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

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AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work was based on an evidence report, Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2023 Update, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

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Preface

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

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

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. 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 systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

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

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

The list of Technical Experts who provided input to the report will be included in the final report.

Peer Reviewers

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

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

The list of Peer Reviewers who reviewed the report will be included in the final report.
Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2024 Update

Structured Abstract

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

Data sources. Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases, and reference lists of included studies were searched to January 15, 2024.

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

Results. Two new randomized controlled trials (RCTs) in three publications (n=134 and 86) and two new observational studies (N=296 and 32,332) were added for this annual update; no study addressed subacute pain or adolescents. One new RCT compared high THC, low THC, and combination THC:CBD ratio products versus placebo in patients with neuropathic pain; the other new RCT evaluated oral CBD plus paracetamol versus paracetamol alone for knee osteoarthritis. Since the inception of this living review, from 5,644 total abstracts identified, 25 RCTs (in 26 publications) (N=2,255) and 12 observational studies (N=48,468) assessing different cannabinoids have been included; no study evaluated kratom. Studies were primarily short term, and 54 percent enrolled patients with neuropathic pain. Comparators were primarily placebo or usual care. Strength of evidence (SOE) was low unless indicated otherwise.

Compared with placebo, plant-extracted comparable ratio THC to CBD oral spray was associated with a small decrease in pain severity (7 RCTs, N=632, 0 to 10 scale, mean difference [MD] −0.54, 95% confidence interval [CI] −0.95 to −0.19, I²=39%; SOE: moderate) and a small decrease in overall function (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI −0.73 to −0.16, I²=32%; SOE: moderate) versus placebo. There was no effect on study withdrawals due to adverse events (WAEs). There was a large increased risk of dizziness and sedation, and a moderate increased risk of nausea (dizziness: 6 RCTs, N=866, relative risk [RR] 3.57, 95% CI 2.42 to 5.60, I²=0%; sedation: 6 RCTs, N=866, RR 5.04, 95% CI 2.10 to 11.89, I²=0%; and nausea: 6 RCTs, N=866, RR 1.79, 95% CI 1.19 to 2.77, I²=0%).

Synthetic and plant-purified high-THC to CBD ratio products were associated with a small improvement in pain severity, a moderate increase in risk of WAEs, a moderate increase in sedation, and a large increase in risk of nausea (pain: 8 RCTs, N=507, 0 to 10 scale, MD −0.78, 95% CI −1.59 to −0.08, I²=64%; WAEs: 6 RCTs, N=487, RR 1.92, 95% CI 1.10 to 4.80, I²=0%; sedation: 5 RCTs, N=458, RR 1.57, 95% CI 1.11 to 2.29, I²=0%; nausea: 4 RCTs, N=425, RR 2.12, 95% CI 1.09 to 3.96; I²=0%). There was also moderate SOE for a large increased risk of dizziness (4 RCTs, N=425, RR 2.30, 95% CI 1.53 to 3.52, I²=22%).
Synthetic or plant-purified oral CBD alone was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale, MD 0.40, 95% CI −0.14 to 1.00, $I^2=20\%$; SOE: moderate), greater likelihood of pain response (4 RCTs, N=334, RR 0.84, 95% CI 0.62 to 1.10; $I^2=0\%$; SOE: moderate), or improved function (3 RCTs, N=272, SMD 0.11, 95% CI −0.14 to 0.41, $I^2=0\%$; SOE: moderate) versus placebo, and combined oral THC plus CBD (~1:2 ratio) was not associated with decreased pain intensity (2 RCTs, N=123, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, $I^2=0\%$), greater likelihood of experiencing ≥30% improvement in pain (2 RCTs, N=123, RR 1.07, 95% CI 0.73 to 1.57, $I^2=0\%$), or improved function (1 RCT, n=60, SMD 0.29, 95% CI −0.21 to 0.80) versus placebo.

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

**Conclusions.** Low- to moderate-strength evidence suggests small improvements in pain (mostly neuropathic), and moderate to large increases in common adverse events (dizziness, sedation, nausea) with plant-extracted comparable THC to CBD ratio and synthetic or plant-purified high-THC to CBD ratio products versus placebo during short-term treatment (1 to 6 months). Low- to moderate-strength evidence suggests that low-THC to CBD ratio products may not be associated with improved outcomes versus placebo. Evidence for whole-plant cannabis and other comparisons, outcomes, and plant-based compounds was unavailable or insufficient to draw conclusions.
Table C. Characteristics of included observational studies of cannabinoids .................................. 5
Table D. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months) .......................................................... 6
Table E. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months) ................................................................. 6
Table 1. Inclusion and exclusion criteria ...................................................................................... 4
Table 2. Organizing principle of cannabis-related studies based on ratios of THC to CBD ........ 6
Table 3. Definitions of effect sizes ............................................................................................... 7
Table 4. Characteristics of included randomized controlled trials of cannabinoids for chronic pain in adults ................................................................. 10
Table 5. Characteristics of included observational studies of cannabinoids for chronic pain in adults ................................................................. 12
Table 6. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months) .......................................................... 33
Table 7. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months) ................................................................. 34
Table 8. Future research needs for cannabis and other plant-based treatments for chronic or subacute pain ................................................................. 40

Figures
Figure 1. Literature flow diagram ............................................................................................... 10
Figure 2. Change in pain severity with plant-extracted, comparable THC to CBD ratio oromucosal spray versus placebo (short term, 4 weeks to 6 months followup) ........................................... 16
Figure 3. Overall function: plant-extracted, comparable THC to CBD ratio oromucosal spray versus placebo (short term, 4 weeks to 6 months followup) .......................................................... 16
Figure 4. Change in pain severity with high-THC ratio versus placebo (short term, 4 weeks to 6 months followup) ........................................................................................................... 21
Figure 5. Change in pain severity with oral low-THC ratio products versus placebo (short term, 4 weeks to 6 months followup) ................................................................. 27

Appendixes
Appendix A. Literature Search Strategies
Appendix B. Methods
Appendix C. Included Studies List
Appendix D. Results - Study Level Summary Tables and Meta-Analyses
Appendix E. Evidence Tables
Appendix F. Risk of Bias Assessment
Appendix G. Details on Strength of Evidence
Appendix H. Excluded Studies List
Appendix I. Funnel Plot of High-THC Ratio Studies Included in Meta-Analysis for Pain Severity
Executive Summary

Main Points

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

Studies of cannabis-related products were grouped based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio using the following categories: comparable THC to CBD, high-THC to CBD (including THC only), and low-THC to CBD (including CBD only). Since the second annual update of the systematic review published in August 2023, two new placebo-controlled randomized controlled trials (RCTs) in three publications and two new observational studies were added, for a total of 25 RCTs (in 26 publications) and 12 observational studies. One of the new RCTs evaluated oral plant-purified THC (dronabinol), synthetic CBD, or both and the other new RCT evaluated plant-purified CBD; the new observational studies evaluated various (low, comparable, or high-THC to CBD ratio) products. In patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months):

- Plant-extracted comparable-THC to CBD ratio oral spray is probably associated with small improvements in pain severity (strength of evidence [SOE]: moderate) and overall function versus placebo (SOE: moderate). There may be no increase in risk of serious adverse events (SAEs) (SOE: low) or withdrawal due to adverse events (WAEs) (SOE: low). There may be a large increased risk of dizziness (SOE: low) and sedation and a moderate increased risk of nausea (SOE: low).
- Synthetic and plant-purified THC (high THC to CBD) may be associated with small improvement in pain severity (SOE: low), but with increased risk of WAEs (SOE: low), sedation (SOE: low), and nausea (SOE: low) versus placebo. Synthetic and plant-purified THC is probably associated with a large increased risk of dizziness (SOE: moderate).
- Low-THC to CBD ratio oral products (synthetic or plant-purified CBD alone, or combined plant-purified THC plus synthetic CBD in ratio ~1:2) may not be associated with improved pain and function versus placebo (SOE: moderate for CBD alone and low for THC/CBD). THC plus CBD is probably associated with large increased risk of nausea (SOE: moderate).
- Other key adverse event outcomes (psychosis, cannabis use disorder, cognitive deficits) and outcomes on the impact on opioid use were not reported or evidence was insufficient to draw conclusions.
- No evidence on other plant-based compounds such as kratom met criteria for this review.

Background and Purpose

Cannabinoids are a group of compounds that are active in cannabis; the two main cannabinoid are THC and CBD. THC has demonstrated analgesic properties,¹,² although its psychoactive effects and abuse potential may limit its suitability as an analgesic. It may also be
associated with serious harms, including those related to potential for use disorder or physiological withdrawal. The purpose of the systematic review is to evaluate the evidence on benefits and harms of cannabinoids and similar plant-based substances (e.g., kratom) to treat chronic or subacute pain on an ongoing basis. This report updates the original 2021 systematic review on cannabis and other plant-based treatments for chronic pain in adults. In the 2023 update, the scope was expanded to include subacute pain and adolescents. Using a living review approach, the literature continues to be monitored quarterly for new studies, and the systematic review may be updated annually.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Effective Health Care Program Methods Guide (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), as described in the full report. Searches for this update covered publication dates from database inception to January 15, 2024. The original review focused on adults with chronic pain. With input from a Technical Expert Panel, the scope in the 2023 update was expanded to include adolescents and subacute pain. We included RCTs and comparative observational studies with a minimum of 4 weeks duration that assessed cannabinoids or kratom for noncancer chronic and subacute pain. Cannabinoids were categorized according to their THC to CBD ratio (comparable, high, low) and type (whole-plant [included extracted or purified products] or synthetic). Strength of evidence was assessed as low, moderate, high, or insufficient, and magnitude of effect was assessed according to Table A. Estimates that were below the threshold for a small effect were categorized as “no effect.”

### Table A. Definitions of effect sizes

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

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

Results

The included RCTs are described in Table B and the included observational studies are described in Table C. There were four new studies in five publications added since the prior annual update. One new RCT in two publications (n=134) compared plant-derived synthetic equivalent THC (dronabinol; high-THC to CBD ratio), synthetic CBD (low-THC to CBD ratio), or both (low-THC to CBD ratio) versus placebo for neuropathic pain and another new RCT (n=86) evaluated a plant-derived CBD (low-THC to CBD ratio) versus placebo for knee osteoarthritis. Both of the new observational studies (n=296 and n=32,332) included patients with various chronic pain conditions and evaluated low, comparable, or high-THC to CBD ratio cannabis products; one of the studies (n=32,332) focused the association between cannabis use and on risk of arrhythmia and acute coronary syndrome. Evidence added for this update enabled a new meta-analysis
which found that low-THC to CBD ratio products (CBD alone or the combination of THC and CBD in a 1:2 ratio) were not associated with improvement in pain or function versus placebo, but some imprecision was present. For synthetic and plant-purified THC (high-THC to CBD ratio) versus placebo, updated meta-analyses changed pooled estimates for nausea (large increase in risk) and WAEs (moderate increase in risk) from non-statistically significant to statistically significant; however, the SOE for these outcomes remained low. For other comparisons and outcomes, the new studies did not change main findings.

Table B. Characteristics of included randomized controlled trials of cannabinoids

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD</th>
<th>THC</th>
<th>CBD</th>
<th>CBDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC to CBD Ratio</td>
<td>Comparable¹</td>
<td>High</td>
<td>Low</td>
<td>NA - other cannabinoids</td>
</tr>
<tr>
<td>Source</td>
<td>Plant-extracted</td>
<td>Synthetic</td>
<td>Plant-purified</td>
<td>Plant-purified</td>
</tr>
<tr>
<td>N Studies</td>
<td>7</td>
<td>13²</td>
<td>6³ (1 topical, 1 sublingual, 4 oral)</td>
<td>1</td>
</tr>
<tr>
<td>Comparator (Study Count)</td>
<td>Placebo (7)</td>
<td>Placebo (10); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low-THC to CBD ratio (CBD or plant-purified THC/CBD) (2)</td>
<td>Placebo (6); Dronabinol (2); Low-THC to CBD ratio (CBD or plant-purified THC/CBD (2); ≥97% purified low-THC to CBD (1:6) sublingual oil (1)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Route of Administration,</td>
<td>Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl</td>
<td>Dronabinol 3 mg oral tablet (1); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Plant-purified dronabinol oral 2.5 mg capsule (2); Oral capsule, 2.5 mg plant-purified THC/0.8 – 1.8 mg CBD extract (1); Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)</td>
<td>Oral capsule, 5 mg synthetic CBD (2)⁶; Oral tablet, 10 mg synthetic CBD (1); Oral capsule, 200 mg plant-purified CBD (1); Oral capsule, 5 mg CBD extract/2.5 mg dronabinol (2); Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1); Topical cream, 83 mg CBD/fluid ounce (1)</td>
<td>Oral oil, 50 mg/ml CBDV</td>
</tr>
<tr>
<td>Formulation (Study Count)</td>
<td></td>
<td>Dronabinol 3 mg oral tablet (1); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Plant-purified dronabinol oral 2.5 mg capsule (2); Oral capsule, 2.5 mg plant-purified THC/0.8 – 1.8 mg CBD extract (1); Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)</td>
<td>Oral capsule, 5 mg synthetic CBD (2)⁶; Oral tablet, 10 mg synthetic CBD (1); Oral capsule, 200 mg plant-purified CBD (1); Oral capsule, 5 mg CBD extract/2.5 mg dronabinol (2); Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1); Topical cream, 83 mg CBD/fluid ounce (1)</td>
<td>Oral oil, 50 mg/ml CBDV</td>
</tr>
</tbody>
</table>

¹ Comparable to placebo in mixed THC/CBD products; THC-only products and CBD-only products were comparable due to small sample size.
² High THC to CBD ratio: ≥1:1 (CBD < 10% of THC).
³ Low THC to CBD ratio: ≤1:10 (CBD ≥10% of THC).
⁴ Other cannabinoids include delta-9-tetrahydrocannabinol (THC), cannabinol (CBN), cannabinol-acid (CBNA), cannabinol-carboxylic acid (CBNCA), and cannabinol carboxylic acid ester (CBNCAE).
## Dosing Regimen

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD</th>
<th>THC</th>
<th>CBD</th>
<th>CBDV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final mean dose 23 mg THC/21 mg CBD daily.</td>
<td>Dronabinol capsules: 2.5 to 5 mg, titrated. Final dose range 13 - 25 mg/day</td>
<td>Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 45 to 50 mg CBD daily (2)</td>
<td>400 mg CBDV daily. Final dose NR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dronabinol (Namisol&lt;sup&gt;®&lt;/sup&gt;) tablet: 3 to 8 mg 3 times daily, titrated. Final dose 1.84</td>
<td>Oral tablet: 10 mg daily, titrated (max 3 times daily)</td>
<td>Final dose NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84</td>
<td>Oral CBD capsule: 200 mg 3 times daily. Final dose 600 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsule: 2.5 -12.5 mg THC twice daily, titrated. Final dose NR</td>
<td>Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 12.5 to 15 mg THC/30 to 45 mg CBD daily (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral oil: 1.2 mg daily</td>
<td>Sublingual oil, titrated to max daily dose of 6 drops 3 times daily (15 mg THC/90 mg CBD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily</td>
<td>Topical cream: applied locally 1-4 times/day (volume/dose, final dose NR)</td>
<td></td>
</tr>
</tbody>
</table>

## Risk of Bias

<table>
<thead>
<tr>
<th></th>
<th>29% high, 57% moderate, 14% low</th>
<th>8% high, 46% moderate, 46% low</th>
<th>50% high, 33% moderate, 17% low</th>
<th>100% moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Randomized</strong></td>
<td>882</td>
<td>1,028</td>
<td>508</td>
<td>34</td>
</tr>
<tr>
<td><strong>Age, Mean Years</strong></td>
<td>53</td>
<td>54</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>66% (2)</td>
<td>62% (4)</td>
<td>60%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Non-White, %</strong></td>
<td>1.6% (2)</td>
<td>5.3% (4)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Primary Pain Type</strong></td>
<td>NPP (6); Inflammatory arthritis (1)</td>
<td>NPP (9); Fibromyalgia (2); Visceral pain (1); Headache (1);</td>
<td>NPP (3); MS (1); OA (2); Unspecified (1)</td>
<td>NPP (1)</td>
</tr>
<tr>
<td><strong>Baseline Pain Score, Mean (Range)&lt;sup&gt;®&lt;/sup&gt;</strong></td>
<td>6.59 (5.3 to 7.3)</td>
<td>6.75 (4.00 to 8.67)&lt;sup&gt;®&lt;/sup&gt;</td>
<td>6.11 (4.67 to 7.4)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>6.28 (6.12 to 6.44)</td>
</tr>
<tr>
<td><strong>Study Duration</strong></td>
<td>4 to 15 weeks</td>
<td>4 to 47 weeks</td>
<td>4 to 16 weeks</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

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

<sup>®</sup> All products were nabiximols.

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

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

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

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

<sup>f</sup> Weighted mean includes median scores for 1 study (5.2 vs. 6.1).
Table C. Characteristics of included observational studies of cannabinoids

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD(^a)</th>
<th>THC</th>
<th>Synthetic THC</th>
<th>THC/CBD Versus Synthetic THC</th>
<th>THC/CBD Versus LAOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC to CBD Ratio</td>
<td>Unclear or mixed</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) or mixed cannabinoids</td>
<td>Plant-extracted</td>
<td>Synthetic (nabilone)</td>
<td>Plant-extracted vs. synthetic</td>
<td>Plant-extracted</td>
</tr>
<tr>
<td>N Studies</td>
<td>8(^b)</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 (2); other cannabinoids (2)</td>
<td>Usual care (1)</td>
<td>Gabapentin only; gabapentin + nabilone (1)</td>
<td>Active comparator; oral mucosal spray vs. dronabinol</td>
<td>Long-acting opioids (MME 69.4 (SD 38.9) mg/day)</td>
</tr>
<tr>
<td>Route of Administration, Formulation</td>
<td>Unreported (any available allowed, patient’s choice) (6); inhaled or oral prescribed cannabis (2)</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>
<tr>
<td>Dosing Regimen</td>
<td>None specified (7)</td>
<td>Final median dose 85 mg CBD vs. 7.8/20 mg THC/CBD vs. 20/25 mg THC/CBD vs. 42 mg THC/day (1)</td>
<td>None specified; titrated to max dose 5 g/day. Final median dose 2.5 g/day</td>
<td>None specified; final mean dose 16.6/15.4 mg THC/CBD/day vs. 17.2 mg THC/day</td>
<td>None specified; based on individual patient needs; final mean dose 16.7/15.5 mg THC/CBD/day vs. MME 69.4 mg/day</td>
</tr>
<tr>
<td>ROB</td>
<td>50% high, 50% moderate</td>
<td>100% high</td>
<td>100% moderate</td>
<td>100% moderate</td>
<td>100% moderate</td>
</tr>
<tr>
<td>N Total</td>
<td>45,897</td>
<td>431</td>
<td>156</td>
<td>674</td>
<td>1,310</td>
</tr>
<tr>
<td>Age, Mean Years</td>
<td>54</td>
<td>49</td>
<td>61</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>Female, %</td>
<td>52%</td>
<td>57%</td>
<td>59%</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>% Non-White (Study Count)</td>
<td>54% (1); NR (7)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Primary Pain Type(s)</td>
<td>Mixed musculoskeletal, chronic non-cancer pain</td>
<td>Chronic non-cancer pain</td>
<td>NPP</td>
<td>Peripheral NPP</td>
<td>Peripheral neuropathic back pain</td>
</tr>
<tr>
<td>Baseline Pain Score, Mean (Range)(^c)</td>
<td>5.75 (4.56 to 7.00)</td>
<td>6.35 (6.1 to 6.6)</td>
<td>4.98 (4.58 to 5.31)</td>
<td>4.4 (4.39 to 4.41)</td>
<td>4.32 (4.31 to 4.33)</td>
</tr>
<tr>
<td>Study Duration, Weeks (Range)</td>
<td>12 to 208</td>
<td>52</td>
<td>26</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

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

\(^a\) Patients could choose any medicinal product they preferred in these studies.

\(^b\) Includes two new studies for this review.

\(^c\) Scores were standardized to a 0 to 10 scale.
Tables D and E summarize the findings of the review. Other prioritized adverse events (cannabis use disorder [CUD], psychosis, cognitive deficits) and the impact on the use of opioids for chronic pain, were not reported in the RCTs.

### Table D. 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>Product, THC to CBD Ratio</th>
<th>Pain Response(^a) 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 - Plant-extracted, Oromucosal Spray</td>
<td>Potential effect (4)(^b) [✓]</td>
<td>Small effect (7) [✓✓]</td>
<td>Small effect (6) [✓✓]</td>
</tr>
<tr>
<td>High THC – Synthetic or Plant-purified, Oral</td>
<td>Insufficient (3, 1 new)</td>
<td>Small effect (8, 1 new) [✓]</td>
<td>No effect (3) [✓]</td>
</tr>
<tr>
<td>High THC – Plant-extracted, Oral</td>
<td>No evidence</td>
<td>Insufficient (2)</td>
<td>Insufficient (1)</td>
</tr>
<tr>
<td>Low THC – Plant-extracted CBD, Topical</td>
<td>No evidence</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
<tr>
<td>Low THC – Synthetic or Plant-purified, Oral(^c)</td>
<td>No effect (4, 2 new)(^c) [✓✓]</td>
<td>No effect (4, 2 new)(^c) [✓✓]</td>
<td>No effect (3, 1 new)(^c) [✓✓]</td>
</tr>
<tr>
<td>Low THC – Synthetic CBD Plus Plant-purified THC, Oral(^d)</td>
<td>No effect (2, 1 new)(^c) [✓]</td>
<td>No effect (2, 1 new)(^c) [✓]</td>
<td>Insufficient (1) [✓]</td>
</tr>
<tr>
<td>Low THC – Sublingual CBD/THC, Plant-extracted</td>
<td>No evidence</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
<tr>
<td>Other Cannabinoids – CBDV, Oral</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
<tr>
<td>Whole-Plant Cannabis (12% THC)(^e)</td>
<td>No evidence</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

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

\(^a\) ≥30% improvement from baseline

\(^b\) Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.

\(^c\) Text is bolded to indicate that the strength of evidence has changed.

\(^d\) Low THC – Synthetic or Plant-purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.

\(^e\) Low THC – Synthetic CBD plus Plant-purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.

\(^f\) Comparison was “usual care.”

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

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

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparable THC/CBD – Plant-extracted, Oromucosal Spray</td>
<td>No effect (5) [✓]</td>
<td>No effect (3) [✓]</td>
<td>Large effect (6) [✓]</td>
<td>Moderate effect (6) [✓]</td>
<td>Large effect (6) [✓]</td>
</tr>
<tr>
<td>High THC – Synthetic or Plant-purified, Oral</td>
<td>Moderate effect(^a) (6, 1 new) [✓]</td>
<td>Insufficient (2, 1 new) [✓✓]</td>
<td>Large effect (4, 1 new) [✓✓]</td>
<td>Large effect(^a) (4, 1 new) [✓✓]</td>
<td>Moderate effect (5, 1 new) [✓]</td>
</tr>
<tr>
<td>High THC – Plant-extracted, Oral</td>
<td>Large effect (1) [✓]</td>
<td>Insufficient (1)</td>
<td>Large effect (1) [✓]</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

Abbreviations: WAE = worst adverse event; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol.

\(^a\) Text is bolded to indicate that the strength of evidence has changed.

\(^b\) Low THC – Synthetic or Plant-purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.

\(^c\) Low THC – Synthetic CBD plus Plant-purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.

\(^d\) Comparison was “usual care.”

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

Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased benefit; SOE: [✓] = low, [✓✓] = moderate, [✓✓✓] = high.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low THC – Plant-extracted CBD, Topical</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Low THC – Synthetic or Plant-purified CBD, Oral</td>
<td>Insufficient (4, 2 new)</td>
<td>Insufficient (2, 1 new)</td>
<td>No effect (3, 2 new)</td>
<td>Insufficient (2 new)</td>
<td>No effect (3, 2 new)</td>
</tr>
<tr>
<td>Low THC – Synthetic CBD plus Plant-purified THC, Oral</td>
<td>Insufficient (2, 1 new)</td>
<td>Insufficient (2, 1 new)</td>
<td>Potential effect (2, 1 new)</td>
<td>Large effect (2, 1 new)</td>
<td>No effect (2, 1 new)</td>
</tr>
<tr>
<td>Low THC – Sublingual CBD/THC, Plant-extracted</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Other Cannabinoids – CBDV, Oral</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Whole-Plant Cannabis (12% THC)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
</tr>
</tbody>
</table>

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

- Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
- Low THC – Synthetic or Plant-purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.
- Text is bolded to indicate that the strength of evidence has changed.
- Low THC – Synthetic CBD plus Plant-purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.
- Comparison was “usual care.”

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

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

**Limitations**

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

**Implications and Conclusions**

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

References


Introduction

Background

Chronic pain, defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,\textsuperscript{1,2} is a serious public health issue in the United States, affecting approximately 100 million people\textsuperscript{3} and resulting in over $560 billion annually in costs.\textsuperscript{4} Chronic pain substantially impacts physical and mental functioning, reducing productivity and quality of life. It is the leading cause of disability and is often refractory to treatment.\textsuperscript{5,6} Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015.\textsuperscript{7} This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality\textsuperscript{7-9} involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdoses related to prescription opioids in the United States,\textsuperscript{1} with an estimated 17,087 prescription opioid overdose deaths in 2016.\textsuperscript{7} In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.\textsuperscript{10}

While opioids are often prescribed for chronic pain, they are associated with small to moderate effects on pain and overall function and frequent adverse effects.\textsuperscript{11} The 2022 Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain recommends nonopioid therapy as preferred treatment for chronic pain.\textsuperscript{12} Recent systematic reviews found that several nonopioid drugs,\textsuperscript{13} and some nonpharmacologic treatments,\textsuperscript{14} also have small to moderate effects on chronic pain and overall function. Some nonopioid pharmacological treatments had frequent overall adverse events and some less frequent but serious adverse effects, while nonpharmacological treatments typically reported few adverse events.\textsuperscript{13}

The challenges of treating chronic pain in light of the limited benefits of commonly prescribed prescription medications and potential harms of opioids have catalyzed a search for alternative pain treatments, including cannabis. Ideally, alternative treatments would have equal or better benefits for pain while avoiding potential unintended consequences that could result in harms. Plants have historically been evaluated for medicinal properties, with some being developed into drug therapies (i.e., the field of pharmacognosy). Some preclinical data suggest that cannabinoids may have analgesic properties, though research in this area is mixed.\textsuperscript{15} Tetrahydrocannabinol (THC), one of over 140 cannabinoids in cannabis,\textsuperscript{16} has demonstrated analgesic properties,\textsuperscript{17,18} though its psychoactive effects and abuse potential may increase its risk and lessen its suitability as an analgesic. Other cannabinoids (e.g., cannabidiol [CBD], cannabigerol [CBG], and cannabichromene [CBC]) may also have some analgesic or anti-inflammatory properties and are not thought to be intoxicating or addictive,\textsuperscript{19,20} but may not be as potent as THC. Observational studies indicate that some patients use cannabis and related compounds as a substitute for opioids.\textsuperscript{21-24}

Other plant-based compounds (PBCs) such as kratom, though pharmacologically distinct from cannabis, may be considered as analgesics, in part due to their community-use as substitutes for opioids.\textsuperscript{25,26} They may also have serious harms, such as dependence, addiction, and physiological withdrawal potential.\textsuperscript{27} Although some PBCs thought to reduce pain are currently classified as Schedule I by the Drug Enforcement Administration, there is disagreement on scheduling others, such as kratom.\textsuperscript{28} Recent legalization of cannabis by several states\textsuperscript{29} may lead to more and higher quality research on PBCs with potential for treating chronic pain.\textsuperscript{30} Initiatives to develop and study alternative interventions for chronic pain are expected to...
Contribute to this increase in research on PBCs, specifically for pain. This living review was initiated in response to a request from Congress on PBCs for chronic pain.\textsuperscript{30,31}

Although the original review and prior surveillance reports and update focused on chronic pain in adults, subacute pain as well as the adolescent population are also relevant. Subacute pain, often defined as pain lasting for 4 to 12 weeks, represents a transitional state between acute (<4 weeks) pain, which often resolves, and chronic pain, which is more likely to persist.\textsuperscript{32} Effective treatments for reducing the likelihood of subacute pain becoming chronic are also needed. Adolescents also experience chronic pain and have a high prevalence of cannabis use (recreational or medical).\textsuperscript{33,34}

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

**Purpose and Scope of the Systematic Review**

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

Review Approach

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

Key Questions

This review will address the following Key Questions (KQs):

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

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through January 15, 2024, with ongoing, automated monthly searches to identify newly published studies. Search strategies were updated for the 2023 review to include terms for subacute pain and applied to databases from inception to identify studies on subacute pain. The original search terms did not exclude adolescents, though, though we did re-assess previously excluded studies for eligibility based on the revised inclusion criteria. The search strategies are shown in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and two prior AHRQ pain reports for studies that met the inclusion criteria for this review. For the original 2021 review, a Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies. Pre-established criteria were used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ Methods Guide, based on the KQs and populations, interventions, comparators,
outcomes, timing, and settings (PICOTS; Table 1). See Appendix B for more details on eligibility criteria and methods for study selection, including dual review of studies screened.

### Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>PICOTS Element</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>All KQs: Adults or adolescents (including pregnant or breastfeeding women) with noncancer chronic (&gt;12 weeks or pain persisting past the time for normal tissue healing) or subacute pain (pain lasting 4 weeks to 3 months). See categorization of specifically included pain populations below.</td>
<td>All KQs: Children; adults with acute pain; patients at end of life or in palliative care (e.g., with late stage cancer-related pain)</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>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</td>
<td>All KQs: Non-plant-based interventions, capsaicin, herbal supplements</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>All KQs: Any comparator, or usual care</td>
<td>All KQs: No comparison</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>All KQs: Primary efficacy outcomes (i.e., pain, general function [e.g., Short-Form 36 Physical Functioning Scale] or pain-related [e.g., Oswestry Disability Index or Roland-Morris Disability Questionnaire, for low back pain] or disability, including pain interferencea); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder, serious adverse events as defined by study); secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, healthcare utilization)</td>
<td>All KQs: Other outcomes</td>
</tr>
<tr>
<td><strong>Time of followup</strong></td>
<td>All KQs: short term (4 weeks to &lt;6 months), intermediate term (6 to &lt;12 months), long term (≥1 year)</td>
<td>All KQs: studies with &lt;1-month (4 weeks) of treatment or followup after treatment</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>All KQs: Any nonhospital setting or setting of self-directed care</td>
<td>All KQs: Hospital care, hospice care, emergency department care</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>All KQs: RCTS; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits</td>
<td>All KQs: Other study designs</td>
</tr>
</tbody>
</table>

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

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

## Data Extraction and Risk of Bias Assessment

After studies were selected for inclusion, data were abstracted into evidence tables in categories that included but not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results. Information relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention (including regulatory status and availability in the United States), and care settings. All study data were verified for accuracy and completeness by a second team member.
The risk of bias of individual studies was assessed using methods consistent with the AHRQ Methods Guide. Separate criteria were used for randomized controlled trials and observational studies. Two reviewers independently assessed risk of bias, resulting in final ratings of low, moderate, or high, with any disagreements resolved by consensus. For full details about data extraction, risk of bias assessment, and other methods, please see Appendix B.

Data Synthesis and Analysis

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

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

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

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

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

Within the same THC to CBD category, we analyzed oral and oromucosal (e.g., sublingual or oromucosal spray) products separately from topical products, unless the topical product was clearly designed to produce systemic (rather than local) effects. In such cases, the topical product with systemic effects was analyzed together with oral and oromucosal products.
Table 2. 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><strong>High THC</strong></td>
<td>Synthetic</td>
<td>Synthetic THC (100% THC or analog)</td>
<td>Dronabinol (Marinol®) or nabilone (Cesamet®)</td>
<td>Available via prescription⁴</td>
</tr>
<tr>
<td>(THC to CBD ratio equals ≥2:1 ratio)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plant-purified</td>
<td>Purified from whole-plant with close to 100% THC</td>
<td>Purified dronabinol¹,² (e.g., Namisol®)</td>
<td>Not available in the U.S.</td>
</tr>
<tr>
<td></td>
<td>Plant-extracted</td>
<td>Commercially marketed product extracted from whole-plant with unknown 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-extracted</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><strong>Comparable THC to CBD</strong></td>
<td>Plant-extracted</td>
<td>Extracted from whole-plant with comparable ratio of THC/CBD</td>
<td>Nabiximols (Sativex®)¹,d</td>
<td>Not available in the U.S.</td>
</tr>
<tr>
<td>(THC to CBD ratio is &lt;2:1 and &gt;1:2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plant-extracted</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-extracted</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><strong>Low THC</strong></td>
<td>Synthetic</td>
<td>Synthetic CBD</td>
<td>CBD oral tablets</td>
<td>Unknown</td>
</tr>
<tr>
<td>(THC to CBD ratio is ≤1:2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plant-purified</td>
<td>Purified from whole-plant with close to 100% CBD</td>
<td>Purified CBD</td>
<td>Not available in the U.S.</td>
</tr>
<tr>
<td></td>
<td>Plant-extracted</td>
<td>Extracted from whole-plant with low ratio of THC/CBD; may undergo further purification</td>
<td>CBD topical, sublingual or oral</td>
<td>Unknown – may be available at dispensaries where allowed</td>
</tr>
<tr>
<td><strong>Whole-Plant Cannabis Products</strong></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>(THC to CBD ratio categorized based on information provided [potentially unknown])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Cannabinoids</strong></td>
<td>Plant-extracted</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>
<tr>
<td>(Cannabinoids other than THC or CBD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CBD = cannabidiol; THC = tetrahydrocannabinol.

¹ These products are approved by the Food and Drug Administration for nonpain indications (anorexia related to HIV infection, nausea related to chemotherapy).
² These plant-derived, purified products are chemically identical to dronabinol, and are therefore grouped together with synthetic dronabinol.
³ Manufactured in the Netherlands and Denmark, may be available in some European countries. Not currently FDA-approved.
⁴ Manufactured and available in Canada and some European countries; not FDA-approved.
Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were similar enough to provide a meaningful combined estimate.\textsuperscript{41} The decision to conduct quantitative synthesis depended on the presence of at least two studies with similar cannabis-related products, methodology, completeness of reported outcomes, and a lack of statistical heterogeneity among the reported results. Statistical heterogeneity among the studies was assessed using Cochran’s $\chi^2$ test and the $I^2$ statistic.\textsuperscript{42} Pain intensity scales were converted to a standardized 0 to 10 scale and the mean difference was used as the effect measure for change in pain. For function or disability, the standardized mean difference (SMD) was used as the effect measure, due to differences in the scales and measures used. For other continuous outcomes, the mean difference on the original scale was used if all studies used the same measure; otherwise, the SMD was used. For primary binary outcomes (pain response and adverse events), relative risk was used as the effect measure. See Appendix B for more details.

We used a random effects model based on the profile likelihood method\textsuperscript{43} to combine interventions with comparable THC to CBD ratios, high-THC trials, and low-THC trials. The primary analysis was stratified by the type of product evaluated. Synthetic and plant-purified products were analyzed together, based on their identical chemical composition, and plant-extracted products were analyzed separately. Sensitivity analysis was conducted by excluding studies rated as high risk of bias and evaluating plant-purified products separately from synthetic products. For meta-analyses with more than five but fewer than twenty studies, we also performed sensitivity analyses by repeating analyses using the Bartlett’s correction, which can provide improved confidence interval coverage probabilities (i.e., wider confidence intervals) in these situations.\textsuperscript{44,45} Meta-analyses were conducted using command \textit{metan} and \textit{admetan} in Stata/SE 16.1 (StataCorp, College Station, TX). Publication bias (small study effect) was assessed using both funnel plots and the Egger test when there were eight or more studies included in a meta-analysis.

The magnitude of effects for primary outcomes were classified according to the same definitions used in other recent AHRQ reviews on chronic pain\textsuperscript{11,13,14,38,39} to provide a consistent benchmark for evaluating results of pain interventions across reviews. The findings were categorized as small, moderate, and large magnitudes of effect based on the criteria shown in Table 3. Results that were below the threshold for a small effect were considered to reflect “no effect” or a trivial effect. Results with a small, medium, or large effect that were not statistically significant were considered to have “potential effects.”

### Table 3. Definitions of effect sizes

<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 = relative risk; SMD = standardized mean difference.
duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients, a small improvement in pain or overall function using a treatment with low cost or no serious harms may be important.

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

**Grading the Strength of the Body of Evidence**

We assessed the strength of evidence for all primary comparisons and outcomes listed above. The strength of evidence was based on the cumulative evidence (evidence identified for the original report plus new evidence added for the update). Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence for each KQ/body of evidence was initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.\(^{35,46}\) To ensure consistency and validity of the evaluation, the strength of evidence was reviewed by the entire team of investigators prior to assigning a final grade, based on the following domains:

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

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

In narratively describing the findings on the strength of the evidence, we followed the principles outlined in recent guidance to improve clarity.\(^{47-49}\) Using these principles, evidence that is low-strength is described as “may” have an effect, moderate strength evidence is described as “probably” has an effect, and high-strength evidence is described as having an effect.

**Living Systematic Review Methods**

This is an annual update of a systematic review originally published in 2021\(^50\) and updated in 2022.\(^51\) Quarterly surveillance of the literature conducted prior to this full update and describing new evidence as it is identified can be found at: [https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review](https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review). Due to the relatively small volume of new studies, the quarterly report format was abridged in late 2023. The new format consists of an updated literature flow diagram, a table of studies included since the 2023 review, and a brief description of whether new studies would impact findings. The availability of new studies likely to significantly impact findings would trigger a more detailed report.
Results

Description of Included Evidence

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

After screening a cumulative total of 5,644 abstracts, 471 full-text publications of studies were dually reviewed, resulting in 25 randomized controlled trials (RCTs) in 26 publications and 12 observational studies being included in this review. One new RCT in two publications (n=134) compared plant-derived synthetic equivalent THC (dronabinol; high-THC to CBD ratio), synthetic CBD (low-THC to CBD ratio), or both (low-THC to CBD ratio) versus placebo for neuropathic pain and another new RCT (n=86) evaluated a plant-derived CBD (low-THC to CBD ratio) versus placebo for knee osteoarthritis. Both of the new observational studies (n=296 and n=32,332) included patients with various chronic pain conditions and evaluated low, comparable, or high-THC to CBD ratio cannabis products; one of the studies (n=32,332) focused the association between cannabis use and on risk of arrhythmia and acute coronary syndrome.

The search results and selection of studies are summarized in the literature flow diagram (Figure 1). Appendix C provides a list of all included studies. In total, seven placebo-controlled RCTs evaluated products that contain a combination of plant-extracted THC and CBD in a comparable ratio. Two RCTs evaluated the effects of plant-extracted high-THC to CBD ratio products. Eleven placebo-controlled RCTs evaluated synthetic or plant-purified THC (high-THC to CBD ratio). Seven placebo-controlled RCTs evaluated low-THC to CBD ratio products. Five of these evaluated CBD alone: three, including one new RCT, evaluated synthetic oral CBD; one new RCT evaluated plant-purified oral CBD, and one RCT evaluated plant-extracted topical CBD. Two of the RCTs of oral synthetic CBD (including one new RCT) also evaluated the combination of plant-purified THC plus synthetic CBD (1:2 ratio) and one prior RCT assessed plant-extracted sublingual THC/CBD oil [1:6 ratio]. One other trial evaluated the phytocannabinoid cannabidivarin (CBDV), administered as an oral oil.

Appendix D summarizes key outcomes from each RCT and results of meta-analyses. Detailed evidence tables for included studies and risk of bias assessments are available in Appendixes E and F. Appendix G contains details on the strength of evidence, and Appendix H lists excluded studies at the full-text level and their reasons for exclusion.
Figure 1. Literature flow diagram

Abstracts of potentially relevant articles identified through Ovid® MEDLINE®, PsycINFO®, EMBASE®, the Cochrane Central Register of Controlled Trials, Scopus, and prior chronic pain reports (n=5,644)

Excluded abstracts (n=5,173)

Full-text articles reviewed for inclusion (n=471)

Excluded articles (n=433)
Ineligible population: 48
Ineligible intervention: 16
Ineligible comparison: 38
Ineligible outcome: 3
Ineligible duration: 18
Ineligible study design: 69
Ineligible publication type: 114
Study not in English: 10
SR or MA: 102
Background information only: 15

Included studies (n=37 studies in 38 publications)

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD</th>
<th>THC</th>
<th>CBD</th>
<th>CBDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC to CBD Ratio</td>
<td>Comparable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>High</td>
<td>Low</td>
<td>NA - other cannabinoids</td>
</tr>
<tr>
<td>Source</td>
<td>Plant-extracted</td>
<td>Synthetic</td>
<td>Plant-purified</td>
<td>Plant-extracted</td>
</tr>
<tr>
<td></td>
<td>Plant-purified</td>
<td>Plant-extracted</td>
<td>Synthetic</td>
<td>Plant-extracted</td>
</tr>
<tr>
<td>N Studies</td>
<td>7</td>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6&lt;sup&gt;c&lt;/sup&gt; (1 topical, 1 sublingual, 4 oral)</td>
<td>1</td>
</tr>
<tr>
<td>Comparator (Study Count)</td>
<td>Placebo (7)</td>
<td>Placebo (10); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low-THC to CBD ratio (CBD or plant-purified THC/CBD) (2)</td>
<td>Placebo (6); Dronabinol (2); Low-THC to CBD ratio (CBD or plant-purified THC/CBD) (2); ≥97% purified low-THC to CBD (1:6) sublingual oil (1)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Characteristic</td>
<td>THC/CBD</td>
<td>THC</td>
<td>CBD</td>
<td>CBDV</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td><strong>Route of Administration, Formulation (Study Count)</strong></td>
<td>Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl</td>
<td>Dronabinol 3 mg oral tablet (1); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Plant-purified dronabinol oral 2.5 mg capsule (2); Oral capsule, 2.5 mg plant-purified THC/0.8 - 1.6 mg CBD extract (1); Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)</td>
<td>Oral capsule, 5 mg synthetic CBD (2); Oral tablet, 10 mg synthetic CBD (1); Oral capsule, 200 mg plant-purified CBD (1); Oral capsule, 5 mg CBD extract/2.5 mg dronabinol (2); Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1); Topical cream, 83 mg CBD/fluid ounce (1)</td>
<td>Oral oil, 50 mg/ml CBDV</td>
</tr>
<tr>
<td><strong>Dosing Regimen</strong></td>
<td>Final mean dose 23 mg THC/21 mg CBD daily.</td>
<td>Dronabinol capsules: 2.5 to 5 mg, titrated. Final dose range 13 - 25 mg/day Dronabinol (Namisol®) tablet: 3 to 8 mg 3 times daily, titrated. Final dose NR Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Capsule: 2.5 - 12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily</td>
<td>Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 45 to 50 mg CBD daily (2) Oral tablet: 10 mg daily, titrated (max 3 times daily) Final dose NR Oral CBD capsule: 200 mg 3 times daily. Final dose 600 mg/day Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 12.5 to 15 mg THC/30 to 45 mg CBD daily (2) Sublingual oil, titrated to max daily dose of 6 drops 3 times daily (15 mg THC/90 mg CBD) Topical cream: applied locally 1-4 times/day (volume/dose, final dose NR)</td>
<td>400 mg CBDV daily. Final dose NR.</td>
</tr>
<tr>
<td><strong>Risk of Bias</strong></td>
<td>29% high, 57% moderate, 14% low</td>
<td>8% high, 46% moderate, 46% low</td>
<td>50% high, 33% moderate, 17% low</td>
<td>100% moderate</td>
</tr>
<tr>
<td><strong>Total Randomized</strong></td>
<td>882</td>
<td>1,028</td>
<td>508</td>
<td>34</td>
</tr>
<tr>
<td><strong>Age, Mean Years</strong></td>
<td>53</td>
<td>54</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>66%</td>
<td>62%</td>
<td>60%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Non-White, c %</strong></td>
<td>1.6% (2)</td>
<td>5.3% (4)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 5. Characteristics of included observational studies of cannabinoids for chronic pain in adults

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD(^a)</th>
<th>THC</th>
<th>Synthetic THC</th>
<th>THC/CBD Versus Synthetic THC</th>
<th>THC/CBD Versus LAOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC to CBD Ratio</td>
<td>Unclear or mixed</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) or mixed cannabinoids</td>
<td>Plant-extracted</td>
<td>Synthetic (nabilone)</td>
<td>Plant-extracted vs. synthetic</td>
<td>Plant-extracted</td>
</tr>
<tr>
<td>N Studies</td>
<td>8 (^b)</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 (2); other cannabinoids (2)</td>
<td>Usual care (1)</td>
<td>Gabapentin only; gabapentin + nabilone (1)</td>
<td>Active comparator; oral mucosal spray vs. dronabinol</td>
<td>Long-acting opioids (MME 69.4 (SD 38.9) mg/day)</td>
</tr>
<tr>
<td>Route of Administration, Formulation</td>
<td>Unreported (any available allowed, patient’s choice) (6); inhaled or oral prescribed cannabis (2)</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>
<tr>
<td>Dosing Regimen</td>
<td>None specified (7) Final median dose 85 mg CBD vs. 7.8/20 mg THC/CBD vs. 20/25 mg THC/CBD vs. 42 mg THC/day (1)</td>
<td>None specified; titrated to max dose 5 g/day. Final median dose 2.5 g/day</td>
<td>None specified; final mean dose 3 mg/day</td>
<td>None specified; final mean dose 16.6/15.4 mg THC/CBD/day vs. 17.2 mg THC/day</td>
<td>None specified; based on individual patient needs; final mean dose 16.7/15.5 mg THC/CBD/day vs. MME 69.4 mg/day</td>
</tr>
<tr>
<td>ROB</td>
<td>50% high, 50% moderate</td>
<td>100% high</td>
<td>100% moderate</td>
<td>100% moderate</td>
<td>100% moderate</td>
</tr>
</tbody>
</table>

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

\(^a\) All products were nabiximols.

\(^b\) Two trials are included in both the THC and CBD columns, as they compared THC to CBD, CBD/THC, and placebo.

\(^c\) (n) = number of studies reporting this characteristic at baseline.

\(^d\) Scores were standardized to a 0 to 10 scale.

\(^e\) Weighted mean includes median scores for 1 study (6 vs. 6).

\(^f\) Weighted mean includes median scores for 1 study (5.2 vs. 6.1).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THC/CBD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>THC</th>
<th>Synthetic THC</th>
<th>THC/CBD Versus Synthetic THC</th>
<th>THC/CBD Versus LAOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Total</td>
<td>45,897</td>
<td>431</td>
<td>156</td>
<td>674</td>
<td>1,310</td>
</tr>
<tr>
<td>Age, Mean Years</td>
<td>54</td>
<td>49</td>
<td>61</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>Female, %</td>
<td>52%</td>
<td>57%</td>
<td>59%</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>% Non-White (Study Count)</td>
<td>54% (1); NR (7)</td>
<td>NR</td>
<td>NR</td>
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</tr>
<tr>
<td>Primary Pain Type(s)</td>
<td>Mixed musculoskeletal, chronic non-cancer pain</td>
<td>Chronic non-cancer pain</td>
<td>NPP</td>
<td>Peripheral NPP</td>
<td>Peripheral neuropathic back pain</td>
</tr>
<tr>
<td>Baseline Pain Score, Mean (Range)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.75 (4.56 to 7.00)</td>
<td>6.35 (6.1 to 6.6)</td>
<td>4.98 (4.58 to 5.31)</td>
<td>4.4 (4.39 to 4.41)</td>
<td>4.32 (4.31 to 4.33)</td>
</tr>
<tr>
<td>Study Duration, Weeks (Range)</td>
<td>12 to 208</td>
<td>52</td>
<td>26</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

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

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

<sup>b</sup> Includes two new studies for this review.

<sup>c</sup> Scores were standardized to a 0 to 10 scale.
KQ 1 and KQ 2. In adults or adolescents with chronic or subacute pain, what are the benefits (KQ 1) and harms (KQ 2) of cannabinoids for treatment of chronic or subacute pain?

Key Points for Comparable THC to CBD Ratio

- All results are short-term (4 weeks to <6 months) in duration.
- Comparable plant-extracted THC to CBD ratio oromucosal spray was associated with small improvements in pain severity (7 RCTs, N=702, 0 to 10 scale, mean difference [MD] −0.54, 95% confidence interval [CI], −0.95 to −0.19, I²=39%) and overall function (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI −0.73 to −0.16, I²=32%) versus placebo (strength of evidence [SOE]: moderate). While more patients experienced a pain response (≥30% improvement from baseline), fewer trials reported this outcome and the difference was small and did not reach statistical significance (4 RCTs, N=733, 38% vs. 31%, relative risk [RR] 1.18, 95% CI 0.93 to 1.71, I²=36%) (SOE: low).
- Compared with placebo, comparable plant-extracted THC to CBD oromucosal spray was associated with a large increase in risk of dizziness (6 RCTs, N=866, 31.0% vs. 8.0%, RR 3.57, 95% CI 2.42 to 5.60, I²=0%) (SOE: low) and sedation (6 RCTs, N=866, 8.0% vs. 1.2%, RR 5.04, 95% CI 2.10 to 11.89, I²=0%) (SOE: low), and a moderate increased risk of nausea (6 RCTs, N=866, 13% vs. 7.5%, RR 1.79, 95% CI 1.19 to 2.77, I²=0%) (SOE: low). There was no effect on study withdrawal due to adverse events (WAEs) (SOE: low).

Summary of Findings for Comparable THC to CBD Ratio

Seven RCTs (N=882, range 18 to 339)\(^{56-62}\) included in prior updates compared plant-extracted THC and CBD in a comparable THC to CBD ratio versus placebo in patients experiencing chronic pain. All used nabiximols, which are extracted from whole-plant cannabis with 2.7 mg of THC and 2.5 mg of CBD per 100 mcl oromucosal spray (specified as the product Sativex\(^{®}\) in 7 studies). Sativex\(^{®}\) is manufactured and available in Canada and some European countries. Other comparable THC to CBD products are available in the United States, where allowed, though the availability of specific products is unknown. Six trials enrolled patients with neuropathic pain\(^{56-60,62}\) and one trial included patients with rheumatoid arthritis. Studies ranged from 4 to 16 weeks in duration of active treatment; all were short-term followup (1 to <6 months). Across trials, the weighted mean daily dose was 8.4 sprays (23 mg THC/21 mg CBD) for patients assigned to THC/CBD and 12.7 sprays for those assigned to placebo. One study did not specify the product name, strength or dosing in milligrams, but the number of sprays per day (8 vs. 11 for intervention vs. placebo), were similar to other trials.\(^{58}\) Two trials were high risk of bias: one was a small (n=16), 4-week, crossover trial, and the other was a small (n=29), 12-week, parallel design trial.\(^{58,61}\) The rest were parallel design trials; four were rated moderate risk of bias\(^{56,59,60,62}\) and one low risk of bias.\(^{57}\) One trial used an enriched enrollment randomized withdrawal design.\(^{57}\) The mean age of participants in the trials was 53 years, and 66 percent were female. Race was poorly reported, with two trials reporting 1.2 percent of participants being non-white, and the others not reporting it at all. Four trials allowed patients using opioids and other analgesics to enroll and to continue using them during the study period.\(^{57,59,62}\) The proportion of patients taking opioids was low in two studies (11% to 24%)\(^{57,62}\) and much greater in the third study (63% in the cannabis group vs. 74% in the placebo group).\(^{59}\) The other three trials did not
report opioid use. All of the RCTs of comparable THC to CBD ratio products allowed prior cannabis use; the proportion of patients that used cannabis previously ranged from 5 to 64 percent. No study analyzed results according to prior cannabis use.

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

Four RCTs\(^57,59,61,62\) found comparable plant-extracted THC/CBD oromucosal spray associated with a nonstatistically significant increased likelihood of pain response (≥30% reduction in pain) versus placebo, (38% vs. 31%, RR 1.18, 95% CI 0.93 to 1.71, \(I^2=36\%\); Appendix D, Figure D-1). Based on pooled analysis of all seven RCTs, comparable THC/CBD was associated with a small, statistically significant reduction in pain severity versus placebo (7 RCTs, 0 to 10 scale, MD −0.54, 95% CI −0.95 to −0.19, \(I^2=39\%\); Figure 2).\(^56-62\) Figure 2 shows that, except for the small, high risk of bias, crossover study, the effect size was larger and statistically significant in shorter studies (4 to 5 weeks) compared with longer studies (12 to 15 weeks); however, all studies met the definition for short duration (1 to <6 months). Sensitivity analysis excluding two high risk of bias studies\(^58,61\) did not alter the findings (0 to 10 scale, MD −0.63, 95% CI −1.15 to −0.24, \(I^2=52\%\)).\(^57,62\) One trial that used an enriched enrollment randomized withdrawal design reported worse results for comparable THC/CBD compared to the pooled estimate (MD −0.19, 95% CI −0.67 to 0.29).\(^57\)

Six studies (N=616) with 5 to 15 weeks followup reported overall function or disability (including measures of pain interference).\(^56,57,59-62\) Pooled analysis showed a small benefit for nabiximols versus placebo (6 RCTs, 0 to 10 scale, MD −0.42, 95% CI −0.73 to −0.16, \(I^2=32\%\); Figure 3).

For secondary outcomes, all of the trials reported quality of life. Overall, there were no statistically significant differences in quality of life between groups. Three used the EQ-5D scale (0 to 100), with none finding a significant difference between groups.\(^57,61,62\) One used the Short General Health Questionnaire (GHQ-12; 0 to 36 scale), and found a small, but nonstatistically significant, difference between groups.\(^59\) Three studies reported on the Short Form-36 (SF-36) Physical and Mental scales (0 to 100).\(^57,58,61\) Two did not find statistically significant between-group differences. The third study, a high risk of bias crossover trial (n=16), reported that the SF-36 Physical scale scores improved with placebo, with little change in the THC/CBD group, while the SF-36 Mental scale scores remained similar in the THC/CBD group and decreased (worsened) in the placebo group.\(^58\) Five RCTs assessed sleep quality or sleep disturbance using a 0 to 10 scale; four reported statistically significantly better sleep outcomes in the THC/CBD groups versus placebo groups.\(^56,57,59,60,62\) The studies did not report on other secondary outcomes (e.g., depression or anxiety).

The four RCTs that allowed opioid use did not report on changes in opioid used during the study period.\(^57,59,62\)
Adverse events were reported in all the trials. Based on two RCTs, rates of any adverse event were significantly higher in the THC/CBD groups than placebo (2 RCTs, 75% vs. 63%, RR 1.19, 95% CI 1.02 to 1.44, I²=0%, Appendix D, Figure D-2).57,60

Serious adverse events (SAEs) were reported in five studies, with two reporting that none occurred.58,60 Pooling results from the other three studies found no effect on SAEs with comparable THC/CBD products (3 RCTs, 5.0% vs. 4.3%, RR 1.18, 95% CI 0.26 to 3.4, I²=0%, Appendix D, Figure D-3).56,59,62

Five RCTs reported on study WAEs. Pooled analysis found no difference between plant-extracted comparable THC to CBD ratio products versus placebo in risk of WAEs, though the estimate was imprecise (5 RCTs, 12.3% vs. 9.5%, RR 1.14, 95% CI 0.65 to 3.02, I²=51%, Appendix D, Figure D-4).56,57,59,60,62

Statistically significant differences in specific adverse events of interest occurred more often in the THC/CBD groups than placebo across six RCTs (one did not report specific adverse events).61 Dizziness occurred significantly more in the THC/CBD groups than placebo groups (6 RCTs, 31.0% vs. 8.0%, RR 3.57, 95% CI 2.42 to 5.60, I²=0%, Appendix D, Figure D-5).56-60,62 Nausea was reported in 13 percent of THC/CBD patients compared with 7.5 percent of placebo
patients (6 RCTs, RR 1.79, 95% CI 1.19 to 2.77, I²=0%, Appendix D, Figure D-6).\textsuperscript{56-60,62}
Sedation was reported in 8 percent of THC/CBD patients compared with 1.2 percent of placebo
patients (6 RCTS, RR 5.04, 95% CI 2.10 to 11.89, I²=0%, Appendix D, Figure D-7).\textsuperscript{56-60,62}
A previously included retrospective cohort study (n=1,310) provided insufficient evidence to
compare outcomes of nabiximols oromucosal spray (plant-based extracted comparable THC to
CBD ratio product) versus long-acting opioids when administered as add-on therapy in patients
with neuropathic pain, due to methodological limitations.\textsuperscript{79}

Key Points for High-THC to CBD Ratio

- All RCT results were short term (4 weeks to <6 months) in duration.
- Synthetic or plant-purified high-THC to CBD ratio (100% THC or THC analogue)
products were associated with a small improvement in pain severity (8 RCTs, N=507, 0
to 10 scale, MD −0.78, 95% CI −1.59 to −0.08, I²=64%) (SOE: low) and no effect on
overall function or disability (3 RCTs, N=unclear, 0 to 10 scale, MD −0.18, 95% CI
−1.25 to 0.77, I²=51%) (SOE: low).
- Synthetic or plant-purified high-THC to CBD ratio (100% THC or THC analogue)
products were associated with a moderate increase in risk of study withdrawal due to
adverse events (WAEs) (6 RCTs, N=487, 14% vs. 6%, RR 1.92, 95% CI 1.10 to 4.80,
I²=0%) (SOE: low), moderate increase in risk of sedation (5 RCTs, N=458, 24% vs. 16%,
RR 1.57, 95% CI 1.11 to 2.29, I²=0%) (SOE: low), a large increase in risk of dizziness (4
RCTs, N=425, 33% vs. 15%, RR 2.30, 95% CI 1.53 to 3.52, I²=22%) (SOE: moderate),
and a large increase in risk of nausea (4 RCTs, N=425, 12% vs. 6%, RR 2.12, 95% CI
1.09 to 3.96, I²=0%), but the differences did not reach statistical significance (SOE: low).
- Synthetic or plant-purified high-THC to CBD ratio (100% THC or THC analogue)
products were associated with inconsistent effects on likelihood of experiencing a pain
response (≥30% improvement) (3 RCTs) (SOE: insufficient).
- Plant-extracted high-THC to CBD ratio products (not 100% THC) were associated with
a large increased risk of study WAEs (1 RCT, N=277, 13.9% vs. 5.7%, RR 3.12, 95% CI
1.54 to 6.33) (SOE: low) and dizziness (1 RCT, N=277, 62.2% vs. 7.5%, RR 8.34, 95%
CI 4.53 to 15.34) (SOE: low). Outcomes assessing benefit were not reported or evidence
was insufficient.
- The combined evidence for synthetic or plant-purified and plant-extracted high-THC to
CBD ratio products indicated moderate improvement in pain severity versus placebo (10
RCTs, N=801, −0.98, 95% CI −1.80 to −0.32, I²=68%) (SOE: moderate).

Summary of Findings for High-THC to CBD Ratio

One new, low risk of bias RCT (n=134) evaluated a high-THC to CBD ratio product.\textsuperscript{52,53}
It was conducted in Denmark and compared the plant-purified THC analogue dronabinol) versus
synthetic CBD, combined THC/CBD (low-THC to CBD ratio), or placebo for chronic (duration
≥3 months) neuropathic (multiple sclerosis or spinal cord injury) pain. Median daily doses were
9 mg per day for dronabinol, 45 mg per day for CBD, and 17.5 mg/35 mg per day for combined
THC/CBD. Median age was 52 and 74 percent were female; average pain duration was not
reported. Race was not reported. The duration of treatment was 7 weeks.

With the new trial, a total of 13 RCTs evaluated high-THC to CBD ratio products.\textsuperscript{52,63-74}
Eleven evaluated synthetic THC (dronabinol, 2 RCTs),\textsuperscript{68,69} a synthetic THC analog (nabilone, 6
or plant-purified dronabinol (3 RCTs). Two other RCTs evaluated plant-extracted products with both THC and CBD (THC to CBD ratio 48:1 in one study and 2:1 in the other). Synthetic dronabinol and nabilone are available by prescription and approved by the Food and Drug Administration for nonpain indications. The availability of plant-purified dronabinol is unclear though it is manufactured in the Netherlands and Denmark and may be available in some European countries. Other plant-extracted and high-THC whole-plant products are available in the United States, where allowed, though the availability of specific products is unclear.

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

**Synthetic or Plant-purified THC**

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

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

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

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

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

**Placebo-Controlled Trials of Synthetic and Plant-purified THC**

Based on an updated pooled analysis of eight RCTs (1 new RCT added), synthetic and plant-purified high-THC to CBD ratio products were associated with a small improvement in pain severity versus placebo (8 RCTs, N=507, 0 to 10 scale, MD –0.78, 95% CI –1.59 to –0.08, I²=64%; Figure 4). However, statistical heterogeneity was present. The estimate was similar to the prior pooled estimate (MD –0.95, 95% CI –1.81 to –0.25, I²=60%). Results were similar when the analysis was restricted to trials of patients with neuropathic pain (7 RCTs, MD –0.77, 95% CI –1.67 to 0.00, I²=70%). However, statistical heterogeneity remained present. Excluding the small (n=26), enriched enrollment randomized withdrawal trial also resulted in a similar pooled estimate and did not resolve statistical heterogeneity. Stratified analysis indicated that the pooled effect estimate for nabilone (MD –1.59, 95% CI –2.49 to –0.82, I²=0%) was larger than with dronabinol (MD –0.23, 95% CI –0.82 to 0.54, I²=45%; Appendix D, Figure D-8, Table D-6); this difference was statistically significant (p=0.027). Analyzing plant-purified THC as a separate category from synthetic THC did not resolve statistical heterogeneity among the high THC trials, although results suggested discordant effects for synthetic (moderate benefit, 5 RCTs, MD –1.20, 95% CI –2.21 to –0.47, I²=58%) and plant-purified products (no benefit, 3 trials, MD 0.10, 95% CI –1.08 to 1.02, I²=48%; Appendix D, Figure D-9).

Three trials (including the new RCT) reported likelihood of pain response (≥30% improvement from baseline) for synthetic or plant-purified high-THC to CBD ratio products. Although the overall estimate indicated no difference between high-THC to CBD products versus placebo in likelihood of pain response (3 trials, N=143, RR 0.99, 95% CI 0.43 to 2.37; Appendix D, Figure D-10), the estimate was imprecise and statistical heterogeneity was present (I²=72%). Two trials, including the new RCT (n=59), found dronabinol for neuropathic pain associated with a non-statistically significant decreased likelihood of experiencing a pain response versus placebo (43% vs. 57%, RR 0.76, 95% CI 0.45 to 1.28 and 29% vs. 57%, RR 0.64, 95% CI 0.31 to 1.31). However, a previously included, small low risk of bias RCT (n=26) of patients with diabetic neuropathy found nabilone associated with a large increase in likelihood of pain response (85% vs. 38%, RR 2.20, 95% CI 1.06 to 4.55). In addition to inconsistency, pain response was only reported in three of seven RCTs evaluating this outcome, potentially introducing a form of selective reporting bias. Therefore, the evidence for this outcome remained insufficient.

Four RCTs reported on overall function (including pain interference) or disability. A pooled analysis of three RCTs (N=98) found little difference between synthetic or plant-purified high-THC to CBD ratio products versus placebo for function, though the estimate was imprecise (0 to 10 scale, MD –0.18, 95% CI –1.25 to 0.77, I²=51%; Appendix D, Figure D-11). Two trials evaluated nabilone and one trial dronabinol. A fourth, small (n=13) RCT reported that neither high-THC nor placebo was associated with change in disability, measured with the Bartell Index, but did not provide data.
Few synthetic or plant-purified THC studies reported secondary outcomes, and results were mixed. A small (n=26), low risk of bias RCT of patients with diabetic neuropathy reported no difference between nabilone versus placebo in depression using the Hospital Anxiety and Depression-D [HADS-D] scale at 5 weeks (0 to 10, MD −0.4, 95% CI −1.26 to 1.46), although there was a statistically significant improvement in anxiety (HADS-A, 0 to 10 scale, MD −2.9, 95% CI −3.80 to −2.0). Quality of life findings were mixed, with a statistically nonsignificant difference in EQ-5D Utility scores (endpoint scores 72.6 vs. 61.4) and a statistically significant difference using the EQ-5D Index scores (endpoint scores 0.74 vs. 0.60, p<0.05 using analysis of covariance [ANCOVA]). A small, moderate risk of bias study (n=40) of patients with fibromyalgia evaluated secondary outcomes using the Fibromyalgia Impact Questionnaire (FIQ). The overall FIQ score improved more at 4 weeks with nabilone than with placebo (MD −12.07, p<0.02). Using the anxiety questions on the FIQ, nabilone was associated with a statistically significant improvement after 4 weeks (0 to 10 scale, MD −2.2, p<0.01). FIQ depression scores were not significantly improved with nabilone. The three RCTs that permitted opioid use during the study period did not report on the effect of the study medications on opioid use.66,69,70 One low risk of bias RCT (n=58) found no differences between plant-purified dronabinol versus placebo in sleep (0 to 10 scale, MD 0.36, 95% CI −1.31 to 2.03 on 0 to 10 scale), quality of life (0 to 10 scale, mean difference −0.35, 95% CI −1.66 to 0.97), Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety scores (MD 0.23, 95% CI −2.04 to 2.50), or PROMIS depression scores (MD 1.64, 95% CI −0.24 to 3.52).

For adverse events, findings were similar with the addition of the new RCT.52. As in the prior update, the addition of the new RCT found synthetic or plant-purified THC associated with a moderate increased risk of WAEs (6 RCTs, 14% vs. 7%, RR 1.92, 95% CI 1.10 to 4.80, I^2=0%, Appendix D, Figure D-12). Although the updated estimate for WAE became statistically significant, imprecision was still present (the lower limit of the confidence interval crosses the threshold for a small effect) and the SOE remained low. Of six RCTs reporting WAEs, two evaluated nabilone70,72 (7% vs. 4%, RR 1.54, 95% CI 0.14 to 17.71, I^2=0%) and four evaluated synthetic or plant-purified dronabinol52,65,69,74 (15% vs. 7%, RR 1.95, 95% CI 1.08 to 6.55, I^2=0%, Appendix D, Figure D-13), with no statistically significant differences between nabilone or dronabinol (p=0.71). A previously reported pooled analysis of two RCTs reporting any adverse event (1 nabilone, 1 dronabinol) found a small, non-statistically significant increase with synthetic THC (2 RCTs, 86% vs. 71%, RR 1.20, 95% CI 0.96 to 1.48, I^2=0%, Appendix D, Figure D-14).69,71 The estimate for SAEs remained very imprecise with the addition of the new RCT(2 RCTs, N=312, 9% vs. 6%, RR 1.53, 95% CI 0.52 to 4.15).52,69

As in prior updates, synthetic or plant-purified high-THC to CBD ratio products were associated with statistically significant increased risk of dizziness (4 RCTs, 33% vs. 15%, RR 2.30, 95% CI 1.53 to 3.52, I^2=22%, Appendix D, Figure D-15)52,65,69,74 and sedation (5 RCTs, 24% vs. 16%, RR 1.57, 95% CI 1.11 to 2.29, I^2=0%, Appendix D, Figure D-16).52,65,69,70,74 As in the prior update, the updated meta-analysis found synthetic or plant-purified THC associated with large increased risk of nausea versus placebo (4 RCTs, 12% vs. 6%, RR 2.12, 95% CI 1.09 to 3.96, I^2=0%, Appendix D, Figure D-18).52,65,69,74 Although the updated estimate for nausea became statistically significant, imprecision was still present and the SOE remained low. A sensitivity analysis using the Bartlett’s correction resulted in a more imprecise pooled estimate for sedation that was no longer statistically significant and imprecise (sedation: 5 RCTs, RR 1.57, 95% CI 0.99 to 2.78, I^2=0%, Figure D-17; Table D-7). In stratified analyses for sedation, one study of nabilone (n=33) reported a greater magnitude of effect (RR 8.40, 95% CI, 1.16 to 60.10).
60.84, Figure D-16) than 4 trials of dronabinol (N=425, RR 1.49, 95% CI 1.04 to 2.12, I²=0%, Figure D-16) with no statistically significant subgroup difference (p=0.09).

**Figure 4. 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>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>Synthetic or Plant-purified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiraghi, 2017</td>
<td>NPP All THC</td>
<td>16</td>
<td>Dronabinol (synthetic)</td>
<td>13 mg/day</td>
<td>Low</td>
<td></td>
<td>124.4 (2.04)</td>
<td>116.4 (2.04)</td>
<td>-0.44 (-0.98, 0.0)</td>
</tr>
<tr>
<td>Skrodle, 2008</td>
<td>FM All THC</td>
<td>4</td>
<td>Nabilone (synthetic)</td>
<td>EP 1 mg/day</td>
<td>Moderate</td>
<td></td>
<td>15.8 (1.62)</td>
<td>18.5 (1.62)</td>
<td>-0.9 (-1.03, 0)</td>
</tr>
<tr>
<td>Wissel, 2006</td>
<td>NPP All THC</td>
<td>4</td>
<td>Nabilone (synthetic)</td>
<td>1 mg per day</td>
<td>High</td>
<td></td>
<td>13.4 (0.0)</td>
<td>13.6 (0.0)</td>
<td>-0.16 (-0.21, -0.0)</td>
</tr>
<tr>
<td>Tolb, 2012</td>
<td>NPP All THC</td>
<td>5</td>
<td>Nabilone (synthetic)</td>
<td>1 to 4 mg/day</td>
<td>Moderate</td>
<td></td>
<td>13.3 (1.30)</td>
<td>13.5 (1.70)</td>
<td>-0.19 (-0.31, -0.09)</td>
</tr>
<tr>
<td>Turcotte, 2015</td>
<td>NPP All THC</td>
<td>9</td>
<td>Nabilone (synthetic)</td>
<td>TD 2 mg/day</td>
<td>Moderate</td>
<td></td>
<td>8.3 (1.29)</td>
<td>7.5 (1.65)</td>
<td>-0.22 (-0.37, -0.07)</td>
</tr>
<tr>
<td>Hensen, 2023, de Vito, 2017</td>
<td>NPP All THC</td>
<td>7</td>
<td>Nabilone (plant-purified)</td>
<td>Up to 22.5 mg/day</td>
<td>Low</td>
<td></td>
<td>24.1 (2.00)</td>
<td>25.1 (2.00)</td>
<td>-0.9 (-1.01, 0)</td>
</tr>
<tr>
<td>Zuberek, 2022</td>
<td>NPP All THC</td>
<td>8</td>
<td>Nabilone (plant-purified)</td>
<td>15 to 24 mg/day</td>
<td>Moderate</td>
<td></td>
<td>21.2 (2.28)</td>
<td>23.3 (2.42)</td>
<td>-1.1 (-1.24, 0.28)</td>
</tr>
<tr>
<td>Subgroup, PL (p=0.007, I²=63.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.79 (-1.59, 0.04)</td>
</tr>
<tr>
<td>Plant-extracted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.99 (-1.01, -0.38)</td>
</tr>
<tr>
<td>Chaves, 2020</td>
<td>FM 48:1</td>
<td>8</td>
<td>Plant-extracted</td>
<td>4.40 (2.49) mg T/C</td>
<td>Low</td>
<td></td>
<td>8.3 (2.49)</td>
<td>9.7 (1.84)</td>
<td>-3.2 (-4.16, -1.66)</td>
</tr>
<tr>
<td>Jazik, 2012</td>
<td>NPP 2:1</td>
<td>8</td>
<td>Plant-extracted</td>
<td>Max 25 mg/day</td>
<td>Moderate</td>
<td></td>
<td>143.3 (-2.00)</td>
<td>134.3 (-3.00)</td>
<td>-1.9 (-9.13)</td>
</tr>
<tr>
<td>Subgroup, PL (p=0.001, I²=64.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.9 (-1.49, -0.31)</td>
</tr>
</tbody>
</table>

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

**Active-Control Studies of Synthetic THC Versus Non-cannabinoids**

Three previously included crossover RCTs compared synthetic THC versus other (non-cannabinoid) medications. One low risk of bias RCT (n=80) found no statistically significant difference between nabilone (0.5 mg per day) versus ibuprofen (400 mg per day) in pain severity at 8 weeks in patients with medication overuse headache.67 There were also no statistically significant differences in depression, anxiety, quality of life), risk of adverse events, or risk of WAEs (SAEs were not reported). At 2 weeks post-study, nabilone was associated with lower daily analgesic intake than ibuprofen (0.89 analgesics/d vs. 1.34 analgesics/d; p=0.03). However, specific analgesic medications were not reported. Adverse events were infrequent and estimates were imprecise (dizziness 7.7% with nabilone vs. 0% with ibuprofen; cognitive deficits 3.8% vs. 0%, nausea 3.8% vs. 7.7% and sedation 0% vs. 3.8%). A moderate risk of bias RCT (n=73) found dihydrocodeine (30 to 240 mg/day) associated with greater reduction in pain severity versus nabilone (max dose of 2 mg/day) at 6 weeks (VAS 0 to 100 scale; MD −5.7, 95% CI −10.9 to −0.5, p=0.03).66 There were no statistically significant differences in secondary outcomes (depression, anxiety, quality of life, or sleep). A very small (n=7), high risk of bias RCT found no difference between dronabinol versus diphenhydramine in pain intensity in patients with spinal cord injury.68 Other efficacy outcomes were reported.

A moderate risk of bias, prospective observational study (n=101 for nabilone and gabapentin arms) found no difference between nabilone versus gabapentin in pain severity between groups at 3 months in patients with mixed neuropathic pain.69 However, at 6 months nabilone was associated with a greater reduction in pain intensity (0 to 100 VAS, MD −5.8, 95% CI −10.18 to −1.42), and better sleep scores on the Medical Outcomes Study Sleep Scale (scale 0 to 60, MD −3.1, 95% CI −7.57 to 1.37 vs. gabapentin) than gabapentin, with no differences in pain interference, quality of life, depression, or anxiety. Nabilone was associated with decreased likelihood of any adverse event (38% vs. 48%, RR 0.72, 95% CI 0.49 to 1.07), WAEs (10% vs. 23%, RR 0.44, 95% CI 0.17 to 1.16) and sedation (35% vs. 60%, RR 0.58, 95% CI 0.37 to 0.91),
although only the estimate was sedation was statistically significant. The likelihood of experiencing dizziness was similar (33% vs. 39%, RR 0.85, 95% CI 0.50 to 1.44).

**Head-to-Head Comparisons of Cannabis-Based Products**

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

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

**Plant-Based Extracted THC**

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

In pooled analysis, pain severity was improved with the plan-extracted high-THC products, but the difference was not statistically significant (2 RCTs, 0 to 10 scale, MD −1.97, 95% CI −5.91 to 1.21, I²=85%; Figure 4). There was a high degree of heterogeneity in this combined estimate, likely due to multiple differences between the studies, including sample size, dose, duration, and pain condition evaluated (fibromyalgia vs. multiple sclerosis), with a large difference in the magnitude of effect across the two studies. Individually, each study found a statistically significant reduction in pain severity. The 8-week, low-dose THC oil study of 17 women with fibromyalgia reported a larger effect (0 to 10 scale, MD −3.92, 95% CI −5.98 to −1.86) on pain intensity than the larger (n=277) 12-week study of a much higher dose of a high-THC capsule product (MD −0.90, 95% CI −1.49 to −0.31).

Pain response was not reported.

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

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

**Combined Analysis of Synthetic THC and Plant-Based Extracted THC Products**

To evaluate whether there was an effect for any form of high-THC product (synthetic, plant-purified, or plant-extracted), we combined results from all studies of high-THC to CBD ratio interventions (Figure 4). The updated (1 new RCT) overall combined mean difference was −0.98 (95% CI −1.80 to −0.32, I²=68%), or similar to the prior pooled estimate (−1.12, 95% CI −1.97 to −0.48, I²=65%). Although substantial statistical heterogeneity was present, a subgroup analysis of synthetic or plant-purified versus plant-extracted forms of high-THC (Appendix D, Table D-8) did not indicate a statistically significant subgroup difference (p=0.318). The number of RCTs included in the combined analysis (≥8 studies) allowed evaluation for publication bias using graphical and statistical methods. Both the funnel plot and the Egger test (p=0.131) suggested potential small sample effects, a marker for publication bias, though the Egger test was above the threshold for statistical significance (Appendix I, Figure I-1).

**Key Points for Low-THC to CBD Ratio**

- Two new trials enabled new meta-analyses of oral CBD alone versus placebo and combined THC plus CBD (low-THC to CBD ratio) versus placebo.
- Synthetic or plant-purified oral CBD alone was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale, MD 0.40, 95% CI −0.14 to 1.00, I²=20%) (SOE:
moderate), greater likelihood of pain response (4 RCTs, N=334, 37.0% vs. 44.4%, RR 0.84, 95% CI 0.62 to 1.10; I²=0%) (SOE: moderate), or improved function (3 RCTs, N=272, SMD 0.11, 95% CI −0.14 to 0.41, I²=0%) (SOE: moderate) versus placebo. CBD was not associated with increased likelihood of any adverse event (2 RCTs, N=205, 71.3% vs. 59.6%, RR 1.12, 95% CI 0.93 to 1.49, I²=0%) (SOE: moderate), dizziness (3 RCTs, N=206, 13.3% vs. 18.5%, RR 0.75, 95% CI 0.28 to 1.81, I²=12%) (SOE: low), or sedation (3 RCTs, N=206, 16.3% vs. 19.4%, RR 1.07, 95% CI 0.21 to 1.93, I²=34%) versus placebo (SOE: low).

- Combined oral plant-purified THC (dronabinol) and synthetic CBD in ~1:2 ratio was not associated with decreased pain intensity (2 RCTs, N=113, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I²=0%) (SOE: low), greater likelihood of experiencing ≥30% improvement in pain (2 RCTs, N=123, 55.2% vs. 50.8%, RR 1.07, 95% CI 0.73 to 1.57, I²=0%) (SOE: low), or improved function (1 RCT, N=60, SMD 0.29, 95% CI −0.21 to 0.80, I²=0%) (SOE: low) versus placebo, but estimates were imprecise. The low-THC to CBD ratio combination was associated with increased risk of nausea versus placebo (2 RCTs, N=123, 24.1% vs. 6.2%, RR 3.80, 95% CI 1.08 to 17.05, I²=0%) (SOE: moderate); combined low-THC to CBD was also associated with a non-statistically significant increase in risk of dizziness (2 RCTs, N=122, 35.1% vs. 23.1%, RR 1.74, 95% CI 0.47 to 3.46, I²=32%) (SOE: low) and sedation (2 RCTs, N=123, 43.1% vs. 29.2%, RR 1.55, 95% CI 0.86 to 2.72, I²=0%) (SOE: low).

**Summary of Findings for Low-THC to CBD Ratio**

Two new RCTs52,54 and four previously included RCTs74,76-78 evaluated short-term outcomes of low-THC to CBD ratio products versus placebo. Four RCTs52,54,74,77 evaluated oral products and two RCTs evaluated non-oral products.76,78 Regarding oral low-THC products, two RCTs (N=177), including one new RCT52 (also included in the high-THC section), evaluated synthetic oral CBD (median 45 or 50 mg/day) or the combination of plant-purified oral THC (dronabinol, median 17.3 or 15 mg/day) plus synthetic CBD (median 35 or 30 mg/day) in a ~1:2 ratio in patients with neuropathic pain (due to multiple sclerosis or spinal cord injury in the new RCT, and peripheral neuropathic pain in the prior RCT). A prior RCT (n=158) evaluated synthetic oral CBD as add-on to usual analgesic regimen (not specified) in patients with hand osteoarthritis or psoriatic arthritis77 and a new RCT (n=86) evaluated plant-purified oral CBD as add-on to acetaminophen in patients with knee osteoarthritis.54 Both RCTs of non-oral low-THC products were previously included. A small (n=15) RCT76 evaluated plant-extracted sublingual THC:CBD oil (1:6 ratio, median dose 15 mg THC:90 mg CBD) or a more purified version of the same product (≥97% pure CBD and THC) in patients with chronic pain undergoing hemodialysis and another small (n=29) RCT evaluated topical CBD cream (250 mg/3 oz) applied to symptomatic areas up to 4 times daily or placebo in patients with neuropathic pain.78 Across trials, the median age ranged from 52 to 68 and the proportion of patients female ranged from 13 to 74 percent. Two trials excluded patients currently undergoing opioid treatment,52,74 three trials allowed concomitant opioids or opioids as rescue medications,54,76,77 and one trial did not report either way.78 Two studies required that patients abstain from cannabis for at least 3 months in order to be eligible,52,76 three studies allowed previous use of cannabinoids,74,77,78 and one study did not report either way.54 The availability in the United States of the low-THC products used in the RCTs is unknown.
Among the RCTs that evaluated oral products, two were rated low risk of bias and two were rated moderate risk of bias. Both RCTs of non-oral products were rated high risk of bias. Methodological limitations in the high and moderate risk of bias RCTs included unclear randomization and allocation concealment methods, high or differential attrition, and unclear blinding of outcome assessors. In addition, a high-risk of bias crossover RCT of sublingual CBD did not report outcomes for the initial (prior to crossover) period. A high risk of bias RCT of topical CBD oil did not report all planned analysis, did not pre-register its protocol, and raised important ethical concerns, as the study authors reported that they were unable to obtain institutional review board approval yet still carried out the trial. Study details and results can be found in Appendix E, Tables E-1 to E-4, and risk of bias assessments are shown in Appendix F, Table F-1.

**Placebo-Controlled Trials of Synthetic or Plant-purified Oral Low-THC Products**

The addition of two new RCTs of synthetic or plant-purified oral CBD enabled a new meta-analysis for this update. We analyzed trials of CBD alone separately from trials of combined THC plus CBD (ratio ~1:2).

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

The combination of plant-derived, synthetic equivalent THC (dronabinol) and synthetic CBD (~1:2 ratio) was also not associated decreased pain intensity (2 RCTs, N=113, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I^2=0%; Figure 5), greater likelihood of experiencing ≥30% improvement in pain (2 RCTs, N=123, 55.2% vs. 50.8%, RR 1.07, 95% CI 0.73 to 1.57, I^2=0%; Appendix D, Figure D-28), or improved function (1 RCT, n=60, SMD 0.29, 95% CI −0.21 to 0.80, I^2=0%; Appendix D, Figure D-29). However, estimates were based on only one or two RCTs each and were imprecise. Estimates for SAEs (Appendix D, Figure D-24) and WAEs (Appendix D, Figure D-20) were extremely imprecise. The combined low-THC to CBD ratio intervention was associated with increased risk of nausea versus placebo (2 RCTs, N=123, 24.1% vs. 6.2%, RR 3.80, 95% CI 1.08 to 17.05, I^2=0%; Appendix D, Figure D-26); low-THC:CBD was also associated with a non-statistically significant increase in risk of dizziness (2 RCTs, N=122, 35.1% vs. 23.1%, RR 1.74, 95% CI 0.47 to 3.46, I^2=32%; Appendix D, Figure D-
Evidence on secondary outcomes was limited. One new RCT (n=86) found no difference between plant-purified CBD versus placebo in SF-36 physical (0 to 100 scale, MD 0.65, 95% CI −3.6 to 4.9) or mental (0 to 100 scale, MD 1.85, 95% CI −1.2 to 4.9) component summary scores. One previously included RCT (n=87) found no difference between either synthetic CBD alone or the combination of plant-purified THC plus CBD versus placebo in mood or quality of life. CBD alone, but not the combination, was associated with improved sleep versus placebo (0 to 10 scale; CBD: MD 2.03, 95% CI 0.35 to 3.71; THC/CBD: MD 0.89, 95% CI −0.64 to 2.42). Another previously included RCT (n=129) found no differences between synthetic CBD versus placebo in sleep quality, depression or anxiety.

Placebo-Controlled Trials of Plant-extracted Low-THC Products

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

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

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

Summary of Findings for Other or Mixed Cannabinoids

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

Another new cohort study (n=296 for primary analysis) compared outcomes of various oral and inhaled cannabis products (ranging from low- to high-THC to CBD ratio) in an Australian cohort of patients with various types of chronic pain. Although outcomes for pain intensity, pain interference, and physical function were somewhat better in the comparable THC to CBD and low THC to CBD ratio groups compared to the high THC to CBD ratio group, the study was
rated high risk of bias due to serious methodological limitations, including failure to control for confounders (Appendix F, Table F-2).

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

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

**Key Point for Whole-Plant Cannabis and Mixed (Patient-Choice) Cannabis Products**

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

**Summary of Findings for Whole-Plant Cannabis and Mixed (Patient-Choice) Cannabis Products**

No new studies evaluated whole-plant cannabis or mixed (patient-choice) cannabis products. Six previously included observational studies (N=12,939) reported on the effects of cannabis, with five (3 high, 2 moderate risk of bias) studies evaluating medical cannabis programs, or self-reported use of cannabis, and one moderate risk of bias study evaluating a specific whole-plant cannabis product. Patient characteristics are summarized across studies in Table 5. The type of pain was not well reported. Mean age was 53 years, and 55 percent were female. Baseline pain was 5.35 (95% CI 4.56 to 8.00) on a 0 to 10 scale. One study evaluated outcomes at 3 months (short duration), and the other five were long duration (1 to 4 years).
The three studies of medical cannabis programs allowed patients to self-select the cannabis products they used and compared them with patients who chose not to enroll in the programs (assumed to be no cannabis use). Two of the studies are retrospective analyses of larger prospective cohort studies of patients with chronic pain taking opioids, based on patient self-report of cannabis use, but specific products used were not reported. In the study of a whole-plant cannabis product, the cannabis group received herbal cannabis containing 12.5 percent (+/- 1.5%) THC. Total daily doses received were reported in two studies with one reporting 93 mg of THC per week (mean) in a medical cannabis program, and the other reporting 2.5 grams per day of a whole-pant cannabis product (dose confirmed with study authors).

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

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

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

In a moderate risk of bias study (n=1,514 at baseline, 1,217 at year 4) of persons with chronic pain using opioids, a statistically nonsignificant difference in OME use at 1 year was found between patients reporting daily or near daily cannabis use (type and dose reported) and those reporting no use. The analysis used a lagged mixed-effects linear regression model, identifying cannabis use in the prior year and opioid use in the current year across four possible years of
study enrollment. The adjusted mean daily OMEs were 97.1 in frequent cannabis users and 85.5 in non-users (difference 32.76 mg/day, 95% CI, −25.04 to 90.57).

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

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

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

Key Point

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

Summary of Findings

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

Findings in Relation to the Decisional Dilemma(s)

The key decisional dilemmas for treating chronic and subacute pain with plant-based compounds include their effectiveness and safety and the effect of route of administration, formulation, dose or potency of products, types of pain, and other patient characteristics on outcomes, including harms. Important harms include typical adverse effects such as dizziness, sedation and nausea, but may also include more serious risks, such as cannabis use disorder (CUD), psychosis, and cognitive impairment. Potential benefits and harms must be considered in the context of frequent, possibly daily, long-term use. This update did not identify studies of plant-based compounds other than cannabis. Four new studies were added for this update (1 placebo-controlled randomized controlled trial [RCT] of oral plant-purified THC [dronabinol], synthetic CBD, and combined THC/CBD [low-THC to CBD ratio],52 1 placebo-controlled RCT of plant-purified oral CBD,54 1 observational study on the association between use of various cannabinoid products [not specified as synthetic or plant-derived] versus non-use and risk of cardiovascular events,55 and 1 observational study comparing different types of cannabis [not specified as synthetic or plant-derived]).82 For synthetic or plant-purified high-THC to CBD products, updated pooled estimates that included one new RCT resulted in findings versus placebo that were similar to the prior update, including small effect on pain intensity, no effect on function or disability, and insufficient evidence for pain response, due to highly inconsistent results (Table 6). Additional RCTs of low-THC to CBD products enabled new meta-analyses which did not find synthetic oral CBD alone or combined oral plant-purified THC plus synthetic CBD (ratio ~1:2) to be associated with improved pain intensity, improved function, or likelihood of pain response versus placebo, although there was imprecision in estimates.

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

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

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

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

New meta-analyses for low-THC to CBD ratio products that included two new trials found that neither oral synthetic or plant-purified CBD alone nor oral plant-purified THC (dronabinol) in combination with CBD (ratio ~1:2) was associated with decreased pain intensity, greater likelihood of pain response, or improved function versus placebo (SOE: moderate for oral CBD alone, low for combined THC/CBD). THC/CBD, but not CBD, was associated with increased risk of nausea (SOE: moderate), dizziness (SOE: low), and sedation (SOE: low).

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

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

The 2022 updated Centers for Disease Control and Prevention guideline on opioids for pain does not make recommendations on cannabis for pain. However, the 2019 U.K. National Institute for Health Care and Excellence clinical practice guideline included a strong recommendations against use of cannabis for pain outside of clinical trials, though the guideline has been challenged as overly restrictive. More recently, an international guideline funded by a cannabis research center issued a weak recommendation for use of non-inhaled medical cannabis for chronic pain when standard care is not sufficient. Additionally, there have been multiple systematic reviews conducted on the use of cannabinoids to treat chronic pain, including a 2015 publication in the Journal of the American Medical Association, a 2018 Cochrane review, and a 2017 Veteran’s Affairs Evidence Synthesis Program review. These high-quality reviews found generally similar results as this review indicating some benefit in pain outcomes, primarily for short-term treatment in patients with neuropathic pain. However, the prior reviews combined all forms of cannabinoids in meta-analyses. Our review has more stratified results based on pre-specified THC to CBD ratio categories, leading to a higher strength of evidence rating in some cases. In addition, some higher-quality are not current and may be missing newer evidence.
Four other systematic reviews examining utility of cannabis for chronic pain were published in 2020; overall, these findings are also consistent with our findings.96-99 One of the reviews conducted meta-regression, finding that the impact on pain was similar between neuropathic and non-neuropathic pain populations98 and that pain reduction was of a small magnitude and similar across formulations (inhaled, oral, oromucosal spray).

Our review did not identify eligible evidence on kratom to treat chronic pain. Two recent reviews of kratom provided limited information, and are based on noncomparative data or pharmacological data. One evaluated surveys, cross-sectional studies, and poison-control center studies on the use of kratom; the other is a nonsystematic review covering pharmacology, pharmacokinetics, prevalence and type of usage, and harms evidence.25,26 Both found that patients report using kratom as a substitute for opioids apparently as a treatment for self-diagnosed opioid addiction or dependence in Thailand and Malaysia. They reported growing use in the United States for chronic pain and for recreational purposes. They also suggested that kratom may have addictive properties itself with symptoms of physiological withdrawal being common. Nonserious adverse effects include hyperpigmentation of the skin, constipation, weight loss, insomnia, xerostomia, and loss of libido. Poison control center data indicated an increase in calls involving kratom over the past 5 years with multi-substance exposures involving kratom associated with a statistically significant increase in a serious medical event. In cases where kratom was the only substance involved (N=1,174), symptoms included agitation or irritability (23%), tachycardia (21%), nausea (15%), drowsiness/lethargy (14%), vomiting (13.2%), confusion (11%), hypertension (10%), and seizures (10%).26

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

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

<table>
<thead>
<tr>
<th>Product, THC to CBD Ratio</th>
<th>Pain Responsea 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 - Plant-extracted, Oromucosal Spray</td>
<td>Potential effect (4)b [✓]</td>
<td>Small effect (7) [✓✓]</td>
<td>Small effect (6) [✓✓]</td>
</tr>
<tr>
<td>High THC – Synthetic or Plant-purified, Oral</td>
<td>Insufficient (3, 1 new)</td>
<td>Small effect (8, 1 new) [✓]</td>
<td>No effect (3) [✓]</td>
</tr>
<tr>
<td>High THC – Plant-extracted, Oral</td>
<td>No evidence</td>
<td>Insufficient (2)</td>
<td>Insufficient (1)</td>
</tr>
<tr>
<td>Low THC – Plant-extracted CBD, Topical</td>
<td>No evidence</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
<tr>
<td>Low THC – Synthetic or Plant-purified, Oralc</td>
<td>No effect (4, 2 new)c [✓✓]</td>
<td>No effect (4, 2 new)c [✓✓]</td>
<td>No effect (3, 1 new)c [✓✓]</td>
</tr>
<tr>
<td>Low THC – Synthetic CBD Plus Plant-purified THC, Oralc</td>
<td>No effect (2, 1 new)c [✓✓]</td>
<td>No effect (2, 1 new)c [✓✓]</td>
<td>Insufficient (1) [✓]</td>
</tr>
<tr>
<td>Low THC – Sublingual CBD/THC, Plant-extracted</td>
<td>No evidence</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
<tr>
<td>Other Cannabinoids – CBDV, Oral</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
<tr>
<td>Whole-Plant Cannabis (12% THC)d</td>
<td>No evidence</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

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

a ≥30% improvement from baseline
b Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.

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

Low THC – Synthetic or Plant-purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.

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

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

Comparison was “usual care.”

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

 dared

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

### Table 7. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Comparable THC/CBD – Plant-extracted, Oromucosal Spray</td>
<td>No effect (5) ([\checkmark])</td>
<td>No effect (3) ([\checkmark])</td>
<td>Large effect (6) ([\checkmark])</td>
<td>Moderate effect (6) ([\checkmark])</td>
<td>Large effect (6) ([\checkmark])</td>
</tr>
<tr>
<td>High THC – Synthetic or Plant-purified, Oral</td>
<td>Moderate effect ([6, 1 \text{ new}]) ([\checkmark\checkmark])</td>
<td>Insufficient (2, 1 new) ([\checkmark])</td>
<td>Large effect (4, 1 new) ([\checkmark\checkmark])</td>
<td>Large effect ([4, 1 \text{ new}]) ([\checkmark\checkmark])</td>
<td>Moderate effect (5, 1 new) ([\checkmark\checkmark])</td>
</tr>
<tr>
<td>High THC – Plant-extracted, Oral</td>
<td>Large effect (1) ([\checkmark])</td>
<td>Insufficient (1) ([\checkmark])</td>
<td>Large effect (1) ([\checkmark])</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Low THC – Plant-extracted CBD, Topical</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Low THC – Synthetic or Plant-purified CBD, Oral</td>
<td>Insufficient (4, 2 new) ([\checkmark])</td>
<td>Insufficient (2, 1 new) ([\checkmark])</td>
<td>No effect (3, 2 new) ([\checkmark])</td>
<td>Insufficient (2 new) ([\checkmark])</td>
<td>No effect (3, 2 new) ([\checkmark])</td>
</tr>
<tr>
<td>Low THC – Synthetic CBD plus Plant-purified THC, Oral</td>
<td>Insufficient (2, 1 new) ([\checkmark])</td>
<td>Insufficient (2, 1 new) ([\checkmark])</td>
<td>Potential effect (2, 1 new) ([\checkmark\checkmark])</td>
<td>Large effect (2, 1 new) ([\checkmark\checkmark])</td>
<td>No effect (2, 1 new) ([\checkmark])</td>
</tr>
<tr>
<td>Low THC – Sublingual CBD/THC, Plant-extracted</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Other Cannabinoids – CBDV, Oral</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Whole-Plant Cannabis (12% THC)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
<td>Insufficient (1)</td>
</tr>
</tbody>
</table>

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

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

Low THC – Synthetic or Plant-purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.

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

Low THC – Synthetic CBD plus Plant-purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.

Comparison was “usual care.”

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

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

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

Another limitation is the lack of consistent nomenclature and details regarding the interventions and products studied. For example, products are described as plant-derived in some studies, but without a consistent way of describing the process or the resulting purity of the products. Other studies used words such as “standardized” to describe the amount of THC in a whole-plant cannabis product, again with lack of description of how this was defined or determined. Studies that evaluated products that contained THC and CBD did not consistently report the ratio of THC to CBD, other than for Sativex oromucosal spray (close to a 1 to 1 ratio). One trial that evaluated a topical product did not describe details regarding extraction methods or product purity, and it was unclear if the product was intended to provide local or systemic effects.78 When necessary, we attempted to obtain additional details regarding products from study authors, not all authors responded to queries. Although we attempted to categorize products accurately, some misclassification is possible. Other limitations include the complete lack of evidence on other plant-based compounds such as kratom, no RCT evidence on whole-plant cannabis products, and only a single, small study each for topical or sublingual CBD or cannabinoids other than THC or CBD.

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

Trials were limited by study design and small sample sizes (range 5 to 339; mean 88), particularly for assessing harms. The SOE of the findings was very commonly downgraded due to imprecise estimates (see Appendix G). There were also differences in some key baseline
characteristics, including baseline pain scores, which were frequently not adjusted for in study analyses. Another methodologic concern is that many conclusions in the included studies were drawn from post-hoc analyses. Study durations of included RCTs were primarily short-term and included less than 6 months followup (1 RCT reported intermediate followup durations of 47 weeks); 40 percent of trials were 4 to 6 weeks long. This is a key limitation, as pain severity in patients with chronic pain may vary substantially in the short-term and may be influenced temporarily by an intervention or treatment; it is most useful to understand the enduring impact of a treatment on pain severity. Similarly, adverse events such as CUD, cognitive deficits, and SAEs may take time to develop and longer studies are required to capture such events. Two RCTs\textsuperscript{57,71} utilized an enriched enrollment randomized withdrawal design in which all patients receive cannabis in a run-in phase; only patients who respond to cannabis and tolerate it are randomized, to continuation or withdrawal. Such trials are intentionally designed to select for patients who respond to and tolerate cannabis, potentially exaggerating treatment effects and underestimating harms compared to patients not selected based on these features.\textsuperscript{100,101} However, our findings were similar when the enriched enrollment randomized withdrawal trials were excluded from analyses. Well-designed head to head studies comparing a plant-based product with a standard of care treatment for chronic pain are lacking. The current evidence consists only of small, poorly designed, crossover or observational studies.

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

There are also some limitations to our review process. We excluded non-English language publications and study results published only as abstracts. For almost all analyses, there were too few trials to apply graphical or statistical methods to detect small sample effects,\textsuperscript{102} a potential marker of publication bias. Although there were sufficient trials when combining synthetic or plant-purified and plant-extracted high-THC to CBD ratio products versus placebo to apply such methods, which indicated potential small sample effects, results are difficult to interpret because a statistical test for small sample effects was above the threshold for statistical significance, and there was potential heterogeneity introduced by combining synthetic and plant-extracted products. We did not identify unpublished trials of high-THC to CBD products; one unpublished trial\textsuperscript{103} of patients with diabetic neuropathy (n=294) found no difference between nabiximols (comparable THC to CBD ratio oromucosal spray) for diabetic neuropathy (0 to 10 scale, mean difference -0.12, 95\% CI -0.60 to 0.36), suggesting that additional unpublished trials could attenuate estimates of effect. Another potential limitation is that we categorized nabilone as a
synthetic high-THC product, although it may be more accurately described as a synthetic cannabinoid – a chemical analog to THC, which could have differing effects than THC/dronabinol. To address this possibility, we performed stratified analyses among outcomes that were pooled for synthetic high-THC interventions. The effect size for change in pain severity was larger with nabilone than with dronabinol, but the difference between the effect sizes was not statistically significant. We also grouped plant-purified THC (dronabinol) or CBD with synthetic dronabinol and CBD, because they are chemically identical to the synthetic product. As noted above, when synthetic THC was analyzed separately from plant-purified THC, benefits were present with synthetic THC but not with plant-purified THC. However, results should be interpreted with caution because they are not based on head-to-head comparisons, and there were potential sources of heterogeneity that could invalidate indirect comparisons. For example, all trials of plant-purified THC evaluated dronabinol, but almost all trials of synthetic THC evaluated nabilone. Meta-analyses were based on relatively small numbers of trials (less than 20), which can result in overly narrow estimates using standard random effects approaches, including the profile likelihood model. Therefore, we conducted sensitivity analyses using the Bartlett’s correction. Although the Bartlett’s correction resulted in wider CIs for pooled estimates, it did not change overall conclusions regarding the statistical significance of findings. The exception was high-THC products and increased risk of sedation, which was imprecise and no longer statistically significant using the Bartlett’s correction. We did not apply the Bartlett’s correction when there were fewer than five studies, because it may result in overly conservative (wide) CIs in this situation. Meta-analyses based on fewer than five studies should be interpreted with caution, as CIs based on the profile likelihood method may be overly precise. Our inclusion criteria required that the study population have chronic or subacute pain, or have subgroup analyses for this group, which may be why we did not find evidence related to kratom. As in other recent systematic reviews of interventions to treat chronic pain, we grouped the magnitude of effects into small, moderate and large effects, rather than according to published minimal clinically important difference (MCID) thresholds. Defining clinical significance in chronic pain is difficult because it is subjective and difficult to correlate with real-life experiences of patients. For example, the MCID for improvement in pain is 15 points on a 0 to 100 scale. However, interventions commonly used for chronic pain, including opioids and nonsteroidal anti-inflammatory drugs do not achieve this level of reduction. The typical reduction with opioids, nonopioid medications, nonpharmacological interventions, and cannabinoids is small, 5 to 10 points and may be considered a clinically important effect by patients and clinicians. In addition, when the pooled estimate is close to a pre-defined effect size threshold, a relatively small change in pooled estimates can result in re-categorization. In this update, for synthetic high-THC to CBD ratio products versus placebo, the effect size for pain intensity was re-classified from moderate to small, based on the addition of one new trial that decreased the pooled estimate from -1.10 to -0.95, which could suggest a more substantial change in the estimate than actually observed. On the other hand, using pre-defined thresholds provides consistency in classifying effect size. With more evidence, pooled estimates should become more stable and less likely to require re-categorization. Since this is a living systematic review, new evidence will be incorporated into the review and findings updated on a regular basis.
Applicability

A number of factors could impact the applicability of our findings. The evidence currently is most applicable to patients with neuropathic pain with mostly moderate to severe pain (mean baseline score in RCTs was 6.6 on a 0 to 10 scale, with a range of 4.0 to 8.67). There is also considerable variability within the included studies among the types of neuropathic pain patients experience, and treatment effects might be different depending on the specific neuropathic pain condition. As described above, two RCTs\textsuperscript{57,71} utilized an enriched enrollment randomized trial design, which is purposefully designed to selectively randomized patients who respond to cannabis and tolerate it.

The evidence applies to adults with chronic pain. The evidence base addressed similar proportion of men and women, with around 58 percent of enrolled participants across all studies being female. While the age range across studies was broad, with mean study ranges of 45 to 68 years, the evidence is mainly applicable to middle-aged patients (overall mean age 54 years). Therefore, the applicability of findings to older patients, in whom the balance of benefits to harms may be very different, with potentially more harms, is uncertain. No study evaluated adolescents and no study enrolled persons with subacute pain. Non-White persons were not well-represented in the studies. It is also unclear how the evidence applies to patients currently taking prescription opioids to treat chronic pain or patients with serious mental illness or other comorbidities who are often excluded from trials. In terms of interventions, this evidence is most applicable to plant-extracted comparable THC to CBD ratio oromucosal spray, high-THC (THC or THC analogue only) synthetic and plant-purified (dronabinol) oral products, and low-THC (CBD only) synthetic oral products. The evidence for comparable THC to CBD oral spray is applicable to mean dosing of 8.4 sprays per day (23 mg THC/21 mg CBD). The evidence for high-THC to CBD ratio synthetic and plant-derived, synthetic equivalent products applies to dosing that was titrated upward, with a maximum dose of 13 to 25 mg per day of dronabinol and 0.25 to 4 mg per day of nabilone (mean doses not reported). For plant-extracted high-THC to CBD products, the evidence was too heterogeneous and limited (2 RCTs) to describe a generally applicable dose. For low-THC to CBD products, findings are most applicable to oral synthetic CBD at a dose of up to 20 to 50 mg/day and combined oral plant-purified THC and synthetic CBD (synthetic) at a dose of 22.5 to 25 mg THC and 45 to 50 mg CBD daily. The applicability of evidence to other products including topical or sublingual low-THC to CBD ratio products and whole plant cannabis is very low or non-existent.

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

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

Only 14 percent of studies were conducted in the United States, with the majority being from Europe (57%). We were unable to assess the impact of country of study or other geographic location characteristics (e.g., rural, metropolitan) on the applicability of specific results.

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

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

The implications of the present findings for clinical practice and policy are mixed. Our results suggest that select individuals with chronic neuropathic pain may experience small short-term improvements in pain when using high-THC to CBD cannabis products (synthetic or plant-derived, synthetic equivalent THC). The impact of this intervention on moderate or long-term outcomes is unknown. Plant-extracted cannabis products with a comparable THC to CBD ratio may also result in small improvements in pain severity. On the other hand, cannabis products with a low-THC to CBD ratio (oral synthetic or plant-purified CBD alone or combined plant-purified THC and synthetic CBD in a ratio of ~1:2) may not result in improvements in pain or function. Those who take products containing comparable or high ratios of THC or combined THC plus CBD in a ~1:2 ratio are also at increased risk for adverse events, including dizziness, sedation and nausea. The expected benefit of cannabis products compared to placebo appears comparable to those observed with prescription opioids, several nonopioid medications, and nonpharmacological interventions.\textsuperscript{11,13,14} However, comparing effects of different interventions based on cross-trial comparisons must be done with extreme caution, due to potential differences across studies in the populations studied, interventions evaluated, and outcomes assessed; head-to-head trials are needed to understand the comparative effectiveness of cannabis products versus other interventions. The evidence on adverse events with cannabis-related products is much less robust than the evidence on similar outcomes with opioids or nonopioid medications. The risk of sedation and dizziness appears similar with cannabis-related products, opioids, and the anticonvulsants pregabalin and gabapentin, while the risk for nausea may be larger with opioids and the antidepressant duloxetine than with cannabis-related products. However, these comparisons are qualitative and indirect and based on limited evidence on cannabis products relative to the other drugs and require confirmation. Evidence is too limited to compare effects on serious and long-term harms, even indirectly, though respiratory depressant effects of opioids potentially resulting in death are well-known. Understanding how cannabis products’ adverse event profiles compare with other available treatments for chronic pain, particularly opioid and non-opioid medications, is essential to determine the benefit to harm ratio. At this time, the strength of this evidence is mostly low, and more data are needed to confidently recommend this as a treatment for various chronic pain-related conditions or for patients with diverse demographic or clinical characteristics. No studies are available to inform decisions regarding use of cannabis for subacute pain or in adolescents.

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

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

**Implications for Future Research**

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

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

<table>
<thead>
<tr>
<th>PICOTS Element</th>
<th>Gap in Evidence</th>
<th>Suggested Future Research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Populations</strong></td>
<td></td>
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<tr>
<td>Patients</td>
<td></td>
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<tr>
<td>Non-White</td>
<td></td>
<td>- Studies to specifically recruit non-White participants to ensure appropriate representation and diversity in studied populations</td>
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<tr>
<td>populations, older adults</td>
<td></td>
<td>- Stratified analyses according to sex, including effects in pregnant and lactating persons</td>
</tr>
<tr>
<td>Pain conditions other than neuropathic pain</td>
<td></td>
<td>- Studies of persons with subacute pain</td>
</tr>
<tr>
<td>Subacute pain</td>
<td></td>
<td>- Studies of adolescents</td>
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<tr>
<td>Adolescents</td>
<td></td>
<td>- Studies to assess effects based on age differences</td>
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<tr>
<td></td>
<td></td>
<td>- Pain populations expanded to include persons with non-neuropathic chronic pain, specifically back pain, other musculoskeletal pain, and fibromyalgia</td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
<td></td>
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<tr>
<td>Plant-extracted high THC to CBD ratio</td>
<td></td>
<td>- Studies of plant-extracted high-THC to CBD ratio products, with clear description of extraction or purification process and consistent nomenclature regarding the final product</td>
</tr>
<tr>
<td>Comparable THC to CBD ratio formulations other than plant-extracted oromucosal spray</td>
<td></td>
<td>- Studies of plant-extracted low-THC to CBD ratio products, with clear description or extraction or purification processes and consistent nomenclature regarding the final product</td>
</tr>
<tr>
<td>Plant-extracted and non-oral low-THC to CBD ratio products, whole-plant cannabis, and other cannabinoids</td>
<td></td>
<td>- Studies to compare different routes of administration (e.g., oromucosal spray, oral oil, oral capsule, smoked, etc.)</td>
</tr>
<tr>
<td>Kratom</td>
<td></td>
<td>- Studies should include and compare standardized treatment plans</td>
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<tr>
<td></td>
<td></td>
<td>- Head-to-head studies on effects of different cannabinoids, including cannabinoids within a THC to CBD ratio category (e.g., synthetic vs. plant-purified THC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Studies to assess kratom and/or other plant-based treatments</td>
</tr>
<tr>
<td>Comparators</td>
<td></td>
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<tr>
<td>Head-to-head comparisons</td>
<td></td>
<td>- Studies comparing plant-based interventions with other plant-based treatments (including head-to-head comparisons of different cannabis-related products), opioids, non-opioid medications, or nonpharmacological interventions to evaluate active-control comparisons to provide direct evidence on comparative effectiveness</td>
</tr>
</tbody>
</table>
### Outcomes

- **Pain response**
  - (≥30% improvement in pain severity)
- **Overall function, quality of life**
- **Depression, anxiety, sleep, opioid use**
- **Adverse event outcomes**

**Suggested Future Research**
- Outcomes should be consistently defined and reported across studies; ideally utilizing core outcome sets developed for studies of treatments for chronic pain.
- Future studies should include pain response, measures of overall function, and adverse events (overall, serious, and withdrawals due to adverse events at a minimum), in addition to changes in pain severity.
- Patient-centered and patient-reported outcomes (e.g., quality of life, depression, anxiety, and sleep) should be measured using validated tools for diagnosis and measurement of change.
- In addition to reporting on opioid use prior to study enrollment, future studies should report on use of opioids, and other pain medications, during the trial. In particular, there is a need for more information on possible opioid sparing effects of plant-based treatments.
- Studies need to assess serious harms such as development of cannabis use disorder, psychosis, and cognitive deficits. Other adverse events (e.g. sexual dysfunction) may need to be studied as new data emerge.

### Timing

- **Limited evidence on studies >6 weeks in duration**

**Suggested Future Research**
- Considering the chronic nature of the conditions, studies should provide followup assessments at longer timepoints, e.g., ≥3, 6 or 12 months.

### Study Design

- **RCTs and cohort studies with adequate sample sizes to evaluate all important outcomes**
- **Cohort studies with adequate control for confounding, ascertainment of exposures and outcomes**
- **RCT and cohort studies with low risk of bias**

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

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

### Conclusions

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


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


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>BPI-SF</td>
<td>Brief Pain Inventory – Short Form</td>
</tr>
<tr>
<td>CBC</td>
<td>cannabichromene</td>
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<tr>
<td>CBD</td>
<td>cannabidiol</td>
</tr>
<tr>
<td>CBDV</td>
<td>cannabidivarin</td>
</tr>
<tr>
<td>CBG</td>
<td>cannabigerol</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CUD</td>
<td>cannabis use disorder</td>
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<tr>
<td>DAS28</td>
<td>28-Joint Disease Activity Scale</td>
</tr>
<tr>
<td>EPC</td>
<td>Evidence-based Practice Center</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>FIQ</td>
<td>Fibromyalgia Impact Questionnaire</td>
</tr>
<tr>
<td>FM</td>
<td>fibromyalgia</td>
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<tr>
<td>GHQ-12</td>
<td>Short General Health Questionnaire</td>
</tr>
<tr>
<td>GNDS</td>
<td>Guy’s Neurological Disability Scale</td>
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<tr>
<td>HADS-D</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>IA</td>
<td>inflammatory arthritis</td>
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<tr>
<td>KQ</td>
<td>Key Question</td>
</tr>
<tr>
<td>LAO</td>
<td>long acting opioid</td>
</tr>
<tr>
<td>MCID</td>
<td>minimal clinically important difference</td>
</tr>
<tr>
<td>MCP</td>
<td>New Mexico Medical Cannabis Program</td>
</tr>
<tr>
<td>MD</td>
<td>mean difference</td>
</tr>
<tr>
<td>MME</td>
<td>morphine milligram equivalents</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
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<td>NA</td>
<td>not applicable</td>
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<tr>
<td>NPP</td>
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<tr>
<td>NR</td>
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<tr>
<td>NRS</td>
<td>numerical rating scale</td>
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<tr>
<td>ODI</td>
<td>Oswestry Disability Index</td>
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<tr>
<td>OME</td>
<td>oral morphine equivalent</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PBC</td>
<td>plant-based compound</td>
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<td>PDI</td>
<td>Pain Disability Index</td>
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<tr>
<td>PICOTS</td>
<td>populations, interventions, comparators, outcomes, timing, and settings</td>
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<tr>
<td>PL</td>
<td>profile likelihood</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<td>RDQ</td>
<td>Roland-Morris Disability Questionnaire</td>
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<td>ROB</td>
<td>risk of bias</td>
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<td>RR</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<td>SEADS</td>
<td>Supplemental Evidence and Data for Systematic review</td>
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<tr>
<td>SF-36</td>
<td>Short Form-36</td>
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<td>SMD</td>
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<td>SOE</td>
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<tr>
<td>THC</td>
<td>tetrahydrocannabinol</td>
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<td>TOO</td>
<td>Task Order Officer</td>
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<td>VAS</td>
<td>visual analogue scale</td>
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<td>VP</td>
<td>visceral pain</td>
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<tr>
<td>WAE</td>
<td>withdrawal due to adverse events</td>
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<tr>
<td>WP</td>
<td>whole plant</td>
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