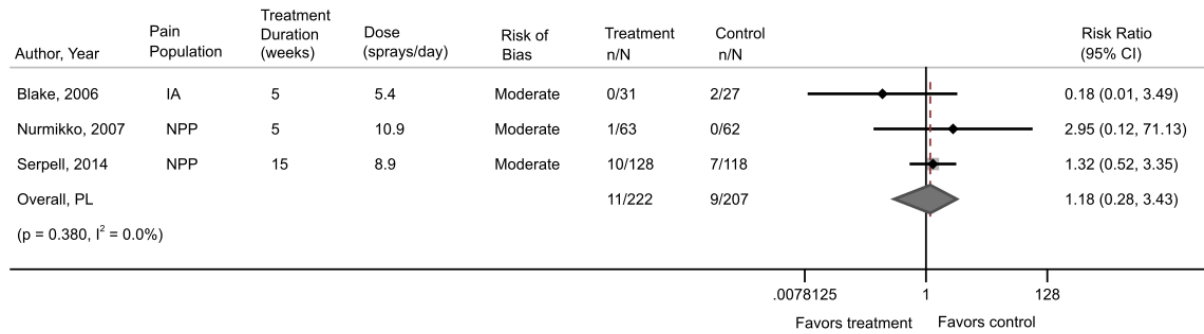
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation.

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



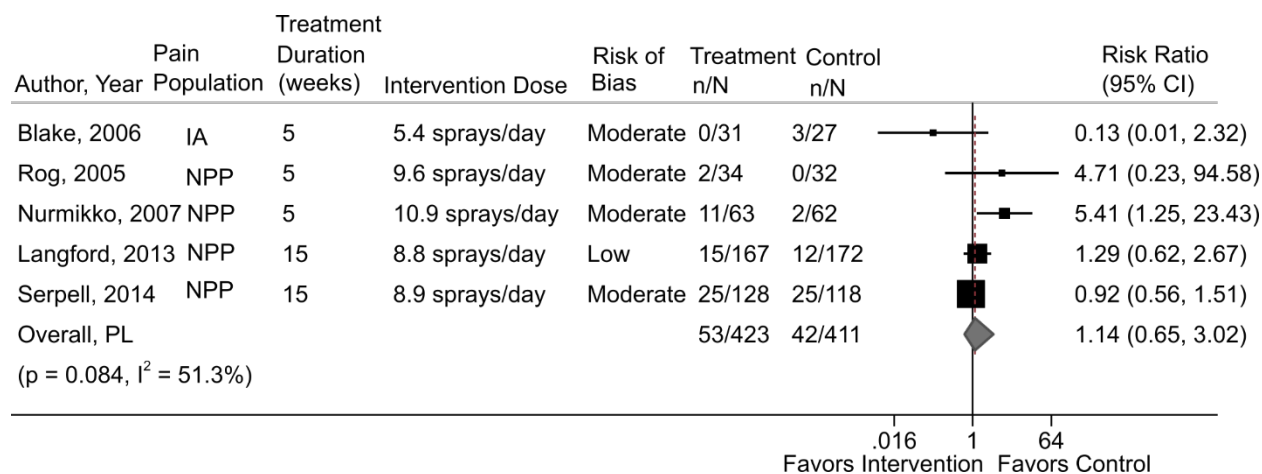
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile-likelihood.

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



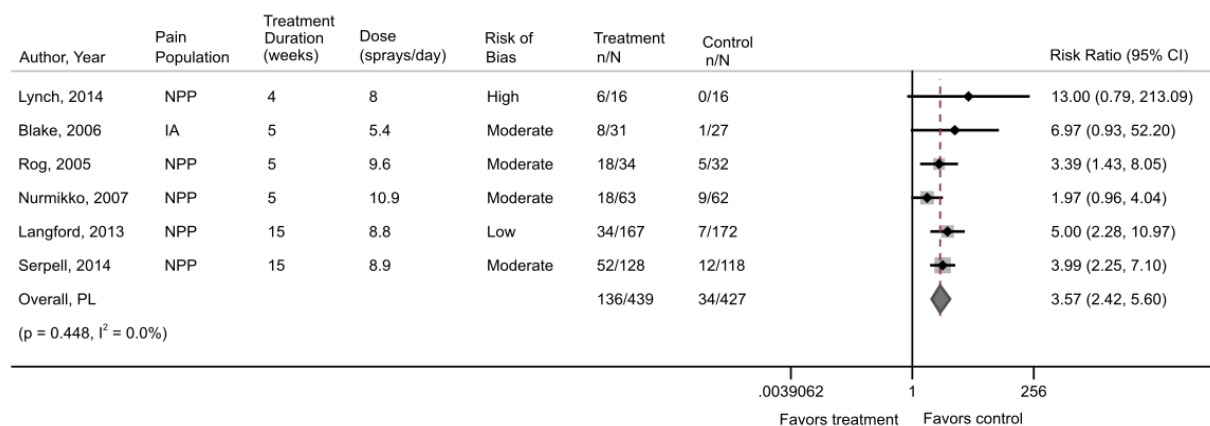
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile-likelihood.

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



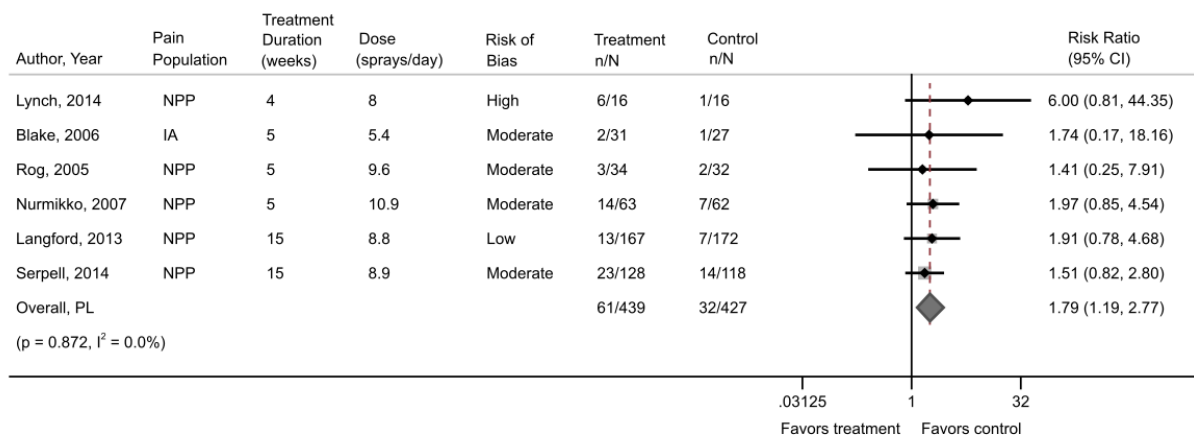
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile-likelihood.

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



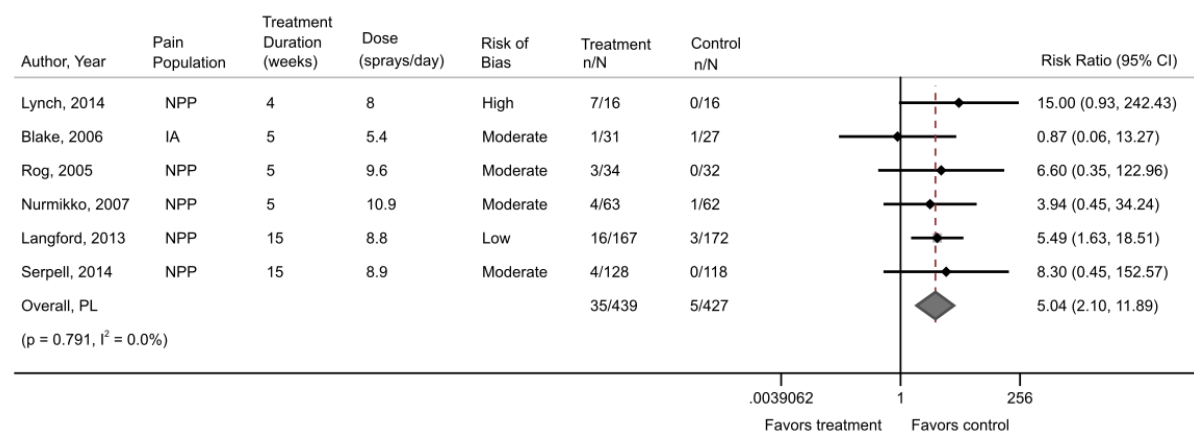
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood.

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



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

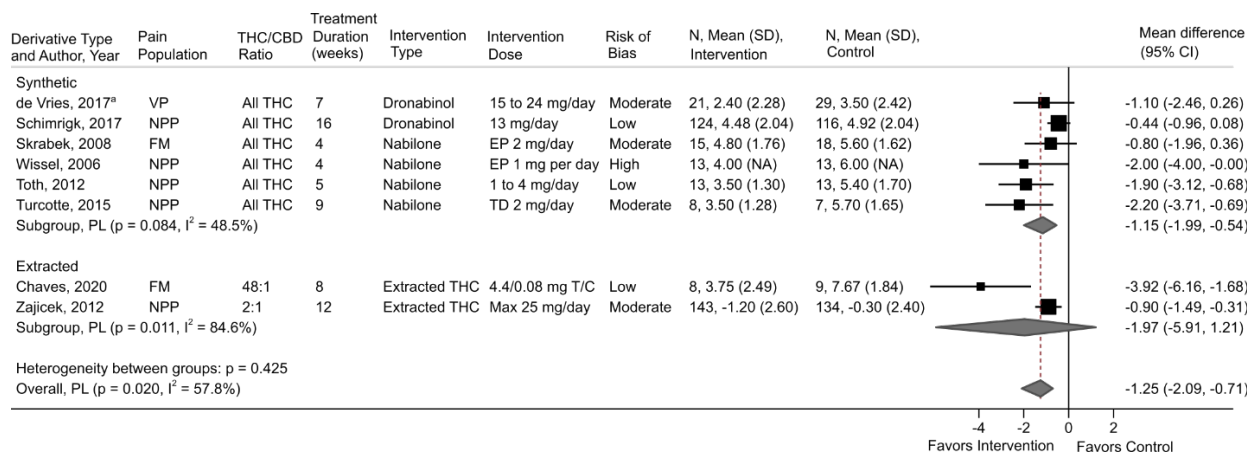
**Figure E-9. Sedation for comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months followup)**



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

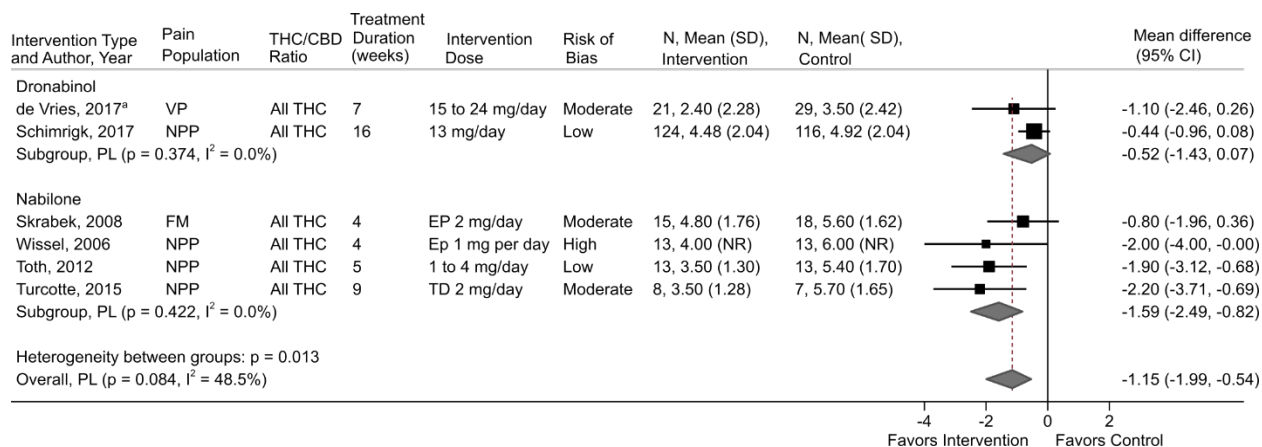
# High THC to CBD Ratio Studies

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



Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end-point; FM = fibromyalgia; NA = not applicable; NPP = neuropathic pain; PD = plant-derived; PL = profile likelihood; SD = standard deviation; TD = total dose; T/C = THC/CBD; THC = tetrahydrocannabinol; VP = visceral pain.  
<sup>a</sup> Dronabinol tablet = plant-derived, purified product Namisol®.

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



Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; RCT = randomized controlled trials; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain.  
<sup>a</sup> Dronabinol tablet = plant-derived, purified product Namisol®.

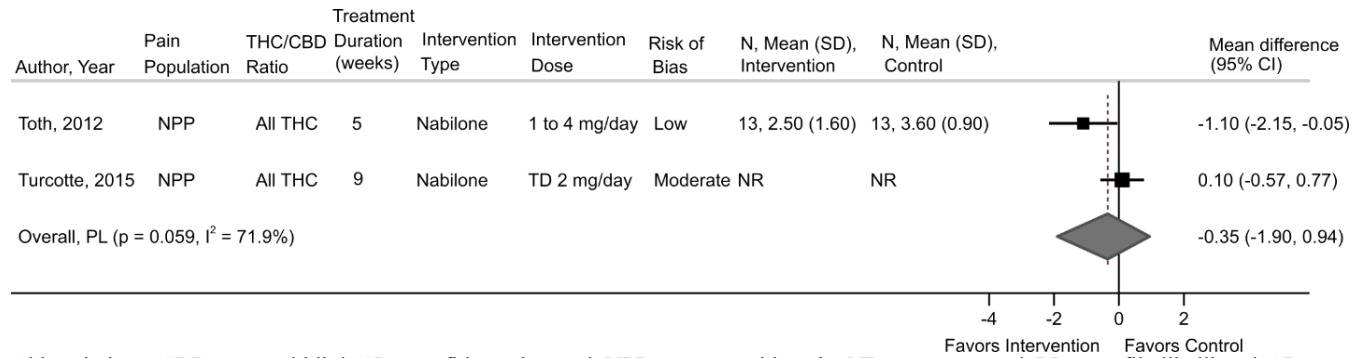
**Table E-6. Interaction effect of RCTs assessing synthetic cannabinoids: nabilone versus dronabinol**

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

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

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

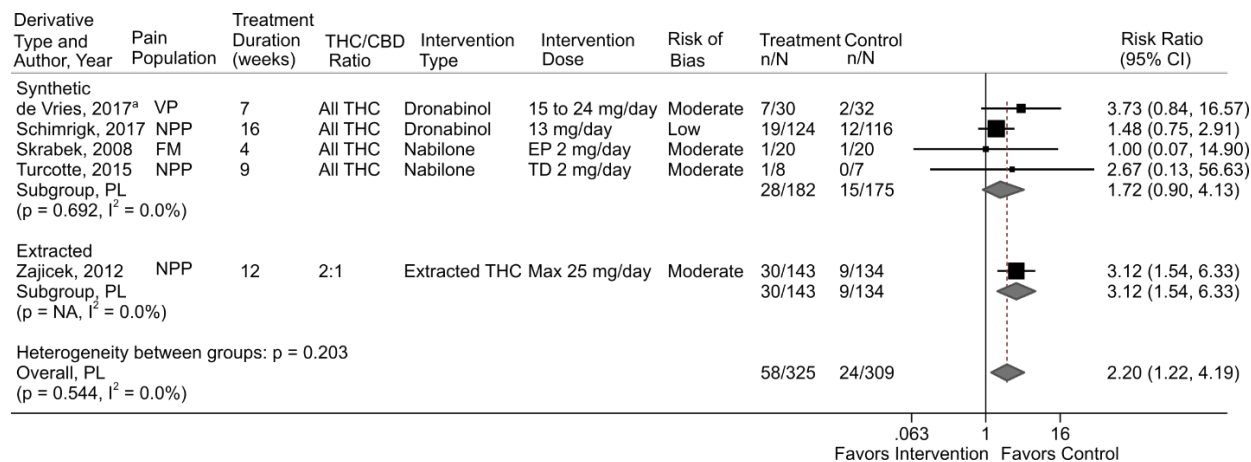
**Figure E-12. Overall function for high THC versus placebo (short-term, 1-6 months followup)**



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



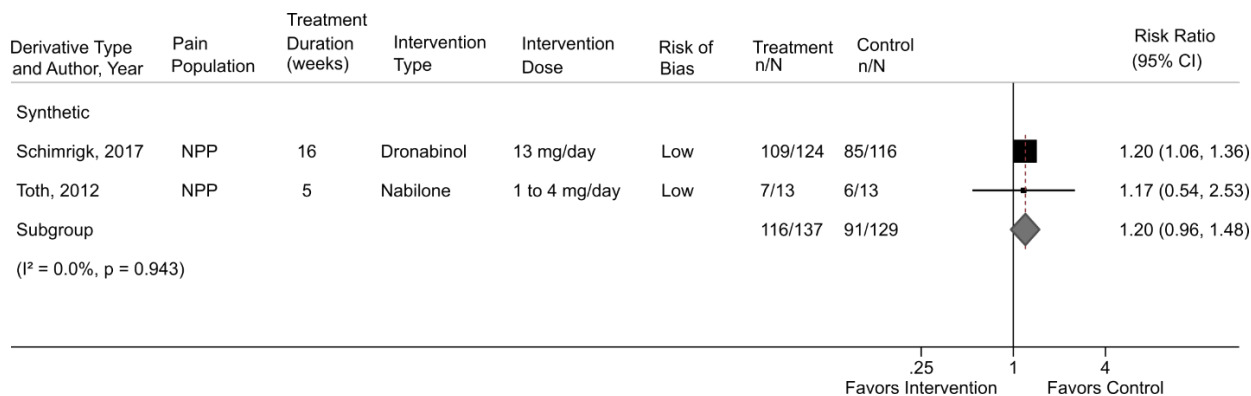
**Figure E-13. Withdrawal due to adverse events for high THC versus placebo (short-term, 4 weeks to 6 months followup)**



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

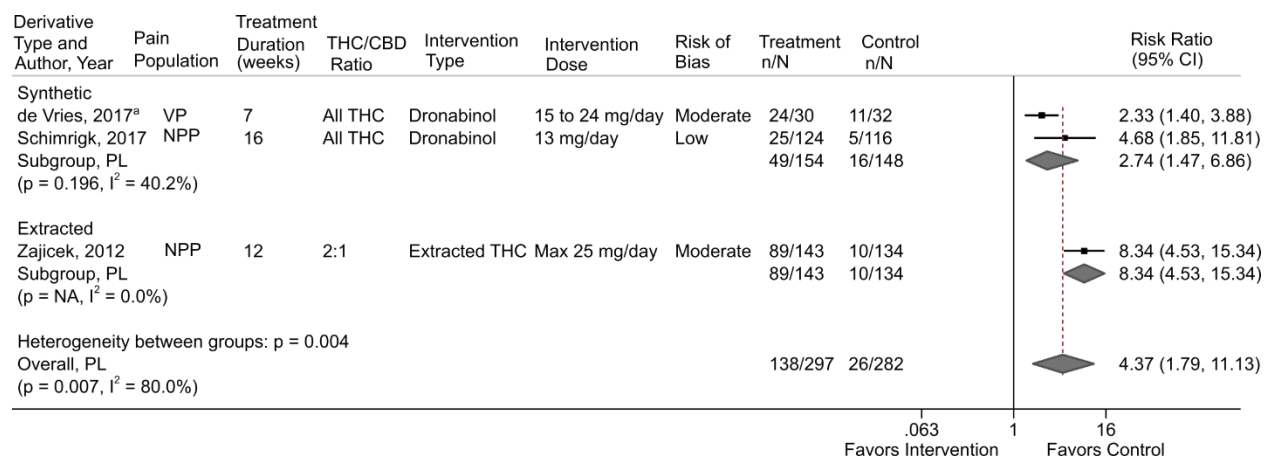
<sup>a</sup>Dronabinol tablet = plant-derived, purified product Namisol®.

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



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

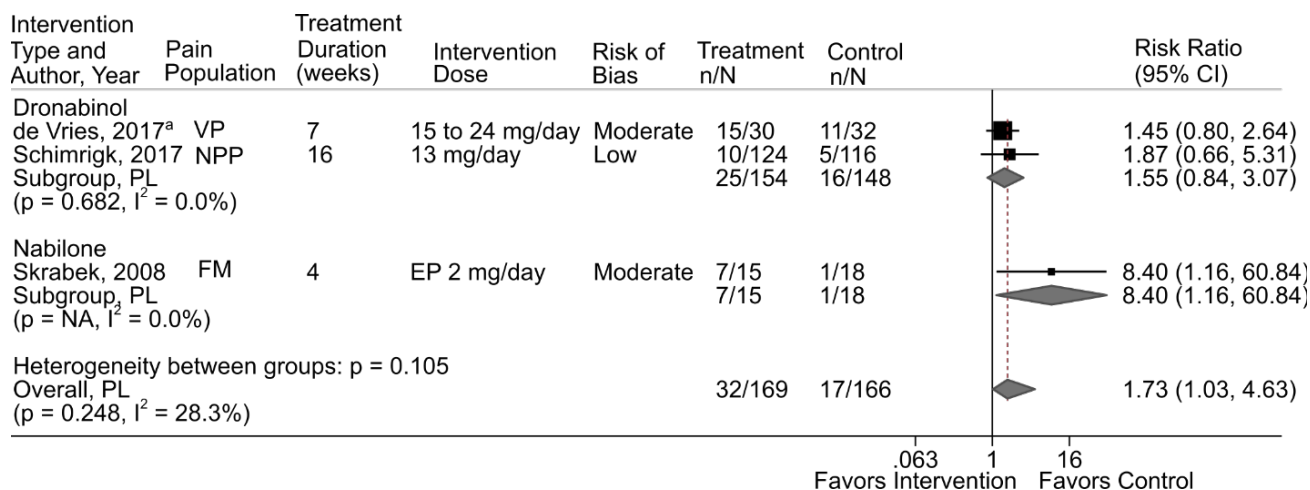
**Figure E-15. Dizziness for high THC versus placebo (short-term, 4 weeks to 6 months followup)**



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

<sup>a</sup> Dronabinol tablet = plant-derived, purified product Namisol<sup>®</sup>.

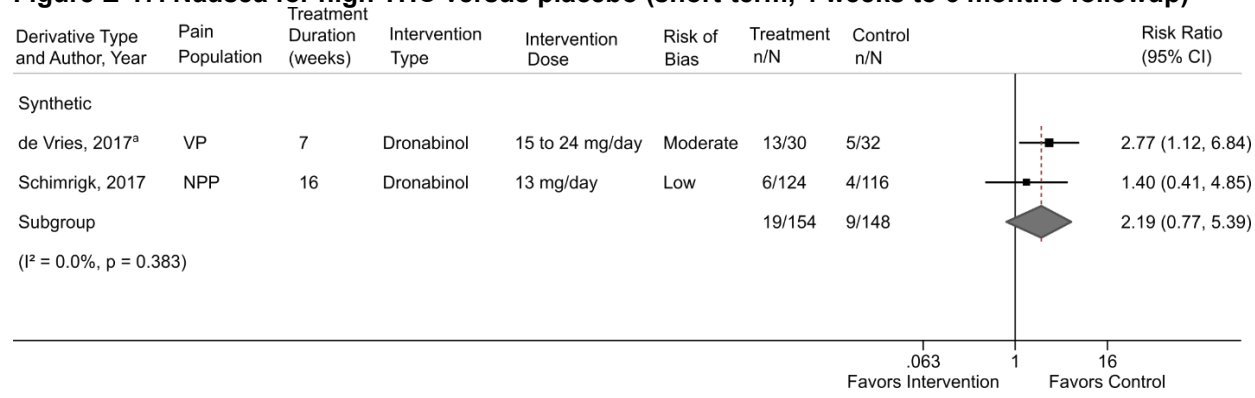
**Figure E-16. Sedation for high THC versus placebo (short-term, 4 weeks to 6 months followup)**



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

<sup>a</sup> Dronabinol tablet = plant-derived, purified product Namisol<sup>®</sup>.

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



Abbreviations: CI = confidence interval; NPP = neuropathic pain; VP = visceral pain.  
<sup>a</sup> Dronabinol tablet = plant-derived, purified product Namisol<sup>®</sup>.

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

THC to CBD Ratio	Outcome	N; k Studies	Point Estimate	PL 95% CI	BC 95% CI	I-Squared
Comparable	Pain severity	N=702; k=7	MD -0.54	-0.95 to -0.19	-1.03 to -0.11	39%
Comparable	Pain response ( $\geq 30\%$ improvement)	N=733; k=4	RR 1.18	0.93 to 1.71	0.67 to 2.43	36%
Comparable	Function	N=616; k=6	MD -0.42	-0.73 to -0.16	-0.80 to -0.10	32%
Comparable	Adverse events	N=405; k=2	RR 1.19	1.02 to 1.44	0.74 to 2.03	0%
Comparable	SAEs	N=427; k=3	RR 1.18	0.26 to 3.43	0.02 to 35.25	0%
Comparable	WAEs	N=834; k=5	RR 1.19	0.60 to 3.72	0.25 to 8.29	54%
Comparable	Dizziness	N=866; k=6	RR 3.57	2.42 to 5.60	2.15 to 6.62	0%
Comparable	Nausea	N=866; k=6	RR 1.79	1.19 to 2.77	1.06 to 3.32	0%
Comparable	Sedation	N=866; k=6	RR 5.04	2.10 to 11.89	1.41 to 17.29	0%
High	Pain severity	N=684; k=8	MD -1.25	-2.09 to -0.71	-2.24 to -0.62	58%
High (synthetic)	Pain severity	N=390; k=6	MD -1.15	-1.99 to -0.54	-2.21 to -0.39	48%
High (synthetic - dronabinol)	Pain severity	N=290; k=2	MD -0.52	-1.43 to 0.07	-3.70 to 2.17	0%
High (synthetic - nabilone)	Pain severity	N=100; k=4	MD -1.59	-2.49 to -0.82	-2.21 to -0.39	0%
High (plant-derived)	Pain severity	N=294; k=2	MD -1.97	-5.91 to 1.21	-11.33 to 6.53	85%
High	Function	N=unclear; k=2	MD -0.35	-1.90 to 0.94	-3.95 to 2.96	72%
High	WAEs	N=634; k=5	RR 2.20	1.22 to 4.19	0.88 to 5.81	0%
High (synthetic)	WAEs	N=357; k=4	RR 1.72	0.90 to 4.13	0.37 to 10.52	0%
High (synthetic - dronabinol)	WAEs	N=302; k=2	RR 1.73	0.79 to 5.87	0.06 to 87.17	18%
High (synthetic - nabilone)	WAEs	N=55; k=2	RR 1.54	0.14 to 17.71	0.01 to 280.12	0%
High	Any adverse event	N=266; k=2	RR 1.20	0.96 to 1.48	0.42 to 3.36	0%
High	Dizziness	N=579; k=3	RR 4.37	1.79 to 11.13	1.11 to 18.00	80%
High (synthetic)	Dizziness	N=302; k=2	RR 2.74	1.47 to 6.86	0.28 to 38.32	40%
High	Sedation	N=335; k=3	RR 1.73	1.03 to 4.63	0.44 to 15.71	28%
High (synthetic - dronabinol)	Sedation	N=302; k=2	RR 1.55	0.84 to 3.07	0.25 to 10.98	0%
High	Nausea	N=302; k=2	RR 2.19	0.77 to 5.39	0.18 to 22.43	0%

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

# Appendix F. Evidence Tables

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

# Appendix G. Risk of Bias Assessment

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

## Appendix H. Details on Strength of Evidence

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
<b>Comparable THC to CBD Ratio vs. Placebo</b>	Pain response (≥30% improvement from baseline)	4 RCTs (N=733) <sup>1-4</sup>	Moderate	Direct	Consistent	Imprecise	Unknown	Potential small effect, not statistically significant, with THC:CBD 38% vs. 31%, RR 1.18 (0.93 to 1.71); I <sup>2</sup> =36%	Low
<b>Comparable THC to CBD Ratio vs. Placebo</b>	Pain severity (change)	7 RCTs (N=878) <sup>1-7</sup>	Moderate	Direct	Consistent	Precise	Unknown	Small benefit with THC:CBD 0 to 10 scale, MD -0.54 (-0.95 to -0.19; I <sup>2</sup> =40%) Subgroup analysis removing high risk of bias studies: Moderate benefit MD -0.64 (-1.15 to -0.24)	Moderate
<b>Comparable THC to CBD Ratio vs. Placebo</b>	Function or Disability	6 RCTs (N=616) <sup>1-5,7</sup>	Moderate	Direct	Consistent	Precise	Unknown	Small benefit with THC:CBD, MD -0.42, 95% CI -0.73 to -0.16, I <sup>2</sup> =32% (scale 0 to 10)	Moderate
<b>Comparable THC to CBD Ratio vs. Placebo</b>	WAEs	5 RCTs (N=834) <sup>1,2,4,5,7</sup>	Moderate	Direct	Consistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 13% vs. 10%, RR 1.14 (0.65 to 3.02); I <sup>2</sup> =51%	Insufficient
<b>Comparable THC to CBD Ratio vs. Placebo</b>	SAEs	3 RCTs (N=429) <sup>2,4,5</sup>	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 5.0% vs. 4.3%, RR 1.18 (0.28 to 3.43; I <sup>2</sup> =0%)	Low

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

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



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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
<b>Synthetic THC vs. Placebo</b>	Pain response (≥30% improvement from baseline)	1 RCT (N=26) <sup>8</sup>	Low	Direct	Unknown	Imprecise	Unknown	Large effect with nabilone 85% vs. 38%, RR 2.20 (1.06 to 4.55)	Low
<b>Synthetic THC vs. Placebo</b>	Pain severity	6 RCTs (N=390) <sup>8-13</sup>	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with synthetic THC 0 to 10 scale, MD -1.15 (-1.99 to -0.54; I <sup>2</sup> =48%)	Low
<b>Synthetic THC vs. Placebo</b>	Function/disability	2 RCTs (N=41) <sup>8,12</sup> 1 RCT (N=13) not included in meta-analysis <sup>13</sup>	Moderate	Direct	Consistent	Imprecise	Unknown	No effect (scale 0 to 10) MD : -0.35, -1.9 to 0.94, 0 to 10 scale, I <sup>2</sup> =72%	Low
<b>Synthetic THC vs. Placebo</b>	WAEs	4 RCTs (N=357) <sup>9-12</sup>	Moderate	Direct	Consistent	Imprecise	Unknown	Potential moderate effect, not statistically significant 13% vs. 9%, RR 1.72 (0.90 to 4.13; I <sup>2</sup> =0%)	Low
<b>Synthetic THC vs. Placebo</b>	SAEs	1 RCT (N=240) <sup>10</sup>	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
<b>Synthetic THC vs. Placebo</b>	Dizziness	2 RCTs (N=302) <sup>9,10</sup>	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 32% vs. 11%, RR 2.74 (1.47 to 6.86; I <sup>2</sup> =40.2%)	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
<b>Synthetic THC vs. Placebo</b>	Nausea	2 RCTs (N=302) <sup>9,10</sup>	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 <sup>2</sup> =0%)	Low
<b>Synthetic THC vs. Placebo</b>	Sedation	3 RCTs (N=335) <sup>9,11</sup>	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with dronabinol 19% vs. 10%, RR 1.73 (1.03 to 4.63; I <sup>2</sup> =28%)	Low

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

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

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
<b>Extracted High THC vs. Placebo</b>	Pain severity	2 RCTs (N=297) <sup>14,15</sup>	Moderate	Direct	Inconsistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD -1.97 (-5.91 to 1.21; I <sup>2</sup> =85%)	Insufficient
	Function/disability	1 RCT (N=18) <sup>15</sup>	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) <sup>14</sup>	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) <sup>14</sup>	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) <sup>14</sup>	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect 62.2% vs. 7.5%, RR 8.34 (4.53 to 15.34)	Low

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

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

<b>Comparison</b>	<b>Outcome</b>	<b>Number of Studies and Total Participants (N)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Publication Bias</b>	<b>Main Findings Effect Size (95% CI)</b>	<b>Strength of Evidence Grade</b>
<b>Combined High THC Ratio Studies (Synthetic and Whole-plant extracted)</b>	Pain severity	8 RCTs (N=684) <sup>8-15</sup>	Moderate	Direct	Consistent	Precise	Unknown	Moderate effect MD -1.25 (-2.09 to -0.71; I <sup>2</sup> =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 H-5. KQ1 and 2: Cannabinoids to treat chronic pain – whole plant cannabis**

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
<b>Whole plant cannabis (standardized to 12% THC) vs. Usual Care</b>	Pain Severity change	1 (N=431, 302 contribute to pain outcome) <sup>16</sup>	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) <sup>16</sup>	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) <sup>16</sup>	High	Direct	Unknown	Imprecise	Unknown	No effect 13% vs. 19%, OR 0.64 (0.38 to 1.04)	Insufficient
	Dizziness	1 (N=431) <sup>16</sup>	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) <sup>16</sup>	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) <sup>16</sup>	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) <sup>16</sup>	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Insufficient

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

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

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

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

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

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

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

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

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
<b>Unknown THC to CBD Ratio vs. Usual Care</b>	Pain response (≥30% improvement from baseline)	No studies	NA	NA	NA	NA	NA	NA	No evidence
<b>Unknown THC to CBD Ratio vs. Usual Care</b>	Pain severity (change) Short-term (3 months)	2 cohort studies: short- to intermediate-term (N=202) <sup>20,21</sup>	High	Direct	Inconsistent	Imprecise	Unknown	VAS (0-100): 41.5 vs. 43.6 at 3 months <sup>20</sup> 34.1 vs. 48.8; mean difference -14.71 (95% CI, -32.71 to 3.29) <sup>21</sup>	Insufficient
<b>Unknown THC to CBD Ratio vs. Usual Care</b>	Long-term (12 months)	1 cohort (N=1,514) <sup>22</sup>	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 <sup>22</sup>	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) <sup>20,21</sup>	High	Direct	Consistent	Imprecise	Unknown	SF-36 Physical Functioning (mean, 0 to 100 scale) 46.5 vs. 43.7 at 6 months <sup>20</sup> 70.0 vs. 69.4; MD 0.56 (95% CI -17.2 to 18.3) at 3 months <sup>21</sup>	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	WAEs	1 cohort study, short- and intermediate-term (N=156) <sup>20</sup>	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) <sup>20</sup>	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) <sup>20</sup>	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



<b>Comparison</b>	<b>Outcome</b>	<b>Number of Studies (N) and Total Participants</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Publication Bias</b>	<b>Main Findings Effect Size (95% CI)</b>	<b>SOE Grade</b>
<b>Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)</b>	Sedation	1 cohort study, short- and intermediate-term (N=156) <sup>20</sup>	Moderate	Direct	Unknown	Imprecise	Unknown	3 months: 54% (28/52) vs. 33% (18/55) RR 1.65 (95% CI 1.04 to 2.59) 6 months: 60% (31/52) vs. 36% (20/55) RR 1.64 (95% CI 1.08 to 2.48)	Insufficient

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

## Appendix H References

1. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol*. 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.
2. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007 Dec 15;133(1-3):210-20. PMID: 17997224.
3. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care*. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.
4. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain*. 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.
5. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)*. 2006 Jan;45(1):50-2. PMID: 16282192.
6. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symptom Manage*. 2014 Jan;47(1):166-73. doi: 10.1016/j.jpainsymman.2013.02.018. PMID: 23742737.
7. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005 Sep 27;65(6):812-9. PMID: 16186518.
8. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain*. 2012 Oct;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024. PMID: 22921260.
9. 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*. 2021;29(2):147-56. doi: 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 I. Excluded Studies List

1. Vaporized Cannabis for Chronic Pain Associated With Sickle Cell Disease. Cannabinoid-Based Therapy and Approaches to Quantify Pain in Sickle Cell Disease. 2013. **Exclusion reason:** Ineligible publication type
2. Proof of Concept Trial of Cannabis Derivatives in Neuropathic Pain. Proof of Concept Trial of Cannabis Derivatives in Neuropathic Pain. 2022. **Exclusion reason:** Ineligible publication type
3. 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
4. Aboud T, Schuster NM. Pain management in multiple sclerosis: a review of available treatment options. *Curr Treat Options Neurol.* 2019 Nov 27;21(12):62. doi: 10.1007/s11940-019-0601-2. PMID: 31773455. **Exclusion reason:** Systematic review used as source document
5. 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
6. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology.* 2007 Feb 13;68(7):515-21. doi: 10.1212/01.wnl.0000253187.66183.9c. PMID: 17296917. **Exclusion reason:** Inadequate duration
7. Abuhassira 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
8. Abuhassira 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
9. Aebischer JH, Dieckmann NF, Jones KD, et al. Chronic Pain Clinical and Prescriptive Practices in the Cannabis Era. *Pain Manag Nurs.* 2021 Dec 29;29:29. doi: 10.1016/j.pmn.2021.11.009. PMID: 34973920. **Exclusion reason:** Systematic review used as source document
10. 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;11doi: 10.1177/1179573519831997. PMID: 30886530. **Exclusion reason:** Systematic review used as source document
11. 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
12. 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
13. Aly E, Masocha W. Targeting the endocannabinoid system for management of HIV-associated neuropathic pain: A systematic review. *IBRO Neurosci Rep.* 2021 Jun;10:109-18. doi: 10.1016/j.ibneur.2021.01.004. PMID: 34179865. **Exclusion reason:** Systematic review used as source document
14. Amato L, Minozzi S, Mitrova Z, et al. Systematic review of safety 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
15. AminiLari M, Wang L, Neumark S, et al. Medical Cannabis and Cannabinoids for Impaired Sleep: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Sleep.* 2021doi: 10.1093/sleep/zsab234. PMID: 34546363. **Exclusion reason:** Systematic review used as source document
  16. Anaya HJM, Ortiz MPT, Valencia DHF, et al. Efficacy of cannabinoids in fibromyalgia: A literature review. *Colomb J Anesthesiol.* 2021;49(4)doi: 10.5554/22562087.e980. **Exclusion reason:** Inadequate duration
  17. 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
  18. Anonymous. National Institute for Health and Care Excellence (UK). 2019 11;11:11. PMID: 35107907. **Exclusion reason:** Systematic review used as source document
  19. Aviram J, Atzmony D, Eisenberg E. Long-term effectiveness and safety of medical cannabis administered through the metered-dose Syqe Inhaler. *Pain reports.* 2022;7(3):e1011. doi: <https://dx.doi.org/10.1097/PR9.0000000000001011>. **Exclusion reason:** Ineligible comparator
  20. 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
  21. Aviram J, Lewitus GM, Vysotski Y, et al. Sex differences in medical cannabis-related adverse effects. *Pain.* 2021doi: 10.1097/j.pain.0000000000002463. PMID: 34538843. **Exclusion reason:** Ineligible comparator
  22. 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
  23. Aviram J, Samuely-Leichtag G. Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. *Pain Physician.* 2017 Sep;20(6):E755-E96. PMID: 28934780. **Exclusion reason:** Systematic review used as source document
  24. Bajtel A, Kiss T, Toth B, et al. The Safety of Dronabinol and Nabilone: A Systematic Review and Meta-Analysis of Clinical Trials. *Pharmaceuticals (Basel).* 2022 Jan 14;15(1):14. doi: 10.3390/ph15010100. PMID: 35056154. **Exclusion reason:** Systematic review used as source document
  25. Ball S, Vickery J, Hobart J, et al. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. *Health Technol Assess.* 2015;19(12):1-187. doi: 10.3310/hta19120. PMID: 25676540. **Exclusion reason:** Ineligible outcome
  26. 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
  27. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opin Pharmacother.* 2006 Apr;7(5):607-15. doi: 10.1517/14656566.7.5.607. PMID: 16553576. **Exclusion reason:** Ineligible publication type
  28. 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
29. 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
30. 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
31. Bennici A, Mannucci C, Calapai F, et al. Safety of Medical Cannabis in Neuropathic Chronic Pain Management. *Molecules (Basel).* 2021;26(20):16. doi: 10.3390/molecules26206257. PMID: 34684842. **Exclusion reason:** Systematic review used as source document
32. Berger AA, Keefe J, Winnick A, et al. Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia. *Best Pract Res Clin Anaesthesiol.* 2020doi: 10.1016/j.bpa.2020.08.010. PMID: 33004171. **Exclusion reason:** Ineligible publication type
33. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain.* 2004 Dec;112(3):299-306. doi: 10.1016/j.pain.2004.09.013. PMID: 15561385. **Exclusion reason:** Inadequate duration
34. Bialas P, Fitzcharles M-A, Klose P, et al. Long-term observational studies with cannabis-based medicines for chronic non-cancer pain: A systematic review and meta-analysis of effectiveness and safety. *Eur J Pain.* 2022doi: <https://dx.doi.org/10.1002/ejp.1957>. **Exclusion reason:** Systematic review used as source document
35. 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
36. Boehnke KF, Clauw DJ. Cannabinoids for Chronic Pain: Translating Systematic Review Findings Into Clinical Action. *Ann Intern Med.* 2022doi: <https://dx.doi.org/10.7326/M22-1512>. **Exclusion reason:** Background only
37. Boehnke KF, Gagnier JJ, Matallana L, et al. Cannabidiol Use for Fibromyalgia: Prevalence of Use and Perceptions of Effectiveness in a Large Online Survey. *J Pain.* 2021doi: 10.1016/j.jpain.2020.12.001. PMID: 33400996. **Exclusion reason:** Ineligible study design
38. Boehnke KF, Gagnier JJ, Matallana L, et al. Substituting Cannabidiol for Opioids and Pain Medications Among Individuals With Fibromyalgia: A Large Online Survey. *J Pain.* 2021doi: 10.1016/j.jpain.2021.04.011. PMID: 33992787. **Exclusion reason:** Background only
39. Boehnke KF, Hauser W, Fitzcharles M-A. Cannabidiol (CBD) in Rheumatic Diseases (Musculoskeletal Pain). *Curr Rheumatol Rep.* 2022doi: <https://dx.doi.org/10.1007/s11926-022-01077-3>. **Exclusion reason:** Systematic review used as source document
40. 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
41. Bonomo Y, Norman A, Collins L, et al. Pharmacokinetics, Safety, and Tolerability of a Medicinal Cannabis Formulation in Patients with Chronic Non-cancer Pain on Long-Term High Dose Opioid Analgesia: A Pilot Study. *Pain Ther.* 2021;18:18. doi: 10.1007/s40122-021-00344-y. PMID: 34921662. **Exclusion reason:** Ineligible comparator

42. 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
43. Busse JW, MacKillop J. Medical cannabis and cannabinoids for chronic pain: Summary of a Rapid Recommendation. *J Mil Veteran Fam Health*. 2021;7:118-22. doi: 10.3138/jmvfh-2021-0056. **Exclusion reason:** Ineligible publication type
44. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *Jama*. 2018 Dec 18;320(23):2448-60. doi: 10.1001/jama.2018.18472. PMID: 30561481. **Exclusion reason:** Systematic review used as source document
45. Canavan C, Inoue T, McMahon S, et al. The Efficacy, Adverse Events, and Withdrawal Rates of the Pharmacological Management of Chronic Spinal Cord Injury Pain: A Systematic Review and Meta-Analysis. *Pain Med*. 2022 Feb 01;23(2):375-95. doi: 10.1093/pm/pnab140. PMID: 33844010. **Exclusion reason:** Systematic review used as source document
46. Carreira DS, Garden S, Huffman A, et al. Cannabinoids in the Orthopedic Setting: A Literature Review. *Orthopedics*. 2022:1-7. doi: 10.3928/01477447-20220225-11. **Exclusion reason:** Systematic review used as source document
47. 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
48. Christ MM. Pain medicine: Cannabis is effective in neuropathic pain. *Arzneimitteltherapie*. 2019;37(6):242-3. **Exclusion reason:** Not in English
49. Clermont-Gnamien S, Atlani S, Attal N, et al. The therapeutic use of  $\Delta^9$ -tetrahydrocannabinol (dronabinol) in refractory neuropathic pain. *Presse Med*. 2002;31(39 I):1840-5. PMID: 12496714. **Exclusion reason:** Not in English
50. Cooper ZD, Abrams DI. Considering abuse liability and neurocognitive effects of cannabis and cannabis-derived products when assessing analgesic efficacy: a comprehensive review of randomized-controlled studies. *Am J Drug Alcohol Abuse*. 2019;45(6):580-95. doi: 10.1080/00952990.2019.1669628. PMID: 31687845. **Exclusion reason:** Systematic review used as source document
51. 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
52. 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
53. Coughlin LN, Ilgen MA, Jannausch M, et al. Progression of cannabis withdrawal symptoms in people using medical cannabis for chronic pain. *Addiction*. 2021doi: 10.1111/add.15370. PMID: 33400332. **Exclusion reason:** Ineligible study design
54. 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
55. Cumenal M, Selvy M, Kerckhove N, et al. The safety of medications used to treat peripheral neuropathic pain, part 2 (opioids, cannabinoids and other drugs): review of double-blind, placebo-controlled, randomized clinical trials. *Expert Opin Drug Saf*. 2020doi: 10.1080/14740338.2021.1842871. PMID: 33103931. **Exclusion reason:** Systematic review used as source document
56. 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
57. 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
58. 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
59. 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
60. Datta S, Ramamurthy PC, Anand U, et al. Wonder or evil?: Multifaceted health hazards and health benefits of Cannabis sativa and its phytochemicals. *Saudi J Biol Sci*. 2021;28(12):7290-313. doi: 10.1016/j.sjbs.2021.08.036. PMID: 34867033. **Exclusion reason:** Ineligible publication type
61. 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
62. 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;43(10):e11-6. doi: 10.3928/01477447-20200928-02. PMID: 33002174. **Exclusion reason:** Ineligible outcome
63. 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
64. 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
65. Domnic G, Narayanan S, Mohana-Kumaran N, et al. Kratom (*Mitragyna speciosa* Korth.) an overlooked medicinal plant in Malaysia. *J Subst Use*. 2022;27(1):1-6. doi: 10.1080/14659891.2021.1885515. **Exclusion reason:** Systematic review used as source document
66. Durán M, Capellà D. Cannabis and cannabinoids in the treatment of neuropathic pain. *DOLOR*. 2005;20(4):213-6. **Exclusion reason:** Not in English
67. Dykukha I, Malessa R, Essner U, et al. Nabiximols in Chronic Neuropathic Pain: A Meta-Analysis of Randomized Placebo-Controlled Trials. *Pain Med*. 2021 04 20;22(4):861-74. doi: 10.1093/pm/pnab050. PMID: 33561282. **Exclusion reason:** Systematic review used as source document
68. Eadie L, Lo LA, Christiansen A, et al. Duration of Neurocognitive Impairment With Medical Cannabis Use: A Scoping Review. *Front Psychiatry*. 2021;12doi: 10.3389/fpsy.2021.638962. PMID: 33790818. **Exclusion reason:** Systematic review used as source document
69. Edinoff AN, Fort JM, Singh C, et al. Alternative Options for Complex, Recurrent Pain States Using Cannabinoids, Psilocybin, and Ketamine: A Narrative Review of Clinical Evidence. *Neurology int*. 2022;14(2):423-36. doi: 10.3390/neurolint14020035. **Exclusion reason:** Ineligible publication type
70. 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
71. 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
72. 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
73. 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
74. 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
75. Filippini G, Minozzi S, Borrelli F, et al. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. *The Cochrane database of systematic reviews.* 2022;5:CD013444. doi: <https://dx.doi.org/10.1002/14651858.CD013444.pub2>. **Exclusion reason:** Systematic review used as source document
76. First L, Douglas W, Habibi B, et al. Cannabis Use and Low-Back Pain: A Systematic Review. *Cannabis Cannabinoid Res.* 2020;5(4):283-9. doi: 10.1089/can.2019.0077. PMID: 33381642. **Exclusion reason:** Systematic review used as source document
77. Fishbain DA, Cutler RB, Rosomoff HL, et al. Validity of self-reported drug use in chronic pain patients. *Clin J Pain.* 1999 Sep;15(3):184-91. doi: 10.1097/00002508-199909000-00005. PMID: 10524471. **Exclusion reason:** Background only
78. Fisher E, Moore RA, Fogarty AE, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials. *Pain.* 2021 Jul 1;162(Suppl 1):S45-s66. doi: 10.1097/j.pain.0000000000001929. PMID: 32804836. **Exclusion reason:** Systematic review used as source document
79. Fitzcharles M-A, Rampakakis E, Sampalis J, et al. Use of medical cannabis by patients with fibromyalgia in Canada after cannabis legalisation: a cross-sectional study. *Clin Exp Rheumatol.* 2021doi: 10.55563/clinexprheumatol/qcyet7. PMID: 33938797. **Exclusion reason:** Ineligible study design
80. 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
81. Fitzcharles MA, Petzke F, Tolle TR, et al. Cannabis-Based Medicines and Medical Cannabis in the Treatment of Nociceptive Pain. *Drugs.* 81(18):2103-16. doi: 10.1007/s40265-021-01602-1. PMID: 34800285. **Exclusion reason:** Ineligible publication type
82. 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
83. 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
84. 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
85. 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
86. Gambino A, Cabras M, Panagiotakos E, et al. Evaluating the Suitability and Potential Efficiency of Cannabis sativa Oil for Patients with Primary Burning Mouth Syndrome: A Prospective, Open-Label, Single-Arm Pilot Study. *Pain Med.* 2020doi: 10.1093/pm/pnaa318. PMID: 33123730. **Exclusion reason:** Ineligible comparator
87. Gilman JM, Schuster RM, Potter KW, et al. Effect of Medical Marijuana Card Ownership on Pain, Insomnia, and Affective Disorder Symptoms in Adults: A Randomized Clinical Trial. *JAMA Netw Open.* 2022;5(3):e222106. doi: 10.1001/jamanetworkopen.2022.2106. PMID: 35302633. **Exclusion reason:** Ineligible intervention
88. Goedel WC, Macmadu A, Shhipar A, et al. Association of medical cannabis licensure with prescription opioid receipt: A population-based, individual-level retrospective cohort study. *Int J Drug Policy.* 2021;100:103502. doi: 10.1016/j.drugpo.2021.103502. PMID: 34695720. **Exclusion reason:** Ineligible comparator
89. Greis A, Larsen E, Liu C, et al. Perceived Efficacy, Reduced Prescription Drug Use, and Minimal Side Effects of Cannabis in Patients with Chronic Orthopedic Pain. *Cannabis Cannabinoid Res.* 2021;12:12. doi: 10.1089/can.2021.0088. PMID: 34767730. **Exclusion reason:** Ineligible comparator
90. Greis A, Renslo B, Wilson-Poe AR, et al. Medical Cannabis Use Reduces Opioid Prescriptions in Patients With Chronic Back Pain. *Cureus.* 2022;14(1):e21452. doi: 10.7759/cureus.21452. **Exclusion reason:** Ineligible comparator
91. Grossman S, Tan H, Gadiwalla Y. Cannabis and orofacial pain: a systematic review. *Br J Oral Maxillofac Surg.* 2021doi: 10.1016/j.bjoms.2021.06.005. **Exclusion reason:** Systematic review used as source document
92. Grotenhermen F. Treatment of severe chronic pain with cannabis preparations. *Arztl Prax Neurol Psychiatr.* 2002(5):28-30. **Exclusion reason:** Not in English
93. Guillouard M, Authier N, Pereira B, et al. Cannabis use assessment and its impact on pain in rheumatologic diseases: a systematic review and meta-analysis. *Rheumatology (Oxford).* 2020doi: 10.1093/rheumatology/keaa534. PMID: 33159797. **Exclusion reason:** Systematic review used as source document
94. Gundin JS, Rubio-Valera M, Romero LG, et al. Off-label use of cannabinoids efficacy and safety. *Eur J Clin Pharm.* 2017;19(3):158-63. **Exclusion reason:** Ineligible study design
95. Gutierrez T, Hohmann AG. Cannabinoids for the treatment of neuropathic pain: Are they safe and effective? *Future Neurol.* 2011;6(2):129-33. doi: 10.2217/fnl.11.6. **Exclusion reason:** Ineligible publication type
96. Habib G, Khazin F, Artul S. The Effect of Medical Cannabis on Pain Level and Quality of Sleep among Rheumatology Clinic Outpatients. *Pain Res Manag.* 2021;2021:1756588. doi: 10.1155/2021/1756588. PMID: 34531934. **Exclusion reason:** Ineligible comparator
97. Häckel A. Cannabis for chronic back pain?: Pivotal study for whole cannabis extract started. *MMW Fortschr Med.* 2021;163(14):63. doi: 10.1007/s15006-021-0197-9. **Exclusion reason:** Ineligible publication type
98. Haddad F, Dokmak G, Karaman R. The Efficacy of Cannabis on Multiple Sclerosis-Related Symptoms. *Life (Basel, Switzerland).* 2022;12(5)doi:

- <https://dx.doi.org/10.3390/life12050682>.  
**Exclusion reason:** Ineligible publication type
99. Haleem R, Wright R. A scoping review on clinical trials of pain reduction with cannabis administration in adults. *J Clin Med Res.* 2020 Jun;12(6):344-51. doi: 10.14740/jocmr4210. PMID: 32587650. **Exclusion reason:** Ineligible population
100. Hansen JS, Hansen RM, Petersen T, et al. The effect of cannabis-based medicine on neuropathic pain and spasticity in patients with multiple sclerosis and spinal cord injury: Study protocol of a national multicenter double-blinded, placebo-controlled trial. *Brain sci.* 2021;11(9)doi: 10.3390/brainsci11091212. PMID: 34573231. **Exclusion reason:** Ineligible publication type
101. Haroutounian S, Arendt-Nielsen L, Belton J, et al. International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia: research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management. *Pain.* 2021 Jul 01;162(Suppl 1):S117-S24. doi: 10.1097/j.pain.0000000000002266. PMID: 34138827. **Exclusion reason:** Background only
102. Harris M, Erridge S, Ergisi M, et al. UK Medical Cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions. *Expert Rev Clin Pharmacol.* 2021:1-13. doi: 10.1080/17512433.2022.2017771. PMID: 34937477. **Exclusion reason:** Ineligible comparator
103. Hassan S, Zheng Q, Rizzolo E, et al. Does integrative medicine reduce prescribed opioid use for chronic pain? A systematic literature review. *Pain Med.* 2020 Apr 01;21(4):836-59. doi: 10.1093/pm/pnz291. PMID: 31755962. **Exclusion reason:** Ineligible intervention
104. Haungs A, Elizondo J. Does smoking cannabis help with chronic neuropathic pain? *Evid Based Pract.* 2018;21(2):E7-E8. doi: 10.1097/01.EBP.0000541985.24333.b1. **Exclusion reason:** Ineligible publication type
105. Hauser W, Fitzcharles M-A. Register-based studies on cannabis-based medicines and medical cannabis need reliable diagnoses and cannabis treatment details. *Eur J Pain.* 2022;26(1):3-4. doi: 10.1002/ejp.1881. **Exclusion reason:** Ineligible publication type
106. Hauser W, Fitzcharles M-A, Radbruch L, et al. Cannabinoids in pain management and palliative medicine: an overview of systematic reviews and prospective observational studies. *Dtsch Arztebl Int.* 2017 Sep;114(38):627-34. doi: 10.3238/arztebl.2017.0627. PMID: 29017688. **Exclusion reason:** Systematic review used as source document
107. Hauser W, Fitzcharles MA, Radbruch L, et al. Cannabinoids in Pain Management and Palliative Medicine. *Dtsch Arztebl Int.* 2017 Sep 22;114(38):627-34. doi: 10.3238/arztebl.2017.0627. PMID: 29017688. **Exclusion reason:** Ineligible population
108. Hayes C, Martin JH. Lack of efficacy of cannabidiol for relieving back pain: time to re-set expectations? *Med J Aust.* 2021doi: 10.5694/mja2.51025. PMID: 33846981. **Exclusion reason:** Ineligible publication type
109. Hefner K, Sofuoglu M, Rosenheck R. Concomitant cannabis abuse/dependence in patients treated with opioids for non-cancer pain. *The American journal on addictions.* 2015 Sep;24(6):538-45. doi: 10.1111/ajad.12260. PMID: 26246069. **Exclusion reason:** Ineligible outcome
110. Heineman JT, Forster GL, Stephens KL, et al. A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis. *J Hand Surg Am.* 2022 May 27doi: 10.1016/j.jhssa.2022.03.002. PMID: 35637038. **Exclusion reason:** Inadequate duration
111. Hendricks O, Andersen TE, Christiansen AA, et al. Efficacy and safety of cannabidiol followed by an open label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid arthritis or ankylosing spondylitis: protocol for a multicentre, randomised, placebo-controlled study. *BMJ Open.* 2019 Jun 04;9(6):e028197. doi: 10.1136/bmjopen-

- 2018-028197. PMID: 31167870. **Exclusion reason:** Ineligible study design
112. Hesselink JM, Kopsky DJ. Enhancing acupuncture by low dose naltrexone. *Acupunct Med.* 2011 Jun;29(2):127-30. doi: 10.1136/aim.2010.003566. PMID: 21415049. **Exclusion reason:** Ineligible publication type
113. Hill KP, Hurley-Welljams-Dorof WM. Low to moderate quality evidence demonstrates the potential benefits and adverse events of cannabinoids for certain medical indications. *Evid Based Med.* 2016 Feb;21(1):17. doi: 10.1136/ebmed-2015-110264. PMID: 26490847. **Exclusion reason:** Ineligible publication type
114. Hill KP, Palastro MD, Johnson B, et al. Cannabis and Pain: A Clinical Review. *Cannabis Cannabinoid Res.* 2017;2(1):96-104. doi: 10.1089/can.2017.0017. PMID: 28861509. **Exclusion reason:** Systematic review used as source document
115. Hjorthøj C, La Cour P, Nordentoft M, et al. Cannabis-based medicines and medical cannabis for patients with neuropathic pain and other pain disorders: Nationwide register-based pharmacoepidemiologic comparison with propensity score matched controls. *Eur J Pain.* 2021doi: 10.1002/ejp.1874. PMID: 34624164. **Exclusion reason:** Ineligible outcome
116. Hjorthoj C, La Cour P, Nordentoft M, et al. Cannabis-based medicines and medical cannabis for patients with neuropathic pain and other pain disorders: Nationwide register-based pharmacoepidemiologic comparison with propensity score matched controls. *Eur J Pain.* 2022;26(2):480-91. doi: 10.1002/ejp.1874. **Exclusion reason:** Ineligible population
117. Hoggart B, Ratcliffe S, Ehler E, et al. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. *J Neurol.* 2015 Jan;262(1):27-40. doi: 10.1007/s00415-014-7502-9. PMID: 25270679. **Exclusion reason:** Ineligible study design
118. Hojsted J, Ekholm O, Kurita GP, et al. Addictive behaviors related to opioid use for chronic pain: a population-based study. *Pain.* 2013;154(12):2677-83. doi: 10.1016/j.pain.2013.07.046. PMID: 23906554. **Exclusion reason:** Ineligible intervention
119. Holdcroft A, Smith M, Jacklin A, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia.* 1997 May;52(5):483-6. doi: 10.1111/j.1365-2044.1997.139-az0132.x. PMID: 9165969. **Exclusion reason:** Ineligible study design
120. Huang IC, Alberts NM, Buckley MG, et al. Change in Pain Status and Subsequent Opioid and Marijuana Use Among Long-Term Adult Survivors of Childhood Cancer. *JNCI Cancer Spectr.* 2020;4(6):pkaa070. doi: 10.1093/jncics/pkaa070. PMID: 33409451. **Exclusion reason:** Ineligible study design
121. Hunter D, Oldfield G, Tich N, et al. Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis. *Osteoarthritis Cartilage.* 2018;26:S26. doi: 10.1016/j.joca.2018.02.067. **Exclusion reason:** Ineligible publication type
122. Hwang JK, Clarke H. Cannabis and pain: A review. *J Pain Manag.* 2016;9(4):395-413. **Exclusion reason:** Ineligible publication type
123. Iskedjian M, Bereza B, Gordon A, et al. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin.* 2007 Jan;23(1):17-24. doi: 10.1185/030079906x158066. PMID: 17257464. **Exclusion reason:** Ineligible publication type
124. Jain N, Moorthy A. Cannabinoids in rheumatology: Friend, foe or a bystander? *Musculoskeletal care.* 2022doi: <https://dx.doi.org/10.1002/msc.1636>. **Exclusion reason:** Ineligible publication type
125. Jashinski J, Grossman E, Quaye A, et al. Randomised, pragmatic, waitlist controlled trial of cannabis added to prescription opioid support on opioid dose reduction and pain in adults with chronic non-cancer pain: study protocol. *BMJ Open.* 2022;12(6):e064457. doi: <https://dx.doi.org/10.1136/bmjopen-2022-064457>. **Exclusion reason:** Ineligible publication type

126. Jawahar R, Oh U, Yang S, et al. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs*. 2013 Oct;73(15):1711-22. doi: 10.1007/s40265-013-0125-0. PMID: 24085618. **Exclusion reason:** Systematic review used as source document
127. Jensen TS, Madsen CS, Finnerup NB. Pharmacology and treatment of neuropathic pains. *Curr Opin Neurol*. 2009 Oct;22(5):467-74. doi: 10.1097/WCO.0b013e3283311e13. PMID: 19741531. **Exclusion reason:** Ineligible publication type
128. Johal H, Devji T, Chang Y, et al. Cannabinoids in chronic non-cancer pain: a systematic review and meta-analysis. *Clin Med Insights Arthritis Musculoskelet Disord*. 2020 Feb 19;13:1179544120906461. doi: 10.1177/1179544120906461. PMID: 32127750. **Exclusion reason:** Systematic review used as source document
129. Jugl S, Okpeku A, Costales B, et al. A Mapping Literature Review of Medical Cannabis Clinical Outcomes and Quality of Evidence in Approved Conditions in the USA from 2016 to 2019. *Med Cannabis Cannabinoids*. 2021;4(1):21-42. doi: 10.1159/000515069. PMID: 34676348. **Exclusion reason:** Systematic review used as source document
130. Kafil TS, Nguyen TM, MacDonald JK, et al. Cannabis for the treatment of ulcerative colitis. *Cochrane Database Syst Rev*. 2018 Nov 08;11:CD012954. doi: 10.1002/14651858.CD012954.pub2. PMID: 30406638. **Exclusion reason:** Ineligible population
131. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *Jama*. 2003 Oct 01;290(13):1757-62. doi: 10.1001/jama.290.13.1757. PMID: 14519710. **Exclusion reason:** Inadequate duration
132. Kaskie B, Kang H, Bhagianadh D, et al. Cannabis Use among Older Persons with Arthritis, Cancer and Multiple Sclerosis: Are We Comparing Apples and Oranges? *Brain sci*. 2021;11(5)doi: 10.3390/brainsci11050532. PMID: 33922425. **Exclusion reason:** Ineligible study design
133. Kawka M, Erridge S, Holvey C, et al. Clinical outcome data of first cohort of chronic pain patients treated with cannabis-based sublingual oils in the United Kingdom - analysis from the UK Medical Cannabis Registry. *J Clin Pharmacol*. 2021doi: 10.1002/jcph.1961. PMID: 34473850. **Exclusion reason:** Ineligible comparator
134. Khurshid H, Qureshi IA, Jahan N, et al. A Systematic Review of Fibromyalgia and Recent Advancements in Treatment: Is Medicinal Cannabis a New Hope? *Cureus*. 2021;13(8):e17332. doi: 10.7759/cureus.17332. PMID: 34567876. **Exclusion reason:** Systematic review used as source document
135. Kocot-Kepska M, Zajackowska R, Mika J, et al. Topical Treatments and Their Molecular/Cellular Mechanisms in Patients with Peripheral Neuropathic Pain-Narrative Review. *Pharmaceutics*. 2021;13(4)doi: 10.3390/pharmaceutics13040450. PMID: 33810493. **Exclusion reason:** Ineligible publication type
136. Korownyk CS, Montgomery L, Young J, et al. PEER simplified chronic pain guideline: Management of chronic low back, osteoarthritic, and neuropathic pain in primary care. *Can Fam Physician*. 2022;68(3):179-90. doi: 10.46747/cfp.6803179. **Exclusion reason:** Systematic review used as source document
137. Kruger DJ, Kruger JS. Consumer Experiences with Delta-8-THC: Medical Use, Pharmaceutical Substitution, and Comparisons with Delta-9-THC. *Cannabis Cannabinoid Res*. 2021;19:19. doi: 10.1089/can.2021.0124. PMID: 34797727. **Exclusion reason:** Ineligible study design
138. Kurlyandchik I, Tiralongo E, Schloss J. Safety and Efficacy of Medicinal Cannabis in the Treatment of Fibromyalgia: A Systematic Review. *J Altern Complement Med*. 2020;27(3):198-213. doi: 10.1089/acm.2020.0331. PMID: 33337931. **Exclusion reason:** Systematic review used as source document
139. Lake S, Walsh Z, Kerr T, et al. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: a

- longitudinal analysis. *PLoS Med.* 2019 Nov 19;16(11):e1002967. doi: 10.1371/journal.pmed.1002967. PMID: 31743343. **Exclusion reason:** Ineligible study design
140. Lee G, Grovey B, Furnish T, et al. Medical cannabis for neuropathic pain. *Curr Pain Headache Rep.* 2018 Feb 01;22(1):8. doi: 10.1007/s11916-018-0658-8. PMID: 29388063. **Exclusion reason:** Systematic review used as source document
141. Liang AL, Gingher EL, Coleman JS. Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review. *Obstet Gynecol.* 2022 Feb 01;139(2):287-96. doi: 10.1097/AOG.0000000000004656. PMID: 35104069. **Exclusion reason:** Ineligible intervention
142. Lichtman AH, Lux EA, McQuade R, et al. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. *J Pain Symptom Manage.* 2017(pagination)doi: 10.1016/j.jpainsymman.2017.09.001. PMID: 28923526. **Exclusion reason:** Ineligible population
143. Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage.* 2018 Feb;55(2):179-88.e1. doi: 10.1016/j.jpainsymman.2017.09.001. PMID: 28923526. **Exclusion reason:** Ineligible population
144. Ling H-Q, Chen Z-H, He L, et al. Comparative Efficacy and Safety of 11 Drugs as Therapies for Adults With Neuropathic Pain After Spinal Cord Injury: A Bayesian Network Analysis Based on 20 Randomized Controlled Trials. *Frontiers in neurology.* 2022;13:818522. doi: <https://dx.doi.org/10.3389/fneur.2022.818522>. **Exclusion reason:** Systematic review used as source document
145. Longo R, Oudshoorn A, Befus D. Cannabis for Chronic Pain: A Rapid Systematic Review of Randomized Control Trials. *Pain Manag Nurs.* 2020;22(2):141-9. doi: 10.1016/j.pmn.2020.11.006. PMID: 33353819. **Exclusion reason:** Systematic review used as source document
146. Lopez-Sendon Moreno JL, Garcia Caldentey J, Trigo Cubillo P, et al. A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease. *J Neurol.* 2016;263(7):1390-400. doi: 10.1007/s00415-016-8145-9. PMID: 27159993. **Exclusion reason:** Ineligible population
147. Lucas P, Boyd S, Milloy MJ, et al. Cannabis Significantly Reduces the Use of Prescription Opioids and Improves Quality of Life in Authorized Patients: Results of a Large Prospective Study. *Pain Med.* 2020doi: 10.1093/pm/pnaa396. PMID: 33367882. **Exclusion reason:** Ineligible population
148. Luchetti M, Zanarella C, Moretti C, et al. Cannabinoids for the treatment of neuropathic pain. *Acta Anaesthesiol Ital.* 2008;59(2):187-95. **Exclusion reason:** Not in English
149. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol.* 2011 Nov;72(5):735-44. doi: 10.1111/j.1365-2125.2011.03970.x. PMID: 21426373. **Exclusion reason:** Ineligible publication type
150. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol.* 2015 Jun;10(2):293-301. doi: 10.1007/s11481-015-9600-6. PMID: 25796592. **Exclusion reason:** Ineligible publication type
151. Maayah ZH, Takahara S, Ferdaoussi M, et al. The anti-inflammatory and analgesic effects of formulated full-spectrum cannabis extract in the treatment of neuropathic pain associated with multiple sclerosis. *Inflamm Res.* 2020 Jun;69(6):549-58. doi: 10.1007/s00011-020-01341-1. PMID: 32239248. **Exclusion reason:** Ineligible publication type
152. MacCallum CA, Eadie L, Barr AM, et al. Practical Strategies Using Medical Cannabis to Reduce Harms Associated With Long Term Opioid Use in Chronic Pain. *Front Pharmacol.* 2021;12doi:

- 10.3389/fphar.2021.633168. PMID: 33995035. **Exclusion reason:** Ineligible publication type
153. Maida V, Ennis M, Irani S, et al. Adjunctive nabilone in cancer pain and symptom management: a prospective observational study using propensity scoring. *J Support Oncol.* 2008 Mar;6(3):119-24. PMID: 18402303. **Exclusion reason:** Ineligible population
154. Malik Z, Bayman L, Valestin J, et al. Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial. *Dis Esophagus.* 2017 Feb 1;30(2):1-8. doi: 10.1111/dote.12455. PMID: 26822791. **Exclusion reason:** Ineligible population
155. Markovà J, Essner U, Akmaz B, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. *Int J Neurosci.* 2019 Feb;129(2):119-28. doi: 10.1080/00207454.2018.1481066. PMID: 29792372. **Exclusion reason:** Ineligible population
156. Martin-Sanchez E, Furukawa TA, Taylor J, et al. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med.* 2009 Nov;10(8):1353-68. doi: 10.1111/j.1526-4637.2009.00703.x. PMID: 19732371. **Exclusion reason:** Ineligible publication type
157. Matarazzo AP, Elisei LMS, Carvalho FC, et al. Mucoadhesive nanostructured lipid carriers as a cannabidiol nasal delivery system for the treatment of neuropathic pain. *Eur J Pharm Sci.* 2021:105698. doi: 10.1016/j.ejps.2020.105698. PMID: 33406408. **Exclusion reason:** Ineligible study design
158. Maurer M, Henn V, Dittrich A, et al. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry Clin Neurosci.* 1990;240(1):1-4. doi: 10.1007/bf02190083. PMID: 2175265. **Exclusion reason:** Inadequate duration
159. Maurotti S, Mare R, Pujia R, et al. Hemp seeds in post-arthroplasty rehabilitation: A pilot clinical study and an in vitro investigation. *Nutrients.* 2021;13(12)doi: 10.3390/nu13124330. PMID: 34959882. **Exclusion reason:** Ineligible intervention
160. Mazza M. Medical cannabis for the treatment of fibromyalgia syndrome: a retrospective, open-label case series. *J Cannabis Res.* 2021;3(1):4. doi: 10.1186/s42238-021-00060-6. PMID: 33597032. **Exclusion reason:** Ineligible comparator
161. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid pharmacologic treatments for chronic pain. Agency for Healthcare Research and Quality (US). 2020 PMID: 32338847. **Exclusion reason:** Systematic review used as source document
162. McDonagh MS, Wagner J, Ahmed AY, et al. Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain - Quarterly Progress Report: May 2021. Agency for Healthcare Research and Quality (US). 2020 12;12:12. PMID: 34228409. **Exclusion reason:** Ineligible publication type
163. McGinty EE, Tormohlen KN, Barry CL, et al. Protocol: mixed-methods study of how implementation of US state medical cannabis laws affects treatment of chronic non-cancer pain and adverse opioid outcomes. *Implement Sci.* 2021;16(1):2. doi: 10.1186/s13012-020-01071-2. PMID: 33413454. **Exclusion reason:** Ineligible publication type
164. McMichael BJ, Van Horn RL, Viscusi WK. The impact of cannabis access laws on opioid prescribing. *J Health Econ.* 2020 Jan;69:102273. doi: 10.1016/j.jhealeco.2019.102273. PMID: 31865260. **Exclusion reason:** Ineligible population
165. Meade E, Hehir S, Rowan N, et al. Mycotherapy: Potential of Fungal Bioactives for the Treatment of Mental Health Disorders and Morbidities of Chronic Pain. *J Fungi (Basel).* 2022;8(3)doi: 10.3390/jof8030290. **Exclusion reason:** Systematic review used as source document
166. Meng H, Johnston B, Englesakis M, et al. Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. *Anesth Analg.* 2017 Nov;125(5):1638-52. doi:

- 10.1213/ANE.000000000002110. PMID: 28537982. **Exclusion reason:** Ineligible publication type
167. Meng H, Page MG, Ajrawat P, et al. Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients. *Canadian journal of anaesthesia = Journal canadien d'anesthésie*. 2021 doi: 10.1007/s12630-020-01903-1. PMID: 33469735. **Exclusion reason:** Ineligible population
168. Meuth SG, Henze T, Essner U, et al. Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: consistency of response across subgroups from the SAVANT randomized clinical trial. *International Journal of Neuroscience* 2020;130(12):1199-205. doi: 10.1080/00207454.2020.1730832. PMID: 32065006. **Exclusion reason:** Ineligible population
169. Mistry M, Simpson P, Morris E, et al. Cannabidiol for the Management of Endometriosis and Chronic Pelvic Pain. *J Minim Invasive Gynecol*. 2021;25:25. doi: 10.1016/j.jmig.2021.11.017. PMID: 34839061. **Exclusion reason:** Ineligible publication type
170. Mohiuddin M, Blyth FM, Degenhardt L, et al. General risks of harm with cannabinoids, cannabis, and cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews. *Pain*. 2021 Jul 01;162(Suppl 1):S80-S96. doi: 10.1097/j.pain.0000000000002000. PMID: 32941319. **Exclusion reason:** Background only
171. Montero-Oleas N, Arevalo-Rodriguez I, Nunez-Gonzalez S, et al. Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews. *BMC Complement Med Ther*. 2020 Jan 15;20(1):12. doi: 10.1186/s12906-019-2803-2. PMID: 32020875. **Exclusion reason:** Systematic review used as source document
172. Moore RA, Fisher E, Finn DP, et al. Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews. *Pain*. 2021 Jul 1;162(Suppl 1):S67-s79. doi: 10.1097/j.pain.0000000000001941. PMID: 32804833. **Exclusion reason:** Systematic review used as source document
173. Moreno Torres I, Sanchez AJ, Garcia-Merino A. Evaluation of the tolerability and efficacy of Sativex in multiple sclerosis. *Expert Rev Neurother*. 2014 Nov;14(11):1243-50. doi: 10.1586/14737175.2014.971758. PMID: 25331416. **Exclusion reason:** Ineligible publication type
174. Moreno-Sanz G, Madiedo A, Hernandez P, et al. Sex-Dependent Prescription Patterns and Clinical Outcomes Associated With the Use of Two Oral Cannabis Formulations in the Multimodal Management of Chronic Pain Patients in Colombia. *Frontiers in pain research (Lausanne, Switzerland)*. 2022;3:854795. doi: <https://dx.doi.org/10.3389/fpain.2022.854795>. **Exclusion reason:** Ineligible comparator
175. Mucke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2018 Mar 07;3(3):CD012182. doi: 10.1002/14651858.CD012182.pub2. PMID: 29513392. **Exclusion reason:** Systematic review used as source document
176. Muller C, Reggio PH. An Analysis of the Putative CBD Binding Site in the Ionotropic Cannabinoid Receptors. *Front Cell Neurosci*. 2020;14:615811. doi: 10.3389/fncel.2020.615811. PMID: 33362478. **Exclusion reason:** Ineligible study design
177. Murff HJ. Review: weak evidence of benefits of cannabis for chronic neuropathic pain; moderate to weak evidence of adverse effects. *Ann Intern Med*. 2017 Dec 19;167(12):JC62. doi: 10.7326/ACPJC-2017-167-12-062. PMID: 29255852. **Exclusion reason:** Ineligible publication type
178. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain*. 2008 Mar;9(3):254-64. doi: 10.1016/j.jpain.2007.10.018. PMID: 18088560. **Exclusion reason:** Ineligible study design



179. Neilson LM, Swift C, Swart ECS, et al. Impact of Marijuana Legalization on Opioid Utilization in Patients Diagnosed with Pain. *J Gen Intern Med.* 2021doi: 10.1007/s11606-020-06530-6. PMID: 33575906. **Exclusion reason:** Background only
180. Nielsen S, Picco L, Murnion B, et al. Opioid-sparing effect of cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2022doi: <https://dx.doi.org/10.1038/s41386-022-01322-4>. **Exclusion reason:** Systematic review used as source document
181. Nielsen S, Picco L, Murnion B, et al. Opioid-sparing effect of cannabinoids for analgesia: An updated systematic review and meta-analysis of preclinical and clinical studies. *Neuropsychopharmacology.* 2022;47(7):1315-30. doi: <https://dx.doi.org/10.1038/s41386-022-01322-4>. **Exclusion reason:** Systematic review used as source document
182. Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open.* 2021 07 28;11(7):e047717. doi: 10.1136/bmjopen-2020-047717. PMID: 34321302. **Exclusion reason:** Systematic review used as source document
183. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols\* (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol.* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x. PMID: 21362108. **Exclusion reason:** Ineligible outcome
184. Nowell WB, Gavigan K, L Silverman S. Cannabis for Rheumatic Disease Pain: a Review of Current Literature. *Curr Rheumatol Rep.* 2022;24(5):119-31. doi: <https://dx.doi.org/10.1007/s11926-022-01065-7>. **Exclusion reason:** Systematic review used as source document
185. Nugent SM, Kansagara D. The effects of cannabis among adults with chronic pain. *Ann Intern Med.* 2018 Apr 03;168(7):525. doi: 10.7326/L17-0732. PMID: 29610910. **Exclusion reason:** Ineligible publication type
186. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. *Ann Intern Med.* 2017 Sep 05;167(5):319-31. doi: 10.7326/M17-0155. PMID: 28806817. **Exclusion reason:** Systematic review used as source document
187. Nunnari P, Ladiana N, Ceccarelli G, et al. Long-term Cannabis-based oil therapy and pain medications prescribing patterns: an Italian observational study. *Eur Rev Med Pharmacol Sci.* 2022;26(4):1224-34. doi: 10.26355/eurev\_202202\_28114. **Exclusion reason:** Ineligible comparator
188. Nurmikko TJ, Serpell MG, Hoggart B, et al. A multi-centre, double-blind, randomized, controlled trial of oro-mucosal cannabis based medicine in the treatment of neuropathic pain characterized by allodynia. *Neurology.* no: PO6;64(Suppl 1):A374. **Exclusion reason:** Ineligible publication type
189. Nutt DJ, Phillips LD, Barnes MP, et al. A Multicriteria Decision Analysis Comparing Pharmacotherapy for Chronic Neuropathic Pain, Including Cannabinoids and Cannabis-Based Medical Products. *Cannabis Cannabinoid Res.* 2021 Mar 17;17:17. doi: 10.1089/can.2020.0129. PMID: 33998895. **Exclusion reason:** Ineligible study design
190. O'Connell M, Sandgren M, Frantzen L, et al. Medical Cannabis: Effects on Opioid and Benzodiazepine Requirements for Pain Control. *Ann Pharmacother.* 2019 Nov;53(11):1081-6. doi: 10.1177/1060028019854221. PMID: 31129977. **Exclusion reason:** Ineligible comparator
191. Okusanya BO, Asaolu IO, Ehiri JE, et al. Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review. *Syst Rev.* 2020 Jul 28;9(1):167. doi: 10.1186/s13643-020-01425-3. PMID: 32723354. **Exclusion reason:** Systematic review used as source document

192. Okusanya BO, Lott BE, Ehiri J, et al. Medical Cannabis for the Treatment of Migraine in Adults: A Review of the Evidence. *Frontiers in Neurology*. 2022;13doi: 10.3389/fneur.2022.871187. **Exclusion reason:** Systematic review used as source document
193. Paulsingh CN, Mohamed MB, Elhaj MS, et al. The Efficacy of Marijuana Use for Pain Relief in Adults With Sickle Cell Disease: A Systematic Review. *Cureus*. 2022;14(5):e24962. doi: <https://dx.doi.org/10.7759/cureus.24962>. **Exclusion reason:** Systematic review used as source document
194. Pellesi L, Licata M, Verri P, et al. Pharmacokinetics and tolerability of oral cannabis preparations in patients with medication overuse headache (MOH)—a pilot study. *Eur J Clin Pharmacol*. 2018;74(11):1427-36. doi: 10.1007/s00228-018-2516-3. PMID: 29980818. **Exclusion reason:** Ineligible study design
195. Perras C. Sativex for the management of multiple sclerosis symptoms. *Issues Emerg Health Technol*. 2005 Sep(72):1-4. PMID: 16317825. **Exclusion reason:** Ineligible publication type
196. Petzke F, Tolle T, Fitzcharles MA, et al. Cannabis-Based Medicines and Medical Cannabis for Chronic Neuropathic Pain. *CNS Drugs*. 2021;21:21. doi: 10.1007/s40263-021-00879-w. PMID: 34802112. **Exclusion reason:** Systematic review used as source document
197. Pham MN, Hudnall MT, Nadler RB. Marijuana, Lower Urinary Tract Symptoms, and Pain in the Urologic Patient. *Urology*. 2020 05;139:8-13. doi: 10.1016/j.urology.2020.01.029. PMID: 32027882. **Exclusion reason:** Systematic review used as source document
198. Phillips KT, Pedula KL, Choi NG, et al. Chronic health conditions, acute health events, and healthcare utilization among adults over age 50 in Hawai'i who use cannabis: A matched cohort study. *Drug Alcohol Depend*. 2022;234:109387. doi: 10.1016/j.drugalcdep.2022.109387. **Exclusion reason:** Ineligible population
199. Pichini S, Pacifici R, Busardo FP, et al. The challenge of clinical application of FM2 cannabis oil produced in Italy for the treatment of neuropathic pain. *Eur Rev Med Pharmacol Sci*. 2018 Feb;22(4):863-5. doi: 10.26355/eurrev\_201802\_14363. PMID: 29509231. **Exclusion reason:** Ineligible publication type
200. Pinsger M, Schimetta W, Volc D, et al. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain—a randomized controlled trial. *Wien Klin Wochenschr*. 2006;118(11-12):327-35. doi: 10.1007/s00508-006-0611-4. PMID: 16855921. **Exclusion reason:** Not in English
201. Pinsger M, Schimetta W, Volc D, et al. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain - A randomized controlled trial. *Wien Klin Wochenschr*. 2006;118(11-12):327-35. doi: 10.1007/s00508-006-0611-4. PMID: 16855921. **Exclusion reason:** Not in English
202. Podda G, Constantinescu CS. Nabiximols in the treatment of spasticity, pain and urinary symptoms due to multiple sclerosis. *Expert Opin Biol Ther*. 2012 Nov;12(11):1517-31. doi: 10.1517/14712598.2012.721765. PMID: 22954177. **Exclusion reason:** Ineligible publication type
203. Poli P, Carnevale S, Scocca A, et al. Promising Health Benefits of Adjuvant Acemella and Zingiber Extracts Combined with Coenzyme Q10 Phytosomes, Supplementation in Chronic Pain Treated with Medical Cannabis: A Prospective and Open-Label Clinical Study. *Evidence-based complementary and alternative medicine : eCAM*. 2022;2022:7099161. doi: <https://dx.doi.org/10.1155/2022/7099161>. **Exclusion reason:** Ineligible comparator
204. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain*. 2012 May;13(5):438-49. doi: 10.1016/j.jpain.2012.01.003. PMID: 22483680. **Exclusion reason:** Ineligible population
205. Prevete E, Hupli A, Marrinan S, et al. Exploring the use of Kratom (*Mitragyna speciosa*) via the YouTube data tool: A

- novel netnographic analysis. *Emerg Trends Drugs Addict Health*. 2021 2021/01/01/;1:100007. doi: 10.1016/j.etdah.2021.100007. **Exclusion reason:** Background only
206. Price RL, Charlot KV, Frieler S, et al. The Efficacy of Cannabis in Reducing Back Pain: A Systematic Review. *Global Spine J*. 2022doi: 10.1177/21925682211065411. **Exclusion reason:** Systematic review used as source document
207. Prieto Gonzalez JM, Vila Silvan C. Safety and tolerability of nabiximols oromucosal spray: a review of real-world experience in observational studies, registries and case reports. *Expert Rev Neurother*. 2021doi: 10.1080/14737175.2021.1904896. PMID: 33749480. **Exclusion reason:** Systematic review used as source document
208. Prieto Gonzalez JM, Vila Silvan C. Safety and tolerability of nabiximols oromucosal spray: a review of more than 15 years' accumulated evidence from clinical trials. *Expert Rev Neurother*. 2021 Jun 07;07:07. doi: 10.1080/14737175.2021.1935879. PMID: 34092180. **Exclusion reason:** Systematic review used as source document
209. Prozialeck WC, Lamar PC, Krupp M, 2nd, et al. Kratom Use Within the Context of the Evolving Opioid Crisis and the COVID-19 Pandemic in the United States. *Front Pharmacol*. 2021;12:729220. doi: 10.3389/fphar.2021.729220. PMID: 34512353. **Exclusion reason:** Background only
210. Quintero J-M, Pulido G, Giraldo L-F, et al. A Systematic Review on Cannabinoids for Neuropathic Pain Administered by Routes Other than Oral or Inhalation. *Plants (Basel, Switzerland)*. 2022;11(10)doi: <https://dx.doi.org/10.3390/plants11101357>. **Exclusion reason:** Systematic review used as source document
211. Rabgay K, Waranuch N, Chaiyakunapruk N, et al. The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: a systematic review and network meta-analysis. *J Am Pharm Assoc (2003)*. 2020 Jan - Feb;60(1):225-34.e6. doi: 10.1016/j.japh.2019.07.015. PMID: 31495691. **Exclusion reason:** Systematic review used as source document
212. Rapin L, Gamaoun R, El Hage C, et al. Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic. *J Cannabis Res*. 2021;3(1)doi: 10.1186/s42238-021-00078-w. PMID: 34162446. **Exclusion reason:** Ineligible outcome
213. Reisdorf S. Analgesia: Cannabis for neuropathic pain. *MMW Fortschr Med*. 2020;162(7):58. doi: 10.1007/s15006-020-0397-8. **Exclusion reason:** Not in English
214. Renslo B, Greis A, Liu CS, et al. Medical Cannabis Use Reduces Opioid Prescriptions in Patients With Osteoarthritis. *Cureus*. 2022;14(1):e21564. doi: 10.7759/cureus.21564. **Exclusion reason:** Ineligible comparator
215. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2012 Jan 18;1:CD008921. doi: 10.1002/14651858.CD008921.pub2. PMID: 22258992. **Exclusion reason:** Ineligible publication type
216. Riera R, Pacheco RL, Bagattini AM, et al. Efficacy and safety of therapeutic use of cannabis derivatives and their synthetic analogs: Overview of systematic reviews. *Phytother Res*. 2021;29:29. doi: 10.1002/ptr.7263. PMID: 34841610. **Exclusion reason:** Systematic review used as source document
217. Rogers AH, Bakhshaie J, Buckner JD, et al. Opioid and Cannabis Co-Use among Adults With Chronic Pain: Relations to Substance Misuse, Mental Health, and Pain Experience. *J Addict Med*. 2019 Jul/Aug;13(4):287-94. doi: 10.1097/ADM.0000000000000493. PMID: 30557213. **Exclusion reason:** Ineligible study design
218. Ross J, Slawek DE, Zhang C, et al. First-year trajectories of medical cannabis use among adults taking opioids for chronic pain: an observational cohort study. *Pain Med*. 2021doi: 10.1093/pm/pnab257. PMID: 34411246. **Exclusion reason:** Background only
219. Rouhollahi E, Macleod BA, Barr AM, et al. Cannabis extract CT-921 has a high efficacy– adverse effect profile in a neuropathic pain model. *Drug Des Devel*

- Ther. 2020;14:3351-61. doi: 10.2147/DDDT.S247584. PMID: 32884239  
**Exclusion reason:** Ineligible population
220. Russo E. Cannabis and Cannabis based medicine extracts: Additional results. *J Cannabis Ther.* 2004;3(4):153-61. doi: 10.1300/J175v03n04\_03. **Exclusion reason:** Ineligible study design
221. Russo M, Naro A, Leo A, et al. Evaluating Sativex in neuropathic pain management: a clinical and neurophysiological assessment in multiple sclerosis. *Pain Med.* 2016 Jun;17(6):1145-54. doi: 10.1093/pm/pnv080. PMID: 26764336. **Exclusion reason:** Ineligible population
222. S G, Hb S, K L, et al. Safety and efficacy of low-dose medical cannabis oils in multiple sclerosis. *Mult Scler Relat Disord.* 2020;48:102708. doi: 10.1016/j.msard.2020.102708. PMID: 33387864. **Exclusion reason:** Ineligible outcome
223. Safakish R, Ko G, Salimpour V, et al. Medical cannabis for the management of pain and quality of life in chronic pain patients: a prospective observational study. *Pain Med.* 2020 Nov 01;21(11):3073-86. doi: 10.1093/pm/pnaa163. PMID: 32556203. **Exclusion reason:** Ineligible study design
224. Sagy I, Bar-Lev Schleider L, Abu-Shakra M, et al. Safety and efficacy of medical cannabis in fibromyalgia. *J Clin Med.* 2019 Jun 05;8(6):807. doi: 10.3390/jcm8060807. PMID: 31195754. **Exclusion reason:** Ineligible comparator
225. Sainsbury B, Bloxham J, Pour MH, et al. Efficacy of cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review with meta-analysis. *J Dent Anesth Pain Med.* 2021;21(6):479-506. doi: 10.17245/jdapm.2021.21.6.479. PMID: 34909469. **Exclusion reason:** Systematic review used as source document
226. Sanchez-Florez JC, Seija-Butnaru D, Valero EG, et al. Pain Management Strategies in Rheumatoid Arthritis: A Narrative Review. *J Pain Pall Care Pharmacother.* 2021;35(4):291-9. doi: 10.1080/15360288.2021.1973647.
- Exclusion reason:** Systematic review used as source document
227. Santos SA, Kontorinis N, Dieterich DT. Management of chronic hepatitis C virus in patients with HIV. *Curr Treat Options Gastroenterol.* 2005;8(6):433-41. doi: 10.1007/s11938-005-0029-5. PMID: 16313860. **Exclusion reason:** Ineligible population
228. Schenk M. Chronic neuropathic pain: Minimal side effects of therapy with cannabis. *MMW Fortschr Med.* 2020;162(3):72. doi: 10.1007/s15006-020-0171-y. **Exclusion reason:** Not in English
229. Schloss J, Lacey J, Sinclair J, et al. A Phase 2 Randomised Clinical Trial Assessing the Tolerability of Two Different Ratios of Medicinal Cannabis in Patients With High Grade Gliomas. *Front Oncol.* 2021;11doi: 10.3389/fonc.2021.649555. PMID: 34094937. **Exclusion reason:** Ineligible population
230. Schulze-Schiappacasse C, Duran J, Bravo-Jeria R, et al. Are Cannabis, Cannabis-Derived Products, and Synthetic Cannabinoids a Therapeutic Tool for Rheumatoid Arthritis? A Friendly Summary of the Body of Evidence. *J Clin Rheumatol.* 2021doi: 10.1097/RHU.0000000000001745. PMID: 33859125. **Exclusion reason:** Background only
231. Scuteri D, Rombolà L, Hamamura K, et al. Is there a rational basis for cannabinoids research and development in ocular pain therapy? A systematic review of preclinical evidence. *Biomed Pharmacother.* 2022;146doi: 10.1016/j.biopha.2021.112505. PMID: 34891121. **Exclusion reason:** Ineligible population
232. Senderovich H, Wagman H, Zhang D, et al. The Effectiveness of Cannabis and Cannabis Derivatives in Treating Lower Back Pain in the Aged Population: A Systematic Review. *Gerontology.* 2021;1-13. doi: 10.1159/000518269. PMID: 34515130. **Exclusion reason:** Systematic review used as source document
233. Senderovich H, Wagman H, Zhang D, et al. The Effectiveness of Cannabis and Cannabis Derivatives in Treating Lower Back Pain in the Aged Population: A Systematic Review.

- Gerontology. 2022;68(6):612-24. doi: 10.1159/000518269. **Exclusion reason:** Systematic review used as source document
234. Shebaby W, Saliba J, Faour WH, et al. In vivo and in vitro anti-inflammatory activity evaluation of Lebanese Cannabis sativa L. ssp. indica (Lam.). J Ethnopharmacol. 2020;113743. doi: 10.1016/j.jep.2020.113743. PMID: 33359187. **Exclusion reason:** Ineligible study design
235. Shoshan S, Solt I. Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review. Obstetrics and gynecology. 2022;139(5):937-8. doi: https://dx.doi.org/10.1097/AOG.0000000000004777. **Exclusion reason:** Ineligible publication type
236. Sihota A, Smith BK, Ahmed SA, et al. Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control. Int J Clin Pract. 2021;75(8):e13871. doi: 10.1111/ijcp.13871. PMID: 33249713. **Exclusion reason:** Ineligible publication type
237. Smaga S, Gharib A. In adults with chronic low back pain, does the use of inhaled cannabis reduce overall opioid use? Evid Based Pract. 2017;20(1):E10-E1. doi: 10.1097/01.EBP.0000541620.26384.bf. **Exclusion reason:** Ineligible publication type
238. Socias ME, Choi J, Lake S, et al. Cannabis use is associated with reduced risk of exposure to fentanyl among people on opioid agonist therapy during a community-wide overdose crisis. Drug Alcohol Depend. 2020;219:108420. doi: 10.1016/j.drugalcdep.2020.108420. PMID: 33342591. **Exclusion reason:** Ineligible population
239. Stephens KL, Heineman JT, Forster GL, et al. Cannabinoids and Pain for the Plastic Surgeon: What Is the Evidence? Annals of plastic surgery. 2022doi: https://dx.doi.org/10.1097/SAP.0000000000003128. **Exclusion reason:** Systematic review used as source document
240. Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018 Oct;159(10):1932-54. doi: 10.1097/j.pain.0000000000001293. PMID: 29847469. **Exclusion reason:** Systematic review used as source document
241. Sturgeon JA, Khan J, Hah JM, et al. Clinical profiles of concurrent cannabis use in chronic pain: a CHOIR study. Pain Med. 2020 Nov 01;21(11):3172-9. doi: 10.1093/pm/pnaa060. PMID: 32232476. **Exclusion reason:** Ineligible population
242. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004 Jul 31;329(7460):253. doi: 10.1136/bmj.38149.566979.AE. PMID: 15258006. **Exclusion reason:** Inadequate duration
243. Swogger MT, Smith KE, Garcia-Romeu A, et al. Understanding Kratom Use: A Guide for Healthcare Providers. Front Pharmacol. 2022;13doi: 10.3389/fphar.2022.801855. **Exclusion reason:** Systematic review used as source document
244. Swogger MT, Walsh Z. Kratom use and mental health: A systematic review. Drug Alcohol Depend. 2018 Feb 1;183:134-40. doi: 10.1016/j.drugalcdep.2017.10.012. PMID: 29248691. **Exclusion reason:** Systematic review used as source document
245. Syed Y, McKeage K, Scott L. Delta-9-Tetrahydrocannabinol/cannabidiol (Sativex(R)): a review of its Use in patients with moderate to severe spasticity due to multiple sclerosis. Drugs. 2014;74(5):563-78. doi: 10.1007/s40265-014-0197-5. PMID: 24671907. **Exclusion reason:** Systematic review used as source document
246. Sznitman S, Mabouk C, Said Z, et al. Opioid and healthcare service use in medical cannabis patients with chronic pain: a prospective study. BMJ Support Palliat Care. 2021;14:14. doi: 10.1136/bmjspcare-2020-002661. PMID: 34521640. **Exclusion reason:** Ineligible comparator
247. Sznitman SR, Vulfsons S, Meiri D, et al. Medical cannabis and cognitive performance in middle to old adults treated for chronic pain. Drug Alcohol Rev. 2020 Sep 22;22:22. doi: 10.1111/dar.13171. PMID: 32964502. **Exclusion reason:** Ineligible study design

248. Sznitman SR, Vulfsons S, Meiri D, et al. Medical cannabis and cognitive performance in middle to old adults treated for chronic pain. *Drug Alcohol Rev.* 2021;40(2):272-80. doi: 10.1111/dar.13171. PMID: 32964502. **Exclusion reason:** Ineligible study design
249. Takakuwa KM, Sulak D. A Survey on the Effect That Medical Cannabis Has on Prescription Opioid Medication Usage for the Treatment of Chronic Pain at Three Medical Cannabis Practice Sites. *Cureus.* 2020;12(12):e11848. doi: 10.7759/cureus.11848. PMID: 33409086. **Exclusion reason:** Ineligible study design
250. Tctr. The Study of Effectiveness of Zingiber cassumunar Roxb.(Plai) Mixed Cannabis sativa L. Leaf Oil for Chronic Pain in Elderly.Randomized controlled trial. <https://trialsearch.who.int/Trial2.aspx?TriallD=TCTR20211116004>. 2021. **Exclusion reason:** Ineligible publication type
251. Terrie YC. Medical cannabis for chronic pain. *US Pharm.* 2020;45(3):24-8. **Exclusion reason:** Ineligible publication type
252. Tervo-Clemmens B, Schmitt W, Wheeler G, et al. Cannabis Use and Sleep Quality in Daily Life: a Daily Diary Study of Adults Starting Cannabis for Health Concerns. medRxiv. 2022 2022-01-01 00:00:00doi: 10.1101/2022.01.19.22269565. **Exclusion reason:** Ineligible population
253. Thomas J. Inhaled cannabis relieves neuropathic pain. *Aust J Pharm.* 2011;92(1091):88. doi: 10.3316/informit.861962231552691. **Exclusion reason:** Ineligible publication type
254. Thomas PA, Carter GT, Bombardier CH. A scoping review on the effect of cannabis on pain intensity in people with spinal cord injury. *J Spinal Cord Med.* 2021:1-12. doi: 10.1080/10790268.2020.1865709. PMID: 33465022. **Exclusion reason:** Systematic review used as source document
255. Tsai SHL, Lin C-R, Shao S-C, et al. Cannabinoid Use for Pain Reduction in Spinal Cord Injuries: A Meta-Analysis of Randomized Controlled Trials. *Front Pharmacol.* 2022;13:866235. doi: <https://dx.doi.org/10.3389/fphar.2022.86623>
5. **Exclusion reason:** Systematic review used as source document
256. Turcotte DA, Namaka MP, Gomori AJ, et al. A randomized, double-blinded, placebo-controlled study evaluating the efficacy and safety of nabilone as an adjunctive to gabapentin in managing multiple sclerosis-induced neuropathic pain: an interim analysis. *Pain Res Manag.* 2011;15(2):99. **Exclusion reason:** Ineligible publication type
257. Uberall MA. A review of scientific evidence for THC:CBD oromucosal spray (nabiximols) in the management of chronic pain. *J Pain Res.* 2020 Feb 14;13:399-410. doi: 10.2147/JPR.S240011. PMID: 32104061. **Exclusion reason:** Systematic review used as source document
258. Ueberall MA, Essner U, Mueller-Schwefe GH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry. *J Pain Res.* 2019 May 20;12:1577-604. doi: 10.2147/JPR.S192174. PMID: 31190969. **Exclusion reason:** Ineligible comparator
259. Ueberall MA, Horlemann J, Schuermann N, et al. Effectiveness and Tolerability of Dronabinol Use in Patients with Chronic Pain - a Retrospective Analysis of 12-Week Open-Label Real-World Data Provided by the German Pain E-Registry. *Pain Med.* 2022 Feb 01;01:01. doi: 10.1093/pm/pnac010. PMID: 35104881. **Exclusion reason:** Ineligible study design
260. Urits I, Adamian L, Fiocchi J, et al. Advances in the understanding and management of chronic pain in multiple sclerosis: a comprehensive review. *Curr Pain Headache Rep.* 2019 Jul 25;23(8):59. doi: 10.1007/s11916-019-0800-2. PMID: 31342191. **Exclusion reason:** Systematic review used as source document
261. Urits I, Charipova K, Gress K, et al. Adverse Effects of Recreational and Medical Cannabis. *Psychopharmacol Bull.* 2021;51(1):94-109. PMID: 33897066. **Exclusion reason:** Ineligible study design
262. van Amerongen G, Kanhai K, Baakman AC, et al. Effects on spasticity and neuropathic

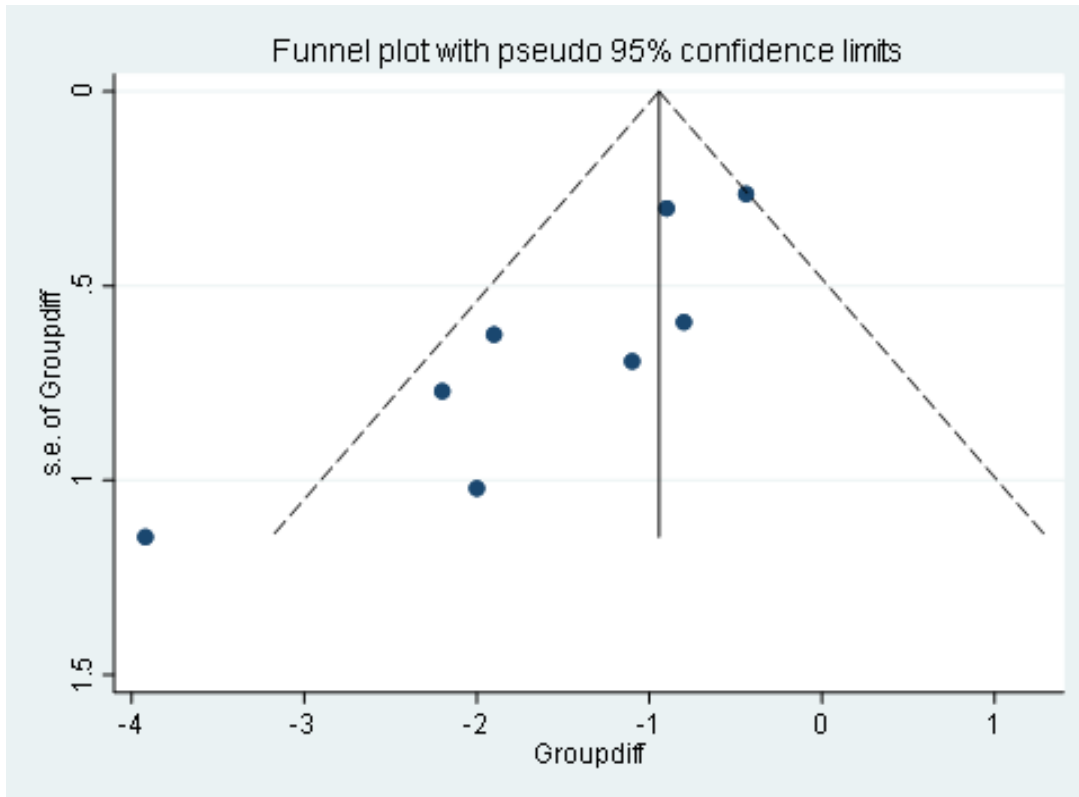
- pain of an oral formulation of DELTA9-tetrahydrocannabinol in patients with progressive multiple sclerosis. *Clin Ther*. 2018 Sep;40(9):1467-82. doi: 10.1016/j.clinthera.2017.01.016. PMID: 28189366. **Exclusion reason:** Ineligible population
263. Vermersch P, Trojano M. Tetrahydrocannabinol:Cannabidiol Oromucosal Spray for Multiple Sclerosis-Related Resistant Spasticity in Daily Practice. *Eur Neurol*. 2016;76(5-6):216-26. doi: 10.1159/000449413. PMID: 27732980. **Exclusion reason:** Ineligible comparator
264. Vicknasingam B, Chooi WT, Rahim AA, et al. Kratom and pain tolerance: a randomized, placebo-controlled, double-blind study. *Yale J Biol Med*. 2020;93(2):229-38. PMID: 32607084. **Exclusion reason:** Ineligible population
265. Vila Silvan C, Vaney C, Dykukha I. Systematic reviews of randomized controlled trials of cannabinoid products in chronic pain conditions and for symptoms associated with multiple sclerosis: what do they tell us? *Expert Rev Clin Pharmacol*. 2022doi: <https://dx.doi.org/10.1080/17512433.2022.2088501>. **Exclusion reason:** Systematic review used as source document
266. Wade DT, Makela P, Robson P, et al. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler*. 2004;10(4):434-41. doi: 10.1191/1352458504ms1082oa. PMID: 15327042. **Exclusion reason:** Ineligible population
267. Walitt B, Klose P, Fitzcharles MA, et al. Cannabinoids for fibromyalgia. *Cochrane Database Syst Rev*. 2016 Jul 18;7:CD011694. doi: 10.1002/14651858.CD011694.pub2. PMID: 27428009. **Exclusion reason:** Ineligible publication type
268. Wallace MS, Marcotte TD, Umlauf A, et al. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain*. 2015 Jul;16(7):616-27. doi: 10.1016/j.jpain.2015.03.008. PMID: 25843054. **Exclusion reason:** Inadequate duration
269. Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ*. 2021;374:n1034. doi: 10.1136/bmj.n1034. PMID: 34497047. **Exclusion reason:** Systematic review used as source document
270. Wang T, Collet JP, Shapiro S, et al. Adverse effects of medical cannabinoids: a systematic review. *CMAJ*. 2008;178(13):1669-78. doi: 10.1503/cmaj.071178. PMID: 18559804. **Exclusion reason:** Ineligible publication type
271. Wang Y, Jean Jacques J, Li Z, et al. Health Outcomes among Adults Initiating Medical Cannabis for Chronic Pain: A 3-month Prospective Study Incorporating Ecological Momentary Assessment (EMA). *Cannabis*. 2021;4(2):69-83. doi: 10.26828/cannabis/2021.02.006. PMID: 34671723. **Exclusion reason:** Ineligible comparator
272. Ware MA, Fitzcharles MA, Joseph L, et al. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg*. 2010 Feb 01;110(2):604-10. doi: 10.1213/ANE.0b013e3181c76f70. PMID: 20007734. **Exclusion reason:** Inadequate duration
273. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *Cmaj*. 2010 Oct 05;182(14):E694-701. doi: 10.1503/cmaj.091414. PMID: 20805210. **Exclusion reason:** Inadequate duration
274. White CM. Pharmacologic and clinical assessment of kratom. *Am J Health-Syst Pharm*. 2018 Mar 1;75(5):261-7. doi: 10.2146/ajhp161035. PMID: 29255059. **Exclusion reason:** Background only
275. White CM. Pharmacologic and clinical assessment of kratom: An update. *Am J Health-Syst Pharm*. 2019 Nov 13;76(23):1915-25. doi: 10.1093/ajhp/zxz221. PMID: 31626272. **Exclusion reason:** Background only
276. Williams AR, Hill KP. Care of the Patient Using Cannabis. *Ann Intern Med*. 2020;173(9):ITC65-ITC80. doi:

- 10.7326/AITC202011030. PMID: 33137270. **Exclusion reason:** Ineligible publication type
277. Williams AR, Mauro CM, Feng T, et al. Adult Medical Cannabinoid Use and Changes in Prescription Controlled Substance Use. *Cannabis Cannabinoid Res.* 2022doi: <https://dx.doi.org/10.1089/can.2021.0212>. **Exclusion reason:** Ineligible comparator
278. Wilsey B, Marcotte T, Deutsch R, et al. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain.* 2013 Feb;14(2):136-48. doi: 10.1016/j.jpain.2012.10.009. PMID: 23237736. **Exclusion reason:** Inadequate duration
279. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain.* 2008 Jun;9(6):506-21. doi: 10.1016/j.jpain.2007.12.010. PMID: 18403272. **Exclusion reason:** Inadequate duration
280. Wong SSC, Chan WS, Cheung CW. Analgesic effects of cannabinoids for chronic non-cancer pain: a systematic review and meta-analysis with meta-regression. *J Neuroimmune Pharmacol.* 2020 Dec;15(4):801-29. doi: 10.1007/s11481-020-09905-y. PMID: 32172501. **Exclusion reason:** Systematic review used as source document
281. Yacyshyn B, Hanauer S, Klassen P, et al. Safety, Pharmacokinetics, and Efficacy of Olorinab, a Peripherally Acting, Highly Selective, Full Agonist of the Cannabinoid Receptor 2, in a Phase 2a Study of Patients with Chronic Abdominal Pain Associated with Crohn's Disease. *Crohns Colitis* 2021;3(1)doi: 10.1093/crocol/otaa089. **Exclusion reason:** Ineligible intervention
282. Yanes JA, McKinnell ZE, Reid MA, et al. Effects of cannabinoid administration for pain: A meta-analysis and meta-regression. *Exp Clin Psychopharmacol.* 2019 Aug;27(4):370-82. doi: 10.1037/pha0000281. PMID: 31120281. **Exclusion reason:** Ineligible population
283. Yassin M, Oron A, Robinson D. Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study. *Clin Exp Rheumatol.* 2019 Jan-Feb;37(Suppl 116):S13-S20. PMID: 30418116. **Exclusion reason:** Ineligible study design
284. Yimam M, O'Neal A, Horm T, et al. Antinociceptive and Anti-Inflammatory Properties of Cannabidiol Alone and in Combination with Standardized Bioflavonoid Composition. *J Med Food.* 2021doi: 10.1089/jmf.2020.0178. PMID: 33570460. **Exclusion reason:** Ineligible population
285. Yu JS, Premkumar A, Liu S, et al. Rates of self-directed perioperative cannabidiol use in patients undergoing total hip or knee arthroplasty. *Pain manag.* 2021 Jun 09;09:09. doi: 10.2217/pmt-2021-0018. PMID: 34102871. **Exclusion reason:** Ineligible study design
286. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet.* 2003 Nov 8;362(9395):1517-26. doi: 10.1016/s0140-6736(03)14738-1. PMID: 14615106. **Exclusion reason:** Ineligible population
287. 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
288. Zeraatkar D, Cooper MA, Agarwal A, et al. Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: A systematic review of non-randomized studies. *medRxiv.* 2021 2021-01-01 00:00:00doi: 10.1101/2021.05.27.21257921. **Exclusion reason:** Systematic review used as source document
289. 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 J. Funnel Plot of High THC Ratio Studies Included in Meta-Analysis for Pain Severity

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



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