Comparative Effectiveness Review
Number 250

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2022 Update

Evidence 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 original systematic review published in October 2021, one new placebo-controlled randomized controlled trial (RCT) of oral CBD[1] and one new observational study of plant-based comparable THC to CBD versus synthetic CBD was added,[2] for a total of 21 RCTs and 8 observational studies. In patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months):

- Comparable THC to CBD ratio oral spray is probably associated with small improvements in pain severity and overall function versus placebo. There was no increase in risk of serious adverse events 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 moderate 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.
- Extracted whole-plant high-THC to CBD ratio products may be associated with large increases in risk of study withdrawal due to adverse events and dizziness versus placebo; outcomes assessing benefit were not reported or insufficient.

Continued on page 2

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- Evidence on whole-plant cannabis (including patient's choice of products), low THC to CBD ratio products (topical or oral CBD), other cannabinoids (cannabidivarin), and comparisons with other active interventions or different cannabis-related products was insufficient to draw conclusions.
- 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

Chronic pain is defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing[3,4] and affects approximately 100 million people in the United States.[5] Chronic pain adversely affects physical and mental functioning, productivity, and quality of life, and is often refractory to treatment and associated with substantial costs.[6-8] While opioids are often prescribed for chronic pain, they have small to moderate effects on pain and overall function, with frequent adverse effects,[9] and the 2016 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends nonopioid therapy as the preferred treatment of chronic pain.[3,4] However, recent systematic reviews found that several nonopioid drugs,[10] and some nonpharmacologic treatments[11] also have small to moderate effects on chronic pain and overall function. Some nonopioid treatments had frequent overall adverse events and some less frequent yet serious adverse effects, while nonpharmacological treatments typically reported few adverse events.[10]

Cannabinoids are a group of closely related compounds that are active in cannabis, with the two main cannabinoid compounds being THC and CBD. THC has demonstrated analgesic properties,[12,13] although its psychoactive effects and abuse potential may limit its suitability as an analgesic. Based on preclinical studies, CBD and related cannabinoids may also have some analgesic or anti-inflammatory properties and are not thought to be intoxicating or addictive.[14,15] While not derived from plants, two synthetic cannabinoid products, dronabinol (synthetic delta-9-THC) and nabilone (a THC analog), have also been studied for treating chronic pain. Dronabinol is also available as a purified plant-based formulation; because it is chemically identical to synthetic dronabinol, we grouped these together for the purpose of this review.[16] Other plant-based compounds with effects similar to opioids or cannabis, such as kratom, have been considered to treat chronic pain.[17-19] These may also have serious harms including dependence, addiction, and physiological withdrawal potential.[20]

The ongoing opioid crisis and the limited efficacy of opioids drive a search for alternative pain treatments, including cannabis and related compounds to better treat chronic pain.[9,21] 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 pain on an ongoing basis. This report updates the original 2021 systematic review on cannabis and other plant-based treatments for chronic pain. Using a living

review approach, the literature continues to be monitored quarterly for new studies, and the systematic review will 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 4, 2022. We included randomized controlled trials and comparative observational studies with a minimum of 4 weeks duration that assessed cannabis, kratom, and other plant-based interventions for noncancer chronic pain in adults. Cannabinoid interventions were categorized according to their THC to CBD ratio (comparable, high, low) and according to the source of the compound (whole-plant, extracted from whole-plant, or synthetic). Strength of evidence was assessed as low, moderate, high, or insufficient, and magnitude of effect was assessed according to Table A. Additionally, results that were below the threshold for a small effect were considered to reflect "no effect." Results with a small, medium, or large effect that were not statistically significant were considered to have "potential effects" if the 95 percent confidence interval included meaningful (i.e., at least small) benefit or harm, but not both (i.e., either the benefit or harm did not meet the threshold for small).[22,23]

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. Eight observational studies were also included and are described in Table C.

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	Plant-extracted
N Studies	7	2	9	2 (1 topical, 1 oral)	1
Comparator (Study Count)	Placebo (7)	Placebo (2)	Placebo (6); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1)	Placebo (2)	Placebo
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 (1); 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 oil, 50 mg/ml CBDV

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Dosing Regimen	108 to 130 mg THC daily (max 22 mg in 3 hours). Final mean dose 23 mg THC/21 mg CBD daily.	Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily. Capsule: 2.5 - 12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily	Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Dronabinol capsules: 2.5 -15 mg daily, titrated. Final dose 12.7 mg/day Namisol®[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.	400 mg CBDV daily. Final dose NR.
Risk of Bias	29% high, 57% moderate, 14% low	50% moderate, 50% low	22% high, 44% moderate, 33% low	50% high (topical), 50% moderate (oral)	100% moderate
Total Randomized	882	297	534	165	34
Age, Mean Years	53	52	50	65	50
Female, %	66%	89%	61%	41%	3%
Non-White,[c] %	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 (6) fibromyalgia (1); headache (1); visceral pain (1)	NPP (1 topical); OA (1 oral)	NPP (1)
Baseline Pain Score, Mean (Range)[d]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.46 (4 to 8.1)[e]	5.38 (4.67 to 6.14)	6.28 (6.12 to 6.44)
Study Duration	4 to 15 weeks	8 to 12 weeks	4 to 47 weeks	4 weeks (topical) and 12 weeks (oral)	4 weeks

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

[a] All products were nabiximols.

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

[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).

Table C. Characteristics of included observational studies

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Vs. Synthetic THC
THC to CBD Ratio	Unclear	High	High	Comparable vs. high
Source	Any cannabis product (patient's choice)	Plant-based	Synthetic (nabilone)	Plant-based vs. synthetic
N Studies	5	1	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (1)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)	Active comparator; oral mucosal spray vs. dronabinol
Route of Administration, Formulation	Unreported (any available allowed, patient's choice)	Whole-plant cannabis, "certified 12.5% THC" (CBD NR) route determined by patient: smoking 27%, oral 8%, vaporization 4%, combination 61%	Nabilone 0.5 mg oral capsule	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Dronabinol oral capsule (strength NR)
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
ROB	60% high, 40% moderate	100% high	100% moderate	100% moderate
N Total	12,508	431	156	674
Age, Mean Years	53	49	61	46
Female, %	55%	57%	59%	57%
% Non-White (Study Count)	54% (1); NR (4)	NR	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic non-cancer pain	Chronic non-cancer pain	NPP	Peripheral NPP
Baseline Pain Score, Mean (Range)[b]	5.35 (4.56 to 8.00)	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)	4.4 (4.39 to 4.41)

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Vs. Synthetic THC
Study Duration, Weeks (Range)	12 to 208	52	26	24

Abbreviations: CBD = cannabidiol; NPP = neuropathic pain; NR = not reported; ROB = risk of bias; THC = tetrahydrocannabinol.
[a] Patients could choose any medicinal product they preferred in these studies.
[b] 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 Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD Oromucosal Spray	Potential effect (4)[a] [+]	Small effect (7) [++]	Small effect (6) [++]
High THC – Synthetic, Oral	Large effect (1) [+]	Moderate effect (6) [+]	No effect (3) [+]
High THC – Extracted From Whole Plant, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Topical CBD	No evidence	Insufficient (1)	No evidence
Low THC – Oral CBD	No evidence	Insufficient (1)	Insufficient (1)
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[b]	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[b] Comparison was "usual care."

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

Table 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 Oromucosal Spray	No effect (5) [+]	No effect (3) [+]	Large effect (6) [+]	Moderate effect (6) [+]	Large effect (6) [+]
High THC – Synthetic, Oral	Potential effect[a] (4) [+]	Insufficient (1)	Large effect (2) [++]	Potential effect[a] (2) [+]	Moderate effect (3) [+]
High THC – Extracted From Whole Plant, Oral	Large effect (1) [+]	Insufficient (1)	Large effect (1) [+]	No evidence	No evidence
Low THC – Topical CBD	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Oral CBD	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC)[b]	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.
[a] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[b] Comparison was "usual care."

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

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 (see Tables B and C), (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 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 to moderate short-term improvements in pain with some cannabis products, but the impact on moderate or long-term outcomes is unknown. The evidence on adverse events with cannabis-related products is much less robust than the evidence on similar outcomes with opioids or nonopioid medications. Comparing the results with recent systematic reviews that used the same methodology, suggests that the risk of sedation and dizziness appear similar between cannabis-related products, opioids, and the anticonvulsants pregabalin and gabapentin, while the risk for nausea appears to be larger with opioids and the antidepressant duloxetine than with cannabis-related products.[9,10] However, these qualitative and indirect comparisons are based on very 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. Understanding how the adverse event profiles of cannabis products compare with other available treatments for chronic pain, particularly opioid and non-opioid medications, is essential to determining the benefit to harm ratio. However, 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.

Only short-term evidence is available for cannabis-related interventions containing THC and/or CBD to treat primarily neuropathic chronic pain. Improvement in pain was small to moderate with high and comparable THC to CBD ratio products. Compared with placebo, these interventions resulted in greater risk of common adverse events (dizziness, nausea, sedation); 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. Additional studies are needed to improve confidence in these findings and to provide evidence on longer-term followup, other outcomes, and other interventions including whole plant cannabis. There was no evidence on other plant-based compounds such as kratom. Important limitations include small sample sizes, lack of evidence for moderate and long-term use, and few data for key outcomes, such as other serious adverse events (e.g., psychosis, CUD) and impact on use of opioids during treatment. In addition, the unavailability or unclear availability of studied cannabis products in specific settings may reduce the generalizability of findings. Some of the best-studied cannabis products are not approved by the Food and Drug Administration or readily available in the United States. In order to better understand the small to moderate improvements in pain, and the complete adverse event profile of cannabinoids used to treat chronic pain, future studies that resolve these limitations are needed. Specific recommendations for future research are included in the full report, including the need for studies evaluating appropriately representative and diverse populations, studies evaluating specific cannabis-based products available in the United

States, studies on long-term outcomes, studies on non-neuropathic chronic pain, and studies comparing effects of cannabis-based products versus other treatments for chronic pain.

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Full Report

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