Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: Surveillance Report 1, September 2022

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

<table>
<thead>
<tr>
<th>Search End Date</th>
<th>Report (Publication Date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2021</td>
<td>Systematic Review (Oct. 27, 2021)</td>
</tr>
<tr>
<td>August 2021</td>
<td>Surveillance Report 1 (Oct. 27, 2021)</td>
</tr>
<tr>
<td>October 2021</td>
<td>Surveillance Report 2 (Jan. 28, 2022)</td>
</tr>
<tr>
<td>Mid-January 2022</td>
<td>Surveillance Report 3 (May 2022)</td>
</tr>
<tr>
<td>March 2022</td>
<td>Surveillance Report 4 (August 2022)</td>
</tr>
<tr>
<td>April 2022</td>
<td>Systematic Review (August 2022)</td>
</tr>
<tr>
<td>Early-July 2022</td>
<td>Surveillance Report 1 (September 2022)</td>
</tr>
</tbody>
</table>

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 THC to 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 comparing nabiximols (plant-extracted comparable tetrahydrocannabinol [THC] to cannabidiol [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), 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

<table>
<thead>
<tr>
<th>Key Questiona</th>
<th>Conclusions From Systematic Review</th>
<th>Findings From Surveillance to Date</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 and KQ2. Comparable THC to CBD Ratio Benefits and Harms</td>
<td>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)</td>
<td>No new studies</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ1 and KQ2. Synthetic High THC to CBD Ratio Benefits and Harms</td>
<td>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)</td>
<td>No new studies</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ1 and KQ2. Extracted Whole-Plant High THC to CBD Ratio Benefits and Harms</td>
<td>Benefits: insufficient evidence (2 RCTs) Harms: large increase in risk of dizziness and in study withdrawal due to adverse events (SOE: low; 1 RCT)</td>
<td>No new studies</td>
<td>No change in conclusions</td>
</tr>
</tbody>
</table>
### Key Question

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

*For Key Question wording, see the Background section below.*

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

### 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)

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

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

While opioids are often prescribed for chronic pain, a recent series of systematic reviews found that opioids,⁸ several nonopioid drugs,⁹ and some nonpharmacologic treatments¹⁰ 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.²,³ 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.¹¹
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, 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. 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.

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® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® 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, 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 and criteria developed by the U.S. Preventive Services Task Force 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 I² 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

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

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.\(^1,20-48\)

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD</th>
<th>THC</th>
<th>Synthetic THC</th>
<th>CBD</th>
<th>CBDV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THC to CBD Ratio</strong></td>
<td>Comparable (Study Count)</td>
<td>High (Study Count)</td>
<td>High (Study Count)</td>
<td>Low (Study Count)</td>
<td>NA - other cannabinoids</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Plant-extracted</td>
<td>Plant-extracted</td>
<td>Synthetic Nabilone Dronabinol Dronabinol/Namisol(^{6a})</td>
<td>Plant-extracted</td>
<td>Plant-extracted</td>
</tr>
<tr>
<td><strong>N Studies</strong></td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>2 (1 topical, 1 oral)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Comparator (Study Count)</strong></td>
<td>Placebo (7)</td>
<td>Placebo (2)</td>
<td>Placebo (6); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1)</td>
<td>Placebo (2)</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Route of Administration, Formulation</strong></td>
<td>Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 ml</td>
<td>Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)</td>
<td>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(^{6a}) 3 mg oral tablet (1)</td>
<td>Topical oil, 83 mg CBD/fluid ounce (k =1), Oral oil, 50 mg/ml CBDV</td>
<td>Oral oil, 50 mg/ml CBDV</td>
</tr>
<tr>
<td><strong>Dosing Regimen</strong></td>
<td>108 to 130 mg THC daily (max 22 mg in 3 hours). Final mean dose 23 mg THC/21 mg CBD daily.</td>
<td>Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily.</td>
<td>Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84</td>
<td>Topical oil: applied locally 1-4 times/day (volume/dose, final dose NR).</td>
<td>400 mg CBDV daily. Final dose NR.</td>
</tr>
<tr>
<td>Characteristic</td>
<td>THC/CBD</td>
<td>THC</td>
<td>Synthetic THC</td>
<td>CBD</td>
<td>CBDV</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>-----</td>
<td>---------------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>Risk of Bias</td>
<td>29% high, 57% moderate, 14% low</td>
<td>50% moderate, 50% low</td>
<td>22% high, 44% moderate, 33% low</td>
<td>50% high (topical), 50% moderate (oral)</td>
<td>100% moderate</td>
</tr>
<tr>
<td>Total Randomized</td>
<td>882</td>
<td>297</td>
<td>534</td>
<td>165</td>
<td>34</td>
</tr>
<tr>
<td>Age, Mean Years</td>
<td>53</td>
<td>52</td>
<td>50</td>
<td>65</td>
<td>50</td>
</tr>
<tr>
<td>Female, %</td>
<td>66%</td>
<td>89%</td>
<td>61%</td>
<td>41%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-White, b %</td>
<td>1.6% (2)</td>
<td>1%  (1)</td>
<td>5.4% (3)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Primary Pain Type (n Studies)</td>
<td>NPP (6); Inflammatory arthritis (1)</td>
<td>NPP (1); Fibromyalgia (1)</td>
<td>NPP (6); fibromyalgia (1); headache (1); visceral pain (1)</td>
<td>NPP (1 topical); OA (1 oral)</td>
<td>NPP (1)</td>
</tr>
<tr>
<td>Baseline Pain Score, Mean (Range)c</td>
<td>6.59 (5.3 to 7.3)</td>
<td>8.47 (8.25 to 8.67)</td>
<td>6.46 (4 to 8.1)d</td>
<td>5.38 (4.67 to 6.14)</td>
<td>6.28 (6.12 to 6.44)</td>
</tr>
<tr>
<td>Study Duration</td>
<td>4 to 15 weeks</td>
<td>8 to 12 weeks</td>
<td>4 to 47 weeks</td>
<td>4 weeks (topical) and 12 weeks (oral)</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

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

a Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.
b (n) = number of studies reporting this characteristic at baseline.
c Scores were standardized to a 0 to 10 scale.
d Weighted mean includes median scores for 1 study (6 vs. 6).

Table 7. Characteristics of included observational studies to date

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD</th>
<th>THC</th>
<th>Synthetic THC</th>
<th>THC/CBD vs. Synthetic THC</th>
<th>THC/CBD vs. LAOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC to CBD Ratio</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Comparable vs. high</td>
<td>Comparable</td>
</tr>
<tr>
<td>Source</td>
<td>Any cannabis product (patient’s choice)</td>
<td>Plant-based</td>
<td>Synthetic (nabilone)</td>
<td>Plant-based vs. synthetic</td>
<td>Plant-based</td>
</tr>
<tr>
<td>N Studies</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Comparator (Study Count)</td>
<td>No cannabis use (3); usual care (1); no medical cannabis authorization (1)</td>
<td>Usual care (1)</td>
<td>Gabapentin only; gabapentin + nabilone (1)</td>
<td>Active comparator; oral mucosal spray vs. dronabinol</td>
<td>Active comparator; oral mucosal spray vs. long-acting opioids, both as add-on therapy to current underlying systemic analgesia</td>
</tr>
<tr>
<td>Route of Administration, Formulation</td>
<td>Unreported (any available allowed, patient’s choice)</td>
<td>Whole-plant cannabis, “certified 12.5% THC” (CBD NR) route determined by patient: smoking 27%, oral 8%, vaporization 4%, combination 61%</td>
<td>Nabilone 0.5 mg oral capsule</td>
<td>Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Dronabinol oral capsule (strength NR)</td>
<td>Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Oral long-acting opioids (dose varied)</td>
</tr>
</tbody>
</table>
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 (LAO) as add-on therapies.¹ 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 MD 9.90, 95% 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 long-acting opioids group (7.9% vs. 29.3%; RR 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


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Disclaimers

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00006). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work is the first surveillance update of a living systematic evidence report, Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ) following the second yearly full systematic review.
Afterword

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

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

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

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

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Appendix 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 cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,kf.
14 or/9-13
15 8 and 14
16 limit 15 to english language
17 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
18 ((animal or animals or avian or bird or birds or bovine or canine or cow* or dog or dogs or cat or cats or feline or hamster* or horse* or lamb or lamb* or mouse or mice or monkey or monkeys or murine or pig or piglet* or pigs or porcine or primate* or rabbit* or rat or rats or rodent* or songbird* or veterinar*) not (human* or patient*).ti,kf,jw.
19 or/17-18
20 16 not 19

Database: EBM Reviews - Cochrane Central Register of Controlled Trials 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 cannabinoil 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 cannabinoil 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 'cannabinol'/exp OR cannabinoil 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 'the' 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 cannabinol OR marijuana OR cannabidiol OR phytocannabinoid* OR tetrahydrocannabinol OR dronabinol OR nabilone OR sativex OR "CBD" OR "THC" OR kratom OR khat OR qat OR psilocybin OR hemp OR hydroxymitragynine ) ) AND ( TITLE ( "chronic pain" OR arthralgia OR "back pain" OR headache OR "musculoskeletal pain" OR "neck pain" OR neuralgia OR "nociceptive pain" OR "intractable pain" OR fibromyalgia OR myalgia OR arthritis OR osteoarthritis OR "neuropathic pain" ) )
Appendix B. Methods

Inclusion and Exclusion Criteria

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

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

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

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

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

<table>
<thead>
<tr>
<th>Table B-1. PICOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICOTS Element</td>
</tr>
<tr>
<td>Population</td>
</tr>
</tbody>
</table>
| Interventions    | **KQs 1 and 2:** Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes  
|                  | **KQs 3 and 4:** Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids  
|                  | All KQs: Co-use of other drugs for pain | All KQs: Non-plant-based interventions, capsaicin, herbal supplements |
| Comparators      | All KQs: Any comparator or usual care | All KQs: No comparison |
| Outcomes         | All KQs: Primary efficacy outcomes (i.e., pain, function, disability, pain interference); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder); secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, health care utilization) | All KQs: Other outcomes |
| Time of followup | All KQs: short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year) | All KQs: Studies with <1-month (4 weeks) of treatment or followup after treatment |
| Setting          | All KQs: Any nonhospital setting or setting of self-directed care | All KQs: Hospital care, hospice care, emergency department care |
| Study design     | All KQs: RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits | All KQs: Other study designs |

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

Important subgroups to consider in evaluating this evidence are:
Specific types of pain: neuropathic pain (including nociceptive and centralized; patients with multiple sclerosis and painful skin disorders are included in this category), musculoskeletal pain (including low-back pain), visceral pain, fibromyalgia, inflammatory arthritis, headache disorders, sickle cell disease, and cancer pain (non-end of life)

- Degree of nociceptivity/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, and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force. 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. Studies were given an overall rating of “low,” “medium,” or “high” risk of bias. We used DistillerSR® software to conduct these assessments, using dual review by two independent reviewers. Disagreements identified by DistillerSR® were resolved through consensus. Assessments and final ratings were converted to evidence tables, and 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 that meet inclusion criteria are included in this review. We evaluated the persistence of benefits or harms by evaluating the three periods identified in prior AHRQ pain reports (3 to 6 months, 6 to 12 months, and ≥12 months).

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. 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 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 I² 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 (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. 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.
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

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

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

Findings that were not statistically significant were interpreted as follows:

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

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. 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."

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

Appendix B References


Appendix C. Included Studies List


Appendix D. Literature Flow Diagram

Figure D-1. Literature flow diagram

Abstracts of potentially relevant articles identified through Ovid®, MEDLINE®, PsycINFO®, Embase®, the Cochrane Central Register of Controlled Trials, and prior chronic pain reports (n=3,419)

- Excluded abstracts (n=3,100)

- Full-text articles reviewed for inclusion (n=319)
  - Excluded articles (n=289)
    - Ineligible population: 36
    - Ineligible intervention: 6
    - Ineligible comparator: 31
    - Ineligible outcome: 7
    - Ineligible duration: 17
    - Ineligible study design: 37
    - Ineligible publication type: 59
    - Study not in English: 9
    - Publication used as source document: 73
    - Background information only: 14

- Included studies (n=30)

Note: Numbers in parenthesis indicate all records identified to date.
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>
<thead>
<tr>
<th>Author, Year</th>
<th>Risk of Bias</th>
<th>Study Design</th>
<th>Pain Condition</th>
<th>Comparison (n)</th>
<th>Followup Duration</th>
<th>Primary Pain Outcomes (Response, Severity)</th>
<th>Serious Adverse Events and Withdrawals Due to Adverse Events</th>
<th>Other Primary Outcomes (Function/Disability, Pain Interference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake, 2006</td>
<td>Moderate</td>
<td>RCT</td>
<td>Inflammatory arthritis-rheumatoid arthritis</td>
<td>A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 5.4 sprays/day (31)</td>
<td>5 weeks</td>
<td>Pain severity (mean [SD NR] 0 to 10 NRS scale): 3.1 vs. 4.1, MD −1.04 (95% CI −1.9 to −0.18)</td>
<td>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)</td>
<td>Function (mean [SD NR] 0 to 10 28−Joint Disease Activity Score scale): 5 vs. 5.9, MD −0.76 (95% CI −1.23 to −0.28)</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>Low</td>
<td>RCT</td>
<td>Neuropathic pain-multiple sclerosis</td>
<td>A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.8 sprays/day (167)</td>
<td>15 weeks</td>
<td>Pain response ≥30% (NRS scale): 83/167 (49.75%) vs. 77/172 (44.77%), RR 1.11 (95% CI 0.89 to 1.39)</td>
<td>WAE: 14/167 (8.38%) vs. 9/172 (5.23%), RR 1.60 (95% CI 0.71 to 3.60)</td>
<td>Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.12, p=0.56</td>
</tr>
<tr>
<td>Lynch, 2014</td>
<td>High</td>
<td>RCT (crossover)</td>
<td>Neuropathic pain-chemotherapy induced</td>
<td>A: THC/CBD oromucosal spray (dose NR), mean dose 8 sprays/day (8)</td>
<td>4 weeks</td>
<td>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)</td>
<td>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)</td>
<td>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)</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Risk of Bias</td>
<td>Study Design</td>
<td>Pain Condition</td>
<td>Comparison (n)</td>
<td>Followup Duration Derivative</td>
<td>Primary Pain Outcomes (Response, Severity)</td>
<td>Serious Adverse Events and Withdrawals Due to Adverse Events&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Other Primary Outcomes (Function/Disability, Pain Interference)</td>
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<tr>
<td>Nurmikko, 2007</td>
<td>Moderate RCT</td>
<td>Neuropathic pain-mixed</td>
<td>A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 10.9 sprays/day (63)</td>
<td>Pain response ≥30% (NRS scale): 16/73 (25.4%) vs. 9/62 (14.52%), RR 1.75 (95% CI 0.84 to 3.66)</td>
<td>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)</td>
<td>Function (0 to 70 Pain Disability Index scale): MD −6.85 (95% CI −9.62 to −2.09)</td>
<td></td>
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<tr>
<td>Rog, 2005</td>
<td>Moderate RCT</td>
<td>Neuropathic pain-multiple sclerosis</td>
<td>A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 9.6 sprays/day (34)</td>
<td>Pain severity (mean [SD] 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)</td>
<td>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)</td>
<td>NR</td>
<td></td>
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</tr>
<tr>
<td>Selvarajah, 2010</td>
<td>High RCT</td>
<td>Neuropathic pain-diabetic neuropathy</td>
<td>A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 7 sprays/day&lt;sup&gt;d&lt;/sup&gt; (15)</td>
<td>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)</td>
<td>NR</td>
<td>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)</td>
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<tr>
<td>Serpell, 2014</td>
<td>Moderate RCT</td>
<td>Neuropathic pain-mixed</td>
<td>A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.9 sprays/day (128)</td>
<td>Pain response ≥30% (NRS scale): 34/123 (27.64%) vs. 19/117 (16.24%), RR 1.7 (95% CI 1.03 to 2.91)</td>
<td>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)</td>
<td>Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.32 (SE 0.241) (95% CI −0.8 to 0.15)</td>
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</table>

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 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>
<thead>
<tr>
<th>Author, Year</th>
<th>Risk of Bias</th>
<th>Study Design</th>
<th>Pain Condition</th>
<th>Comparison (n)</th>
<th>Primary Pain Outcomes (Response, Severity)</th>
<th>Serious Adverse Events and Withdrawals Due to Adverse Events&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Other Primary Outcomes (Function/Disability, Pain Interference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaves, 2020</td>
<td>Low</td>
<td>RCT</td>
<td>Fibromyalgia</td>
<td>A: 1.2 mg THC/0.02 mg CBD sublingual drops, mean 3.6 drops/day (8) B: Placebo (9)</td>
<td>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)</td>
<td>WAE: 0/8 (0%) vs. 0/9 (0%), RR 1.11 (95% CI 0.02 to 50.43)</td>
<td>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)</td>
</tr>
<tr>
<td>de Vries, 2017</td>
<td>Moderate</td>
<td>RCT</td>
<td>Visceral pain- chronic pancreatitis and postsurgical abdominal pain</td>
<td>A: THC oral tablet (Dronabinol), range 15 to 24 mg/day (30) B: Placebo (32)</td>
<td>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)</td>
<td>WAE: 7/30 (23.33%) vs. 2/32 (6.25%), RR 3.73 (95% CI 0.84 to 16.57)</td>
<td>NR</td>
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<tr>
<td>Frank, 2008</td>
<td>Moderate</td>
<td>RCT (crossover)</td>
<td>Neuropathic pain</td>
<td>A: THC oral capsule (Nabilone), max dose 2 mg/day (48) B: Dihydrocodeine 30 mg, max dose 240 mg/day (48)</td>
<td>Pain severity (mean [SD NR] 0 to 100 VAS scale): Treatment effect 5.7 (95% CI 0.5 to 10.9)</td>
<td>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)</td>
<td>Function (mean [SD NR] 0 to 100 SF−36 Physical Functioning scale): Treatment effect 10.8 (95% CI 2.3 to 19.2)</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Risk of Bias</td>
<td>Study Design</td>
<td>Pain Condition</td>
<td>Comparison (n) Followup Duration Derivative</td>
<td>Primary Pain Outcomes (Response, Severity)</td>
<td>Serious Adverse Events and Withdrawals Due to Adverse Eventsa</td>
<td>Other Primary Outcomes (Function/Disability, Pain Interference)</td>
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<tr>
<td>Pini, 2012</td>
<td>Low</td>
<td>RCT (crossover)</td>
<td>Headache- medication overuse headache</td>
<td>A: THC 0.5 mg oral capsule (Nabilone) daily (26) B: Ibuprofen 400 mg/day (26) 8 weeks Synthetic</td>
<td>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)</td>
<td>WAE: 1/30 (3.33%) vs. 1/30 (3.33%), RR 1.00 (95% CI 0.07 to 15.26)</td>
<td>NR</td>
</tr>
<tr>
<td>Rintala, 2010</td>
<td>High</td>
<td>RCT (crossover)</td>
<td>Neuropathic pain- spinal cord injury</td>
<td>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</td>
<td>Pain severity (mean [SD NR] 0 to 10 BPI scale): 5.8 vs. 5.8</td>
<td>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)</td>
<td>NR</td>
</tr>
<tr>
<td>Schimrigk, 2017</td>
<td>Low</td>
<td>RCT</td>
<td>Neuropathic pain- multiple sclerosis</td>
<td>A: THC 2.5 mg oral capsule (Dronabinol), mean dose 13 mg/day (124) B: Placebo (116) 16 weeks Synthetic</td>
<td>Pain severity (mean [SD] 0 to 10 NRS scale): 4.48 (2.04) vs. 4.92 (2.04), MD NR, p=0.676</td>
<td>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)</td>
<td>NR</td>
</tr>
<tr>
<td>Skrabek, 2008</td>
<td>Moderate</td>
<td>RCT</td>
<td>Fibromyalgia</td>
<td>A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 2 mg/day (15) B: Placebo (18) 4 weeks Synthetic</td>
<td>Pain severity (mean [SD NR] 0 to 10 VAS scale): 4.8 vs. 5.6, MD −1.43, p&lt;0.05</td>
<td>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)</td>
<td>NR</td>
</tr>
<tr>
<td>Toth, 2012</td>
<td>Low</td>
<td>RCT</td>
<td>Neuropathic pain- diabetic neuropathy</td>
<td>A: THC 0.5 mg oral capsule (Nabilone), max dose 4 mg/day (13) B: Placebo (13) 5 weeks Synthetic</td>
<td>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)</td>
<td>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)</td>
<td>NR</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Risk of Bias</td>
<td>Study Design</td>
<td>Pain Condition</td>
<td>Comparison (n)</td>
<td>Primary Pain Outcomes (Response, Severity)</td>
<td>Serious Adverse Events and Withdrawals Due to Adverse Events(^a)</td>
<td>Other Primary Outcomes (Function/Disability, Pain Interference)</td>
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<tr>
<td>Turcotte, 2015</td>
<td>Moderate RCT</td>
<td>Neuropathic pain- multiple sclerosis</td>
<td>A: THC 0.5 mg oral capsule (Nabilone), max dose 2 mg/day (8)</td>
<td>Pain severity (mean [SD NR] 0 to 100 VAS scale): 35 vs. 57(^b)</td>
<td>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)</td>
<td>Pain interference (mean [SD NR] 0 to 100 VAS impact scale): 41 vs. 40(^b)</td>
<td></td>
</tr>
<tr>
<td>Wissel, 2006</td>
<td>High RCT (crossover)</td>
<td>Neuropathic pain- multiple sclerosis</td>
<td>A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 1 mg/day (13)</td>
<td>Pain severity (median [SD NR] 11 Point Box Test): 4 vs. 6, (p&lt;0.05)</td>
<td>WAE: 2/13 (15.38%) vs. 0/13 (0%), RR 5.00 (95% CI 0.26 to 95.02)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Zajicek, 2012</td>
<td>Moderate RCT</td>
<td>Neuropathic pain- multiple sclerosis</td>
<td>A: THC 2.5 mg capsule, max dose 25 mg/day (143)</td>
<td>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)</td>
<td>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)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

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 adverse events.

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

\(^b\) Estimated from graph.
Table E-3. Low THC to CBD ratio study primary outcomes

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Risk of Bias Study Design Pain Condition</th>
<th>Comparison (n) Followup Duration Derivative</th>
<th>Primary Pain Outcomes (Response, Severity)</th>
<th>Serious Adverse Events and Withdrawals Due to Adverse Eventsa</th>
<th>Other Primary Outcomes (Function/Disability, Pain Interference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vela, 2021 Moderate RCT Musculoskeletal - hand osteoarthritis and psoriatic arthritis</td>
<td>A: CBD oral tablet (20 to 30 mg/day) (68) B: Placebo (61) 12 weeks Synthetic CBD</td>
<td>Pain response ≥30% (VAS 0 to 100 scale): 27/68 (39.7%) vs. 24/61 (39.3%), RR 1.01 (95% CI 0.66 to 1.55) Pain severity (0 to 100 VAS scale): mean NR, MD 0.23 (95% CI -9.41 to 9.9)</td>
<td>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)</td>
<td>Function/disability (0 to 3 HAQ-DI scale): mean NR, MD 0.03 (95% CI -0.11 to 0.18)</td>
<td></td>
</tr>
<tr>
<td>Xu, 2020 High RCT (crossover) Neuropathic pain-mixed</td>
<td>A: CBD cream (250 mg/3 oz) up to 4 times daily (15) B: Placebo (14) 4 weeks Whole plant extracted</td>
<td>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)</td>
<td>SAE: 0/15 (0%) vs. 0/14 (0%)</td>
<td>NR</td>
<td></td>
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</tbody>
</table>

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

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

Table E-4. Other cannabinoids study primary outcomes

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Risk of Bias Study Design Pain Condition</th>
<th>Comparison (n) Followup Duration Derivative</th>
<th>Primary Pain Outcomes (Response, Severity)</th>
<th>Serious Adverse Events and Withdrawals Due to Adverse Eventsa</th>
<th>Other Primary Outcomes (Function/Disability, Pain Interference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eibach, 2020 Moderate RCT (crossover) Neuropathic pain- HIV associated</td>
<td>A: CBDV oral solution (50 mg/mL) 400 mg/day (16) B: Placebo (16) 4 weeks Whole plant extracted</td>
<td>Pain response ≥30% (NRS scale): 6/16 (37.5%) vs. 13/16 (81.25%), RR NR Pain severity (mean [SD] 0 to 10 NRS scale): 2.74 (1.47) vs. 3.67 (2.62), MD -0.62 (95% CI -2.27 to 1.51)</td>
<td>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)</td>
<td>Pain interference (0 to 10 BPI-SF scale): MD -0.35 (95% CI -1.36 to 0.43)</td>
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</tbody>
</table>

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

a Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Risk of Bias</th>
<th>Study Design</th>
<th>Pain Condition</th>
<th>Comparison (n)</th>
<th>Primary Pain Outcomes (Response, Severity)</th>
<th>Serious Adverse Events and Withdrawals Due to Adverse Events&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Other Primary Outcomes (Function/Disability, Pain Interference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bestard, 2011</td>
<td>Moderate Prospective cohort Neuropathic pain-mixed</td>
<td>A: THC oral capsule (Nabilone), mean dose 3.05 mg/day (49)</td>
<td>Pain intensity (mean [SD]; 0 to 10 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</td>
<td>SAE: 0/49 (0%) vs. 0/52 (0%) vs. 0/55 (0%)</td>
<td>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 0.98 to 0.88) for A vs. C</td>
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<tr>
<td>Campbell, 2018</td>
<td>Moderate</td>
<td>A: Self-reported frequent cannabis use of ≥20 days/mo</td>
<td>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</td>
<td>A vs. B (reference)</td>
<td>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</td>
<td>NR</td>
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<tr>
<td>Gruber, 2021</td>
<td>High Prospective cohort Mixed (primarily musculoskeletal)</td>
<td>A: THC/CBD: Medicinal cannabis program, mean dose THC 13.3 mg/day, CBD 28.9 mg/day (37)</td>
<td>Pain intensity (mean [SD]; 0 to 10 VAS scale): 34.07 (22.36) vs. 48.78 (30.42); MD −14.71 (95% CI, −32.71 to 3.29)</td>
<td>NR</td>
<td>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)</td>
<td>SF-36 Function (mean [SD], 0 to 100 scale&lt;sup&gt;a&lt;/sup&gt;): 70.00 (22.87) vs. 69.44 (26.98); MD 0.56 (95% CI −17.17 to 18.29)</td>
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</tr>
<tr>
<td>Author, Year</td>
<td>Risk of Bias</td>
<td>Study Design</td>
<td>Pain Condition</td>
<td>Comparison (n)</td>
<td>Followup Duration</td>
<td>Derivative</td>
<td>Primary Pain Outcomes (Response, Severity)</td>
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<tr>
<td>Lee, 2021&lt;sup&gt;b&lt;/sup&gt; Moderate Matched cohort NR</td>
<td>Moderate</td>
<td>Matched cohort</td>
<td>NR</td>
<td>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)</td>
<td>20 months Unknown THC concentration; patient-driven choice</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Merlin, 2019&lt;sup&gt;b&lt;/sup&gt; High Prospective cohort Chronic non-cancer pain (HIV)</td>
<td>High</td>
<td>Prospective cohort</td>
<td>Chronic non-cancer pain (HIV)</td>
<td>A: Daily or weekly use of marijuana (55) B: Monthly or 1-2 times a month use of marijuana (65) C: No use (313)</td>
<td>52 weeks Unknown THC concentration; patient-driven choice</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ueberall, 2022&lt;sup&gt;a&lt;/sup&gt; Moderate Retrospective cohort Peripheral neuropathic pain</td>
<td>Moderate</td>
<td>Retrospective cohort</td>
<td>Peripheral neuropathic pain</td>
<td>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)</td>
<td>24 weeks Whole plant extracted vs. synthetic</td>
<td>A vs. B Pain intensity index (VAS 0-100 scale) mean relative change (improvement) rates at week 24 83.4% vs. 75.9%, p&lt;0.001 Pain intensity index (VAS 0-100 scale, converted to 0-10) mean difference: 3.50 (95% CI 1.6 to 5.4)</td>
<td>NR</td>
</tr>
<tr>
<td>Author, Year Risk of Bias Study Design Pain Condition</td>
<td>Comparison (n) Followup Duration Derivative</td>
<td>Primary Pain Outcomes (Response, Severity)</td>
<td>Serious Adverse Events and Withdrawals Due to Adverse Events*</td>
<td>Other Primary Outcomes (Function/Disability, Pain Interference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>---------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>---------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueberall, 2022b Moderate Retrospective cohort Peripheral neuropathic back pain- mixed</td>
<td>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</td>
<td>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)</td>
<td>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&lt;0.001</td>
<td>WAE: 7.9% vs. 29.3%, RR 0.27 (95% CI 0.20 to 0.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigil, 2017 b High Preliminary historical cohort Mixed musculoskeletal pain</td>
<td>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</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ware, 2015 High Prospective cohort Chronic non-cancer pain</td>
<td>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</td>
<td>NR</td>
<td>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)</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

* Higher scores indicate better outcomes.

b Only included outcome reported was opioid-use.
## Meta-Analysis Results

### Comparable THC to CBD Ratio Studies

Pooled results and the forest plot for the sensitivity analysis conducted for improvement in pain severity are available upon request by emailing 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)**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>N, Mean (SD), Intervention</th>
<th>N, Mean (SD), Control</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch, 2014</td>
<td>NPP</td>
<td>4</td>
<td>8 sprays/day</td>
<td>High</td>
<td>8, 6.31 (0.67)</td>
<td>8, 6.38 (0.65)</td>
<td>-0.07 (-0.91, 0.77)</td>
</tr>
<tr>
<td>Blake, 2006</td>
<td>IA</td>
<td>5</td>
<td>5.4 sprays/day</td>
<td>Moderate</td>
<td>31, 3.10 (NR)</td>
<td>27, 4.10 (NR)</td>
<td>-1.04 (-1.90, -0.18)</td>
</tr>
<tr>
<td>Rog, 2005</td>
<td>NPP</td>
<td>5</td>
<td>9.6 sprays/day</td>
<td>Moderate</td>
<td>33, 3.85 (2.04)</td>
<td>32, 4.96 (2.12)</td>
<td>-1.25 (-2.11, -0.39)</td>
</tr>
<tr>
<td>Nurmikko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9 sprays/day</td>
<td>Moderate</td>
<td>63, 5.82 (NR)</td>
<td>62, 6.68 (NR)</td>
<td>-0.96 (-1.59, -0.33)</td>
</tr>
<tr>
<td>Selvanrajah, 2010</td>
<td>NPP</td>
<td>12</td>
<td>7 sprays/day</td>
<td>High</td>
<td>15, 5.16 (2.19)</td>
<td>14, 5.19 (2.41)</td>
<td>-0.03 (-1.78, 1.72)</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8 sprays/day</td>
<td>Low</td>
<td>167, 4.54 (2.24)</td>
<td>172, 4.73 (2.26)</td>
<td>-0.19 (-0.67, 0.29)</td>
</tr>
<tr>
<td>Serpell, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9 sprays/day</td>
<td>Moderate</td>
<td>NR</td>
<td>NR</td>
<td>-0.34 (-0.79, 0.11)</td>
</tr>
<tr>
<td>Overall, PL (p = 0.133, I² = 38.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.54 (-0.95, -0.19)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation.
Figure E-2. Proportion of patients with pain response (>30% improvement) with comparable THC to CBD ratio versus placebo (short-term, 4 weeks to 6 months follow-up)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nummikko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9 sprays/day</td>
<td>Moderate</td>
<td>16/63</td>
<td>9/62</td>
<td>1.75 (0.84, 3.66)</td>
</tr>
<tr>
<td>Selvarajah, 2010</td>
<td>NPP</td>
<td>12</td>
<td>7 sprays/day</td>
<td>High</td>
<td>8/15</td>
<td>9/14</td>
<td>0.83 (0.45, 1.53)</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8 sprays/day</td>
<td>Low</td>
<td>83/167</td>
<td>77/172</td>
<td>1.11 (0.89, 1.39)</td>
</tr>
<tr>
<td>Serpell, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9 sprays/day</td>
<td>Moderate</td>
<td>34/123</td>
<td>19/117</td>
<td>1.70 (1.03, 2.81)</td>
</tr>
<tr>
<td>Overall, PL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>141/368</td>
<td>114/365</td>
<td>1.18 (0.93, 1.41)</td>
</tr>
</tbody>
</table>

(p = 0.195, I² = 36.1%)

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)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>N, Mean (SD), Intervention</th>
<th>N, Mean (SD), Control</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake, 2006</td>
<td>IA</td>
<td>5</td>
<td>5.4 sprays/day</td>
<td>Moderate</td>
<td>31, 5.00 (NR)</td>
<td>27, 5.90 (NR)</td>
<td>-0.76 (-1.23, -0.29)</td>
</tr>
<tr>
<td>Rog, 2005</td>
<td>NPP</td>
<td>5</td>
<td>9.6 sprays/day</td>
<td>Moderate</td>
<td>33, -0.27 (0.75)</td>
<td>32, -0.08 (0.73)</td>
<td>-0.26 (-0.62, 0.10)</td>
</tr>
<tr>
<td>Nummikko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9 sprays/day</td>
<td>Moderate</td>
<td>63, -0.80 (NR)</td>
<td>62, 0.03 (NR)</td>
<td>-0.84 (-1.37, -0.31)</td>
</tr>
<tr>
<td>Selvarajah, 2010</td>
<td>NPP</td>
<td>12</td>
<td>7 sprays/day</td>
<td>High</td>
<td>15, 0.95 (1.66)</td>
<td>14, 6.35 (2.79)</td>
<td>-0.60 (-2.33, 1.13)</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8 sprays/day</td>
<td>Low</td>
<td>167, -1.47 (NR)</td>
<td>172, -1.35 (NR)</td>
<td>-0.12 (-0.52, 0.28)</td>
</tr>
<tr>
<td>Serpell, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9 sprays/day</td>
<td>Moderate</td>
<td>NR</td>
<td>NR</td>
<td>-0.32 (-0.79, 0.15)</td>
</tr>
<tr>
<td>Overall, PL (p = 0.193, I² = 32.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.42 (-0.73, -0.16)</td>
</tr>
</tbody>
</table>

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 follow-up)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Dose (sprays/day)</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rog, 2005</td>
<td>NPP</td>
<td>5</td>
<td>9.6</td>
<td>Moderate</td>
<td>30/34</td>
<td>22/32</td>
<td>1.28 (0.99, 1.67)</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8</td>
<td>Low</td>
<td>120/167</td>
<td>106/172</td>
<td>1.17 (1.00, 1.36)</td>
</tr>
<tr>
<td>Overall, PL</td>
<td>NPP</td>
<td>15</td>
<td>8.8</td>
<td>Low</td>
<td>150/201</td>
<td>128/204</td>
<td>1.19 (1.02, 1.44)</td>
</tr>
</tbody>
</table>

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 follow-up)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Dose (sprays/day)</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake, 2006</td>
<td>IA</td>
<td>5</td>
<td>5.4</td>
<td>Moderate</td>
<td>0/31</td>
<td>2/27</td>
<td>0.18 (0.01, 3.49)</td>
</tr>
<tr>
<td>Nummikko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9</td>
<td>Moderate</td>
<td>1/63</td>
<td>0/62</td>
<td>2.95 (0.12, 71.13)</td>
</tr>
<tr>
<td>Serebri, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9</td>
<td>Moderate</td>
<td>10/128</td>
<td>7/118</td>
<td>1.32 (0.52, 3.35)</td>
</tr>
<tr>
<td>Overall, PL</td>
<td>NPP</td>
<td>15</td>
<td>8.9</td>
<td>Moderate</td>
<td>11/222</td>
<td>9/207</td>
<td>1.18 (0.28, 3.43)</td>
</tr>
</tbody>
</table>

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)**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>Treatment Control</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake, 2006</td>
<td>IA</td>
<td>5</td>
<td>5.4 sprays/day</td>
<td>Moderate</td>
<td>0/31</td>
<td>3/27</td>
</tr>
<tr>
<td>Rog, 2005</td>
<td>NPP</td>
<td>5</td>
<td>9.6 sprays/day</td>
<td>Moderate</td>
<td>2/34</td>
<td>0/32</td>
</tr>
<tr>
<td>Nummiiko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9 sprays/day</td>
<td>Moderate</td>
<td>11/63</td>
<td>2/62</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8 sprays/day</td>
<td>Low</td>
<td>15/167</td>
<td>12/172</td>
</tr>
<tr>
<td>Serpell, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9 sprays/day</td>
<td>Moderate</td>
<td>25/128</td>
<td>25/118</td>
</tr>
<tr>
<td>Overall, PL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53/423</td>
<td>42/411</td>
</tr>
</tbody>
</table>

(p = 0.084, $I^2 = 51.3\%$)

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)**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Dose (sprays/day)</th>
<th>Risk of Bias</th>
<th>Treatment Control</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch, 2014</td>
<td>NPP</td>
<td>4</td>
<td>8</td>
<td>High</td>
<td>6/16</td>
<td>0/16</td>
</tr>
<tr>
<td>Blake, 2006</td>
<td>IA</td>
<td>5</td>
<td>5.4</td>
<td>Moderate</td>
<td>8/31</td>
<td>1/27</td>
</tr>
<tr>
<td>Rog, 2005</td>
<td>NPP</td>
<td>5</td>
<td>9.6</td>
<td>Moderate</td>
<td>18/34</td>
<td>5/32</td>
</tr>
<tr>
<td>Nummiiko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9</td>
<td>Moderate</td>
<td>18/63</td>
<td>9/62</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8</td>
<td>Low</td>
<td>34/167</td>
<td>7/172</td>
</tr>
<tr>
<td>Serpell, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9</td>
<td>Moderate</td>
<td>52/128</td>
<td>12/118</td>
</tr>
<tr>
<td>Overall, PL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>136/439</td>
<td>34/427</td>
</tr>
</tbody>
</table>

(p = 0.448, $I^2 = 0.0\%$)

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)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Dose (sprays/day)</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch, 2014</td>
<td>NPP</td>
<td>4</td>
<td>8</td>
<td>High</td>
<td>6/16</td>
<td>1/16</td>
<td>6.00 (0.81, 44.35)</td>
</tr>
<tr>
<td>Blake, 2006</td>
<td>IA</td>
<td>5</td>
<td>5.4</td>
<td>Moderate</td>
<td>2/31</td>
<td>1/27</td>
<td>1.74 (0.17, 18.16)</td>
</tr>
<tr>
<td>Rog, 2005</td>
<td>NPP</td>
<td>5</td>
<td>9.6</td>
<td>Moderate</td>
<td>3/34</td>
<td>2/32</td>
<td>1.41 (0.25, 7.91)</td>
</tr>
<tr>
<td>Nurmiikko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9</td>
<td>Moderate</td>
<td>14/63</td>
<td>7/62</td>
<td>1.97 (0.85, 4.54)</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8</td>
<td>Low</td>
<td>13/167</td>
<td>7/172</td>
<td>1.91 (0.78, 4.88)</td>
</tr>
<tr>
<td>Serpell, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9</td>
<td>Moderate</td>
<td>23/128</td>
<td>14/118</td>
<td>1.51 (0.82, 2.80)</td>
</tr>
<tr>
<td>Overall, PL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61/439</td>
<td>32/427</td>
<td>1.79 (1.19, 2.77)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Dose (sprays/day)</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch, 2014</td>
<td>NPP</td>
<td>4</td>
<td>8</td>
<td>High</td>
<td>7/16</td>
<td>0/16</td>
<td>15.00 (0.93, 242.43)</td>
</tr>
<tr>
<td>Blake, 2006</td>
<td>IA</td>
<td>5</td>
<td>5.4</td>
<td>Moderate</td>
<td>1/31</td>
<td>1/27</td>
<td>0.87 (0.06, 13.27)</td>
</tr>
<tr>
<td>Rog, 2005</td>
<td>NPP</td>
<td>5</td>
<td>9.6</td>
<td>Moderate</td>
<td>3/34</td>
<td>0/32</td>
<td>6.60 (0.39, 122.96)</td>
</tr>
<tr>
<td>Nurmiikko, 2007</td>
<td>NPP</td>
<td>5</td>
<td>10.9</td>
<td>Moderate</td>
<td>4/63</td>
<td>1/62</td>
<td>3.94 (0.45, 34.24)</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>NPP</td>
<td>15</td>
<td>8.8</td>
<td>Low</td>
<td>16/167</td>
<td>3/172</td>
<td>5.49 (1.63, 18.51)</td>
</tr>
<tr>
<td>Serpell, 2014</td>
<td>NPP</td>
<td>15</td>
<td>8.9</td>
<td>Moderate</td>
<td>4/128</td>
<td>0/118</td>
<td>8.30 (0.45, 152.57)</td>
</tr>
<tr>
<td>Overall, PL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35/439</td>
<td>5/427</td>
<td>5.04 (2.10, 11.89)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Derivative Type and Author, Year</th>
<th>Pain Population</th>
<th>THC/CBD Ratio</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Type</th>
<th>Intervention Dose</th>
<th>N, Mean (SD), Intervention</th>
<th>N, Mean (SD), Control</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic de Vries, 2017*</td>
<td>VP All THC</td>
<td>7</td>
<td>Dronabinol 15 to 24 mg/day</td>
<td>Moderate</td>
<td>98</td>
<td>21, 2.40 (2.25)</td>
<td>29, 3.50 (2.42)</td>
<td>-1.16 (-2.46, 0.26)</td>
</tr>
<tr>
<td>Schenning, 2017 NPP</td>
<td>All THC</td>
<td>16</td>
<td>Dronabinol 13 mg/day</td>
<td>Low</td>
<td>124</td>
<td>116, 4.60 (2.04)</td>
<td>116, 4.92 (2.04)</td>
<td>-0.44 (-0.88, 0.98)</td>
</tr>
<tr>
<td>Skrbeck, 2008 FM</td>
<td>All THC</td>
<td>4</td>
<td>Nabibnone EP 2 mg/day</td>
<td>Moderate</td>
<td>15</td>
<td>18, 5.80 (1.62)</td>
<td>13, 4.80 (1.76)</td>
<td>-0.80 (-1.96, 0.36)</td>
</tr>
<tr>
<td>Wissel, 2006 NPP</td>
<td>All THC</td>
<td>4</td>
<td>Nabibnone EP 1 mg per day</td>
<td>High</td>
<td>13</td>
<td>13, 6.00 (NA)</td>
<td>13, 6.00 (NA)</td>
<td>-2.00 (-4.00, 0.00)</td>
</tr>
<tr>
<td>Tolst, 2012 NPP</td>
<td>All THC</td>
<td>5</td>
<td>Nabibnone 1 to 4 mg/day</td>
<td>Low</td>
<td>13</td>
<td>13, 3.50 (1.30)</td>
<td>13, 5.40 (1.70)</td>
<td>-1.90 (-3.32, -0.50)</td>
</tr>
<tr>
<td>Turcothe, 2015 NPP</td>
<td>All THC</td>
<td>9</td>
<td>Nabibnone TD 2 mg/day</td>
<td>Moderate</td>
<td>8</td>
<td>8, 3.50 (1.28)</td>
<td>7, 5.70 (1.65)</td>
<td>-2.22 (-3.71, -0.69)</td>
</tr>
<tr>
<td>Subgroup, PL (p = 0.084, I² = 46.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.15 (-1.99, -0.54)</td>
</tr>
</tbody>
</table>

Extracted

| Chevres, 2020 FM               | 48:1            | 8              | Extracted THC 4.40.08 mg T/C Low | 8               | 3.75 (2.49)     | 9, 7.67 (1.84)           | -3.92 (-4.16, -1.68)   |
| Zajicek, 2012 NPP             | 2.1             | 12             | Extracted THC Max 25 mg/day Moderate | 143             | -1.20 (2.68)    | 134, -0.30 (2.49)        | -0.98 (-1.49, -0.31)   |
| Subgroup, PL (p = 0.011, I² = 84.6%) |                 |                |                           |                   |                  |                           |                       | -1.97 (-5.91, 1.21)     |

Heterogeneity between groups: p = 0.425
Overall, PL (p = 0.020, I² = 57.8%)

Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end-point; FM = fibromyalgia; NA = not applicable; NPP = neuropathic pain; PD = plant-derived; PL = profile likelihood; SD = standard deviation; TD = total dose; T/C = THC/CBD; THC = tetrahydrocannabinol; VP = visceral pain.

A 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)

<table>
<thead>
<tr>
<th>Intervention Type and Author, Year</th>
<th>Pain Population</th>
<th>THC/CBD Ratio</th>
<th>Treatment Duration (weeks)</th>
<th>Risk of Bias</th>
<th>N, Mean (SD), Intervention</th>
<th>N, Mean (SD), Control</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
</table>
| Dronabinol  
 de Vries, 2017*  
 Schimrigk, 2017  
 Subgroup, PL (p = 0.374, I² = 0.0%) | VP  
 NPP | All THC  
 All THC  
 All THC | 7  
 16  
 16 | 15 to 24 mg/day  
 13 mg/day  
 13 mg/day | Moderate  
 Low  
 Low | 21, 2.40 (2.28)  
 124, 4.48 (2.04)  
 116, 4.92 (2.04) | 29, 3.50 (2.42)  
 116, 4.92 (2.04)  
 116, 4.92 (2.04) | -1.10 (-2.46, 0.26)  
 -0.44 (-0.96, 0.08)  
 -0.92 (-1.43, 0.07) |
| Nabilone  
 Skrabek, 2008  
 Wissel, 2006  
 Trott, 2012  
 Turcotte, 2015  
 Subgroup, PL (p = 0.422, I² = 0.0%) | FM  
 NPP  
 NPP  
 NPP | All THC  
 All THC  
 All THC  
 All THC | 4  
 4  
 5  
 9 | EP 2 mg/day  
 Ep 1 mg per day  
 1 to 4 mg/day  
 TD 2 mg/d | Moderate  
 High  
 Low  
 Moderate | 15, 4.80 (1.76)  
 13, 4.00 (NR)  
 13, 3.90 (1.30)  
 6, 3.50 (1.28) | 18, 5.60 (1.62)  
 13, 6.00 (NR)  
 13, 5.40 (1.70)  
 7, 5.70 (1.65) | -0.80 (-1.96, 0.36)  
 -2.00 (-4.00, -0.00)  
 -1.90 (-3.12, -0.68)  
 -2.20 (-3.71, -0.69) |

Heterogeneity between groups: p = 0.013  
 Overall, PL (p = 0.084, I² = 48.5%)  
 -1.15 (-1.99, -0.54)

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

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

<table>
<thead>
<tr>
<th>Group Difference</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>t-Test</th>
<th>p-Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>-1.06</td>
<td>0.445</td>
<td>-2.37</td>
<td>0.077</td>
<td>-2.29 to 0.18</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Group Difference</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>t-Test</th>
<th>p-Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>-0.682</td>
<td>0.81</td>
<td>-0.84</td>
<td>0.423</td>
<td>-2.55 to 1.18</td>
</tr>
</tbody>
</table>
**Figure E-12. Overall function for high THC versus placebo (short-term, 1-6 months followup)**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pain Population</th>
<th>THC/CBD Ratio</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Type</th>
<th>Risk of Bias</th>
<th>N, Mean (SD), Intervention</th>
<th>N, Mean (SD), Control</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toth, 2012</td>
<td>NPP</td>
<td>All THC</td>
<td>5</td>
<td>Nabilone</td>
<td>Low</td>
<td>13. 2.50 (1.60)</td>
<td>13. 3.60 (0.90)</td>
<td>-1.10 (-2.15, -0.05)</td>
</tr>
<tr>
<td>Turcotte, 2015</td>
<td>NPP</td>
<td>All THC</td>
<td>9</td>
<td>Nabilone</td>
<td>Moderate</td>
<td>NR</td>
<td>NR</td>
<td>0.10 (-0.57, 0.77)</td>
</tr>
</tbody>
</table>

Overall, PL (p = 0.059, $I^2 = 71.9\%$)

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)**

<table>
<thead>
<tr>
<th>Derivative Type and Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>THC/CBD Ratio</th>
<th>Intervention Type</th>
<th>Risk of Bias</th>
<th>Treatment Control</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic de Vries, 2017 a VP</td>
<td>NPP</td>
<td>7</td>
<td>All THC</td>
<td>Dronabinol</td>
<td>Moderate</td>
<td>7/30</td>
<td>2/32</td>
</tr>
<tr>
<td>Schmig, 2017 NPP</td>
<td>NPP</td>
<td>16</td>
<td>All THC</td>
<td>Dronabinol</td>
<td>Low</td>
<td>19/124</td>
<td>12/116</td>
</tr>
<tr>
<td>Skrabek, 2008 FM</td>
<td>NPP</td>
<td>4</td>
<td>All THC</td>
<td>Nabilone</td>
<td>Low</td>
<td>1/20</td>
<td>1/20</td>
</tr>
<tr>
<td>Turcotte, 2015 NPP</td>
<td>NPP</td>
<td>9</td>
<td>All THC</td>
<td>Nabilone</td>
<td>Moderate</td>
<td>1/8</td>
<td>0/7</td>
</tr>
<tr>
<td>Subgroup, PL (p = 0.692, $I^2 = 0.0%$)</td>
<td>NPP</td>
<td>2.1</td>
<td>Extracted THC Max 25 mg/day</td>
<td>Moderate</td>
<td>30/143</td>
<td>9/134</td>
<td>3.12 (1.54, 6.33)</td>
</tr>
</tbody>
</table>

Extracted Zajacek, 2012 NPP       | NPP             | 12                          | 2:1            | Extracted THC Max 25 mg/day | Moderate     | 30/143             | 9/134               | 3.12 (1.54, 6.33)   |

Heterogeneity between groups: p = 0.203

Overall, PL (p = 0.544, $I^2 = 0.0\%$)

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.

*aDronabinol 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)

<table>
<thead>
<tr>
<th>Derivative Type and Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Type</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schimrigk, 2017 NPP</td>
<td>16</td>
<td>Dronabinol</td>
<td>13 mg/day</td>
<td>Low</td>
<td>109/124</td>
<td>85/116</td>
<td>1.20 (1.06, 1.36)</td>
<td></td>
</tr>
<tr>
<td>Toth, 2012 NPP</td>
<td>5</td>
<td>Nabulone</td>
<td>1 to 4 mg/day</td>
<td>Low</td>
<td>7/13</td>
<td>6/13</td>
<td>1.17 (0.54, 2.53)</td>
<td></td>
</tr>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>116/137</td>
<td>91/129</td>
<td>1.20 (0.96, 1.48)</td>
<td></td>
</tr>
</tbody>
</table>

($I^2 = 0.0\%, p = 0.943$)

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

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

<table>
<thead>
<tr>
<th>Derivative Type and Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>THC/CBD Ratio</th>
<th>Intervention Type</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Vries, 2017 VP</td>
<td>7</td>
<td>All THC</td>
<td>Dronabinol</td>
<td>15 to 24 mg/day</td>
<td>Moderate</td>
<td>24/30</td>
<td>11/32</td>
<td>2.33 (1.40, 3.88)</td>
<td></td>
</tr>
<tr>
<td>Schimrigk, 2017 NPP Subgroup, PL (p = 0.196, I² = 40.2%)</td>
<td>16</td>
<td>All THC</td>
<td>Dronabinol</td>
<td>13 mg/day</td>
<td>Low</td>
<td>25/124</td>
<td>5/116</td>
<td>4.68 (1.85, 11.81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49/154</td>
<td>16/148</td>
<td>2.74 (1.47, 6.86)</td>
<td></td>
</tr>
<tr>
<td>Extracted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zajicek, 2012 NPP</td>
<td>12</td>
<td>2:1</td>
<td>Extracted THC</td>
<td>Max 25 mg/day</td>
<td>Moderate</td>
<td>89/143</td>
<td>10/134</td>
<td>8.34 (4.53, 15.34)</td>
<td></td>
</tr>
<tr>
<td>Subgroup, PL (p = NA, I² = 0.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89/143</td>
<td>10/134</td>
<td>8.34 (4.53, 15.34)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity between groups: p = 0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, PL (p = 0.007, I² = 80.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>138/297</td>
<td>26/282</td>
<td>4.37 (1.79, 11.13)</td>
<td></td>
</tr>
</tbody>
</table>

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

a Dronabinol tablet = plant-derived, purified product Namisol®.
**Figure E-16. Sedation for high THC versus placebo (short-term, 4 weeks to 6 months followup)**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Type and Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
<td>de Vries, 2017&lt;sup&gt;a&lt;/sup&gt;</td>
<td>VP</td>
<td>7</td>
<td>15 to 24 mg/day</td>
<td>Moderate</td>
<td>15/30</td>
<td>11/32</td>
<td>1.45 (0.80, 2.64)</td>
</tr>
<tr>
<td></td>
<td>Schirrmich, 2017</td>
<td>NPP</td>
<td>16</td>
<td>13 mg/day</td>
<td>Low</td>
<td>10/124</td>
<td>5/116</td>
<td>1.87 (0.66, 5.31)</td>
</tr>
<tr>
<td></td>
<td>Subgroup, PL (p = 0.682, I² = 0.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25/154</td>
<td>16/148</td>
<td>1.55 (0.84, 3.07)</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Skrabek, 2008</td>
<td>FM</td>
<td>4</td>
<td>EP 2 mg/day</td>
<td>Moderate</td>
<td>7/15</td>
<td>1/18</td>
<td>8.40 (1.16, 60.84)</td>
</tr>
<tr>
<td></td>
<td>Subgroup, PL (p = NA, I² = 0.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7/15</td>
<td>1/18</td>
<td>8.40 (1.16, 60.84)</td>
</tr>
</tbody>
</table>

Heterogeneity between groups: p = 0.105
Overall, PL (p = 0.248, I² = 28.3%)

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®.

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

<table>
<thead>
<tr>
<th>Derivative Type and Author, Year</th>
<th>Pain Population</th>
<th>Treatment Duration (weeks)</th>
<th>Intervention Type</th>
<th>Intervention Dose</th>
<th>Risk of Bias</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic</td>
<td>de Vries, 2017&lt;sup&gt;a&lt;/sup&gt;</td>
<td>VP</td>
<td>7</td>
<td>Dronabinol</td>
<td>15 to 24 mg/day</td>
<td>Moderate</td>
<td>13/30</td>
<td>5/32</td>
</tr>
<tr>
<td></td>
<td>Schirrmich, 2017</td>
<td>NPP</td>
<td>16</td>
<td>Dronabinol</td>
<td>13 mg/day</td>
<td>Low</td>
<td>6/124</td>
<td>4/116</td>
</tr>
<tr>
<td></td>
<td>Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19/154</td>
<td>9/148</td>
<td>2.19 (0.77, 5.39)</td>
</tr>
</tbody>
</table>

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

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

<sup>a</sup> Dronabinol tablet = plant-derived, purified product Namisol®.
Table E-8. Meta-analysis results and sensitivity analysis using the Bartlett’s Correction

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

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

Appendix G. Risk of Bias Assessment

## Appendix H. Details on Strength of Evidence

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of Studies (N) and Total Participants</th>
<th>Study Limitations</th>
<th>Directness</th>
<th>Consistency</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Main Findings Effect Size (95% CI)</th>
<th>SOE Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparable THC to CBD Ratio vs. Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain response (≥30% improvement from baseline)</td>
<td>4 RCTs (N=733)&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Potential small effect, not statistically significant, with THC:CBD 38% vs. 31%, RR 1.18 (0.93 to 1.71); $I^2=36%$</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Pain severity (change)</td>
<td>7 RCTs (N=878)&lt;sup&gt;1-7&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Precise</td>
<td>Unknown</td>
<td>Small benefit with THC:CBD 0 to 10 scale, MD −0.54 (−0.95 to −0.19); $I^2=40%$ Subgroup analysis removing high risk of bias studies: Moderate benefit MD −0.64 (−1.15 to −0.24)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Function or Disability</td>
<td>6 RCTs (N=616)&lt;sup&gt;1-5,7&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Precise</td>
<td>Unknown</td>
<td>Small benefit with THC:CBD, MD −0.42, 95% CI −0.73 to −0.16, $I^2=32%$ (scale 0 to 10)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>WAEs</td>
<td>5 RCTs (N=834)&lt;sup&gt;1,2,4,5,7&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Failed to demonstrate or exclude a detrimental effect 13% vs. 10%, RR 1.14 (0.65 to 3.02); $I^2=51%$</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td>3 RCTs (N=429)&lt;sup&gt;2,4,5&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>No effect 5.0% vs. 4.3%, RR 1.18 (0.28 to 3.43); $I^2=0%$</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>Number of Studies (N) and Total Participants</td>
<td>Study Limitations</td>
<td>Directness</td>
<td>Consistency</td>
<td>Precision</td>
<td>Publication Bias</td>
<td>Main Findings Effect Size (95% CI)</td>
<td>SOE Grade</td>
</tr>
<tr>
<td>------------</td>
<td>------------------</td>
<td>-----------------------------------------------</td>
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<td>-------------</td>
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<td>------------------</td>
<td>-----------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Comparable THC to CBD Ratio vs. Placebo</td>
<td>Dizziness</td>
<td>6 RCTs (N=866)(^1)(^2)(^3)(^4)(^5)(^7)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Large effect with THC:CBD 30% vs. 8%, RR 3.57 (2.42 to 5.60; I(^2)=0%)</td>
<td>Low</td>
</tr>
<tr>
<td>Comparable THC to CBD Ratio vs. Placebo</td>
<td>Nausea</td>
<td>6 RCTs (N=866)(^1)(^2)(^3)(^4)(^5)(^7)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Moderate effect with THC:CBD 14% vs. 7.5%, RR 1.79 (1.19 to 2.77; I(^2)=0%)</td>
<td>Low</td>
</tr>
<tr>
<td>Comparable THC to CBD Ratio vs. Placebo</td>
<td>Sedation</td>
<td>6 RCTs (N=866)(^1)(^2)(^3)(^4)(^5)(^7)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Large effect with THC:CBD RR 5.04 (2.10 to 11.89; I(^2)=0%)</td>
<td>Low</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of Studies and Total Participants (N)</th>
<th>Study Limitations</th>
<th>Directness</th>
<th>Consistency</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Main Findings Effect Size (95% CI)</th>
<th>Strength of Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>Pain response (≥30% improvement from baseline)</td>
<td>1 RCT (N=26)(^8)</td>
<td>Low</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Large effect with nabilone 85% vs. 38%, RR 2.20 (1.06 to 4.55)</td>
<td>Low</td>
</tr>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>Pain severity</td>
<td>6 RCTs (N=390)(^6,13)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Moderate effect with synthetic THC 0 to 10 scale, MD −1.15 (−1.99 to −0.54; I(^2)=48%)</td>
<td>Low</td>
</tr>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>Function/disability</td>
<td>2 RCTs (N=41)(^8,12)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>No effect (scale 0 to 10) MD : −0.35, −1.9 to 0.94, 0 to 10 scale, I(^2)=72%</td>
<td>Low</td>
</tr>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>WAEs</td>
<td>4 RCTs (N=357)(^6,12)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Potential moderate effect, not statistically significant 13% vs. 9%, RR 1.72 (0.90 to 4.13; I(^2)=0%)</td>
<td>Low</td>
</tr>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>SAEs</td>
<td>1 RCT (N=240)(^10)</td>
<td>Low</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Failed to demonstrate or exclude a detrimental effect 10% vs. 6%, RR 1.60 (0.65 to 3.93)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>Dizziness</td>
<td>2 RCTs (N=302)(^9,10)</td>
<td>Low</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Large effect with dronabinol 32% vs. 11%, RR 2.74 (1.47 to 6.86; I(^2)=40.2%)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>Number of Studies and Total Participants (N)</td>
<td>Study Limitations</td>
<td>Directness</td>
<td>Consistency</td>
<td>Precision</td>
<td>Publication Bias</td>
<td>Main Findings Effect Size (95% CI)</td>
<td>Strength of Evidence Grade</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>-----------------------------------------------</td>
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<td>-----------</td>
<td>------------------</td>
<td>------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>Nausea</td>
<td>2 RCTs (N=302)(^{9,10})</td>
<td>Low</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Potential large effect with dronabinol, not statistically significant 12% vs. 6%, RR 2.19 (0.77 to 5.39; (I^2)=0%)</td>
<td>Low</td>
</tr>
<tr>
<td>Synthetic THC vs. Placebo</td>
<td>Sedation</td>
<td>3 RCTs (N=335)(^{9,11})</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Moderate effect with dronabinol 19% vs. 10%, RR 1.73 (1.03 to 4.63; (I^2)=28%)</td>
<td>Low</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of Studies and Total Participants (N)</th>
<th>Study Limitations</th>
<th>Directness</th>
<th>Consistency</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Main Findings Effect Size (95% CI)</th>
<th>Main Findings Strength of Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracted High THC vs. Placebo</td>
<td>Pain severity</td>
<td>2 RCTs (N=297)&lt;sup&gt;14,15&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Failed to demonstrate or exclude a detrimental effect MD −1.97 (−5.91 to 1.21; I²=85%)</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Function/disability</td>
<td>1 RCT (N=18)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>High</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Failed to demonstrate or exclude a detrimental effect MD 1.75 (−0.46 to 3.98)</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>WAEs</td>
<td>1 RCT (N=277)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Large increased risk 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>SAEs</td>
<td>1 RCT (N=277)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Failed to demonstrate or exclude a detrimental effect 4.9% vs. 2.2%, RR 2.19 (0.58 to 8.28)</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>1 RCT (N=277)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Large effect 62.2% vs. 7.5%, RR 8.34 (4.53 to 15.34)</td>
<td>Low</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of Studies and Total Participants (N)</th>
<th>Study Limitations</th>
<th>Directness</th>
<th>Consistency</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Main Findings Effect Size (95% CI)</th>
<th>Strength of Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined High THC Ratio Studies (Synthetic and Whole-plant extracted)</td>
<td>Pain severity</td>
<td>8 RCTs (N=684)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Consistent</td>
<td>Precise</td>
<td>Unknown</td>
<td>Moderate effect MD −1.25 (−2.09 to −0.71; I²=58%)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of Studies (N) and Total Participants</th>
<th>Study Limitations</th>
<th>Directness</th>
<th>Consistency</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Main Findings Effect Size (95% CI)</th>
<th>Strength of Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical CBD vs. Placebo</td>
<td>Pain severity (change)</td>
<td>1 RCT (N=29)(^7)</td>
<td>High</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>Small effect with CBD cream MD −0.75, P=0.009 by ANCOVA (0 to 10 scale)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Oral Synthetic CBD vs. Placebo</td>
<td>Pain response (≥30% improvement)</td>
<td>1 RCT (N=136)(^8)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>No effect with oral synthetic CBD RR 1.01 (0.66 to 1.55)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

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

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

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)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of Studies (N) and Total Participants</th>
<th>Study Limitations</th>
<th>Directness</th>
<th>Consistency</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Main Findings Effect Size (95% CI)</th>
<th>SOE Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown THC to CBD Ratio vs. Usual Care</td>
<td>Pain response (≥30% improvement from baseline)</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Unknown THC to CBD Ratio vs. Usual Care</td>
<td>Pain severity (change) Short-term (3 months)</td>
<td>2 cohort studies: short- to intermediate-term (N=202)&lt;sup&gt;30,31&lt;/sup&gt;</td>
<td>High</td>
<td>Direct</td>
<td>Inconsistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>VAS (0-100): 41.5 vs. 43.6 at 3 months&lt;sup&gt;30&lt;/sup&gt; 34.1 vs. 48.8; mean difference −14.71 (95% CI, −32.71 to 3.29)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Unknown THC to CBD Ratio vs. Usual Care</td>
<td>Long-term (12 months)</td>
<td>1 cohort (N=1,514)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>High</td>
<td>Direct</td>
<td>Unknown</td>
<td>Precise</td>
<td>Unknown</td>
<td>Adjusted mean; BPI, 0-10 scale 5.2 vs. 4.9; Beta: 0.37 (95% CI −0.23 to 1.10), p=0.20&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of Studies (N) and Total Participants</th>
<th>Study Limitations</th>
<th>Directness</th>
<th>Consistency</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Main Findings Effect Size (95% CI)</th>
<th>SOE Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unknown THC to CBD Ratio vs. Usual Care</strong></td>
<td><strong>Function or Disability (SF-36 Physical Function)</strong></td>
<td>2 cohorts = short to medium-term (N=202)\textsuperscript{20,21}</td>
<td>High</td>
<td>Direct</td>
<td>Consistent</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>SF-36 Physical Functioning (mean, 0 to 100 scale) 46.5 vs. 43.7 at 6 months\textsuperscript{20} 70.0 vs. 69.4; MD 0.56 (95% CI –17.2 to 18.3) at 3 months\textsuperscript{21}</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Unknown THC to CBD Ratio vs. Usual Care</strong></td>
<td><strong>WAEs</strong></td>
<td>1 cohort study, short- and intermediate-term (N=156)\textsuperscript{20}</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>6 months: 23% (12/52) vs. 9% (5/55), RR 2.54 (95% CI 0.95 to 6.71)</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Unknown THC to CBD Ratio vs. Usual Care</strong></td>
<td><strong>SAEs</strong></td>
<td>1 cohort study, short- and intermediate-term (N=156)\textsuperscript{20}</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>None in any group</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Unknown THC to CBD Ratio vs. Usual Care</strong></td>
<td><strong>Dizziness</strong></td>
<td>1 cohort study, short- and intermediate-term (N=156)\textsuperscript{20}</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>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)</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Unknown THC to CBD Ratio vs. Usual Care</strong></td>
<td><strong>Nausea</strong></td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No evidence</td>
<td>NA</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>Number of Studies (N) and Total Participants</td>
<td>Study Limitations</td>
<td>Directness</td>
<td>Consistency</td>
<td>Precision</td>
<td>Publication Bias</td>
<td>Main Findings Effect Size (95% CI)</td>
<td>SOE Grade</td>
</tr>
<tr>
<td>------------------------------------</td>
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</tr>
<tr>
<td>Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)</td>
<td>Sedation</td>
<td>1 cohort study, short- and intermediate-term (N=156)(^1)</td>
<td>Moderate</td>
<td>Direct</td>
<td>Unknown</td>
<td>Imprecise</td>
<td>Unknown</td>
<td>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)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

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


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


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


Exclusion reason: Inadequate duration


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


10.3389/fphar.2021.633168. PMID: 33995035. **Exclusion reason:** Ineligible publication type


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


251. Terrie YC. Medical cannabis for chronic pain. US Pharm. 2020;45(3):24-8. **Exclusion reason:** Ineligible publication type


5. **Exclusion reason:** Systematic review used as source document


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.