Comparative Effectiveness Review
Number 250

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2023 Update

Executive Summary

Main Points

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, and low-THC to CBD (including CBD only). Since the first annual update of the systematic review published in September 2022, two new placebo-controlled randomized controlled trials (RCTs), one of oral THC, CBD, and combination THC/CBD[1] and one of two low THC to CBD ratio products versus placebo,[2] and two new observational studies, one of plant-based comparable THC to CBD versus long-acting opioids and one on inhaled dry flower, sublingual cannabis oils, or both,[3,4] were added, for a total of 23 RCTs and 10 observational studies. In patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months):

- Comparable plant-extracted THC to CBD ratio oral spray is probably associated with small improvements in pain severity and overall function versus placebo. There may be no increase in risk of serious adverse events (strength of evidence [SOE]: low) or withdrawal due to adverse events. There may be a large increased risk of dizziness and sedation and a moderate increased risk of nausea.
- Synthetic THC (high-THC to CBD) may be associated with small improvement in pain severity, but with increased risk of sedation, and potential increased risk of nausea versus placebo. Synthetic THC is probably associated with a large increased risk of dizziness.
- 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.

Agency for Healthcare Research and Quality

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,[5,6] 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.[7] For this 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 April 23, 2023. The original review focused on adults with chronic pain.[8] With input from a Technical Expert Panel, the scope for this update was expanded to include adolescents and subacute pain. We included randomized controlled trials 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."[9,10]

Table A. Definitions of effect sizes

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

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

Results

The included RCTs are described in Table B and the included observational studies are described in Table C. There were a total of four new studies since the prior annual update. One new RCT (n=115) compared synthetic high-THC to CBD ratio and low-THC to CBD ratio cannabis products versus placebo for neuropathic pain[1] and another new RCT (n=15) evaluated two extracted low THC to CBD ratio products versus placebo.[2] One new observational study (n=1,310) compared an extracted comparable THC to CBD ratio product versus long-acting opioids for neuropathic back pain,[4] and another new observational study compared various extracted cannabinoid products (comparable to low THC to CBD ratio) in patients with chronic pain (mixed conditions).[3] The addition of one new RCT[1] slightly reduced the pooled effect size for improvement in pain intensity with synthetic high-THC to CBD ratio products versus placebo, crossing the threshold from moderate (prior pooled estimate -1.15 on a 0 to 10 scale, 95% confidence interval [CI] -1.99 to -0.54) to small (updated pooled estimate -0.95, 95% CI -1.81 to -0.25) and changed the SOE for pain response from low to insufficient, due to inconsistent results from two RCTs (Tables D and E). Otherwise, the new studies did not change main findings.

Table B. Characteristics of included randomized controlled trials of cannabinoids

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
THC to CBD Ratio	Comparable[a]	High	High	Low	NA - other cannabinoids
Source	Plant-extracted	Plant-extracted	Synthetic Nabilone Dronabinol Dronabinol/Namisol®[b]	Plant-extracted (2)[c] Synthetic (1) Unclear (1)	Plant-extracted
N Studies	7	2	10	4[d] (1 topical, 1 sublingual, 2 oral)	1
Comparator (Study Count)	Placebo (7)	Placebo (2)	Placebo (7); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low-THC to CBD ratio (CBD or Dronabinol/CBD[e]) (1)	Placebo (4); Dronabinol[e] (1); Dronabinol/CBD[e] (1); ≥97% purified low-THC to CBD (1:6) sublingual oil (1)	Placebo

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Route of Administration, Formulation **(Study Count)**	Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl	Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1) Oral capsule, 2.5 mg THC/0.8 – 1.8 mg CBD extract (1)	Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Dronabinol 2.5 mg oral capsule (2); Dronabinol 5 mg oral capsule (1); Namisol®[a] 3 mg oral tablet (1)	Topical oil, 83 mg CBD/fluid ounce (1), Oral tablet, 10 mg CBD (1) Oral capsule, 5 mg CBD (1) Oral capsule, 5 mg CBD/2.5 mg dronabinol (1)[e] Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1)	Oral oil, 50 mg/ml CBDV

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Dosing Regimen	Final mean dose 23 mg THC/21 mg CBD daily.	Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily. Capsule: 2.5 - 12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily	Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Dronabinol capsules: 2.5 -15 mg once or twice daily, titrated. Final dose range 15 - 25 mg/day Namisol®[a] tablet: 3 - 8 mg 3 times daily, titrated. Final dose NR.	Topical oil: applied locally 1-4 times/day (volume/dose, final dose NR). Oral tablet: 10 mg daily, titrated (max 3 times daily) Final dose NR. Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 50 mg CBD daily. Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 15 mg THC/30 mg CBD daily. Sublingual oil, titrated to max daily dose of 6 drops 3 times daily (15 mg THC/90 mg CBD)	400 mg CBDV daily. Final dose NR.
Risk of Bias	29% high, 57% moderate, 14% low	50% moderate, 50% low	20% high, 40% moderate, 40% low	50% high, 25% moderate, 25% low	100% moderate
Total Randomized	882	297	592	267	34
Age, Mean Years	53	52	53	65	50

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Female, %	66%	89%	61%	40%	3%
Non-White,[f] %	1.6% (2)	1% (1)	5.4% (3)	NR	NR
Primary Pain Type (Study Count)	NPP (6); Inflammatory arthritis (1)	NPP (1); Fibromyalgia (1)	NPP (7); Fibromyalgia (1); Headache (1); Visceral pain (1)	NPP (2); OA (1); Unspecified (1)	NPP (1)
Baseline Pain Score, Mean (Range)[g]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.48 (4 to 8.1)[h]	5.87 (4.67 to 7.4)[i]	6.28 (6.12 to 6.44)
Study Duration	4 to 15 weeks	8 to 12 weeks	4 to 47 weeks	4 to 16 weeks	4 weeks

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] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.
[c] One trial evaluated a plant-extracted low THC to CBD product and product that underwent further purification.
[d] One trial is included in both the synthetic THC and CBD columns, as it compared THC to CBD, CBD/THC, and placebo.
[e] Includes two new RCTs for this review.
[f] (n) = number of studies reporting this characteristic at baseline.
[g] Scores were standardized to a 0 to 10 scale.
[h] Weighted mean includes median scores for 1 study (6 vs. 6).
[i] Weighted mean includes median scores for 1 study (5.2 vs. 6.1).

Table C. Characteristics of included observational studies of cannabinoids

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
THC to CBD Ratio	Unclear or mixed	High	High	Comparable vs. high	Comparable
Source	Any cannabis product (patient's choice) or mixed cannabinoids	Plant-based	Synthetic (nabilone)	Plant-based vs. synthetic	Plant-based
N Studies	6[b]	1	1	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (1); other cannabinoids (1)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)	Active comparator; oral mucosal spray vs. dronabinol	Long-acting opioids (MME 69.4 (SD 38.9) mg/day)

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
Route of Administration, Formulation	Unreported (any available allowed, patient's choice) (5); inhaled or sublingual prescribed cannabis (1)	Whole-plant cannabis, "certified 12.5% THC" (CBD NR) route determined by patient: smoking 27%, oral 8%, vaporization 4%, combination 61%	Nabilone 0.5 mg oral capsule	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Dronabinol oral capsule (strength NR)	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Oral long-acting opioids (dose varied)
Dosing Regimen	None specified. Final dose NR	None specified; titrated to max dose 5 g/day. Final median dose 2.5 g/day	None specified; final mean dose 3 mg/day	None specified; final mean dose 16.6/15.4 mg THC/CBD/day vs. 17.2 mg THC/day	None specified; based on individual patient needs; final mean dose 16.7/15.5 mg THC/CBD/day vs. MME 69.4 mg/day
ROB	50% high, 50% moderate	100% high	100% moderate	100% moderate	100% moderate
N Total	13,269	431	156	674	1,310
Age, Mean Years	52	49	61	46	51
Female, %	55%	57%	59%	57%	57%
% Non-White (Study Count)	54% (1); NR (5)	NR	NR	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic non-cancer pain	Chronic non-cancer pain	NPP	Peripheral NPP	Peripheral neuropathic back pain
Baseline Pain Score, Mean (Range)[c]	5.75 (4.56 to 7.00)	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)	4.4 (4.39 to 4.41)	4.32 (4.31 to 4.33)
Study Duration, Weeks (Range)	12 to 208	52	26	24	24

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

[a] Patients could choose any medicinal product they preferred in these studies.
[b] Includes one new study 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)

Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD - Extracted From Whole Plant, Oromucosal Spray	Potential effect (4)[b] [✓]	Small effect (7) [✓✓]	Small effect (6) [✓✓]
High THC – Synthetic, Oral	**Insufficient (2, 1 new)[c]**	↓***Small effect*** **(7, 1 new)[c, d]** [✓]	No effect (4, 1 new) [✓]
High THC – Extracted From Whole Plant, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Topical CBD, Extracted From Whole Plant	No evidence	Insufficient (1)	No evidence
Low THC – Oral CBD, Synthetic	No evidence	Insufficient (1)	Insufficient (1)
Low THC – Oral CBD or CBD/THC, Unclear Origin	**Insufficient (1 new)[c]**	**Insufficient (1 new)[c]**	**Insufficient (1 new)[c]**
Low THC – Sublingual CBD/THC, Extracted from Whole Plant	No evidence	**Insufficient (1 new)[c]**	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[e]	No evidence	Insufficient (1)	No evidence

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

Note: 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.

[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] Downwards arrow indicates that the pooled effect size decreased from moderate.
[e] Comparison was "usual care."

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

Product/THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Comparable THC/CBD – Extracted From Whole Plant, Oromucosal Spray	No effect (5) [✓]	No effect (3) [✓]	Large effect (6) [✓]	Moderate effect (6) [✓]	Large effect (6) [✓]
High THC – Synthetic, Oral	Potential effect[a] (5, 1 new) [✓]	Insufficient (1)	Large effect (3, 1 new) [✓✓]	Potential effect[a] (3, 1 new) [✓]	Moderate effect (4, 1 new) [✓]
High THC – Extracted From Whole Plant, Oral	Large effect (1) [✓]	Insufficient (1)	Large effect (1) [✓]	No evidence	No evidence
Low THC – Topical CBD, Extracted From Whole Plant	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Oral CBD, Synthetic	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Low THC – Oral CBD or CBD/THC, Unclear Origin	**Insufficient (1, 1 new)[b]**	**Insufficient (1, 1 new)[b]**	**Insufficient (1, 1 new)[b]**	**Insufficient (1, 1 new)[b]**	**Insufficient (1, 1 new)[b]**
Low THC – Sublingual CBD/THC, Extracted from Whole Plant	**Insufficient (1, 1 new)[b]**	**Insufficient (1, 1 new)[b]**	No evidence	No evidence	No evidence

Product/THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC)[c]	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)

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

Note: 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.

[a] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[b] Text is bolded to indicate that the strength of evidence has changed.
[c] Comparison was "usual care."

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 high-THC to CBD products extracted from whole-plant cannabis, whole-plant cannabis products, low-THC to CBD products (e.g., topical CBD); 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 withdrawal due to adverse events. 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 the need for 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, and studies on subacute pain.

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Full Report

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