Comparative Effectiveness Review
Number 250

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

Evidence Summary

Main Points

In RCTs (mostly placebo controlled) of patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months):

- Studies of cannabis-related products were grouped based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio using the following categories: high-THC to CBD, comparable THC to CBD, and low-THC to CBD.
- Comparable THC to CBD ratio oral spray is probably associated with small improvements in pain severity and overall function. There was no effect on serious 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, no effect on overall function and increased risk of sedation, and large increased risk of nausea. Synthetic THC is probably associated with a large increased risk of dizziness.
- Extracted whole-plant high-THC to CBD ratio products may be associated with large increases in risk of study withdrawal due to adverse events and dizziness.
- Evidence on whole-plant cannabis (including patient's choice of products), low-THC to CBD ratio products (topical CBD), other cannabinoids (cannabidivarin), and comparisons with other active interventions 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.
- No evidence on other plant-based compounds such as kratom met criteria for this review.

Agency for Healthcare Research and Quality

Background and Purpose

Chronic pain is defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing[1,2] and affects approximately 100 million people in the United States.[3] Chronic pain adversely affects physical and mental functioning, productivity, and quality of life, and is often refractory to treatment and associated with substantial costs.[4-6] While opioids are often prescribed for chronic pain, they have small to moderate effects on pain and overall function, with frequent adverse effects,[7] 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.[1,2] However, recent systematic reviews found that several nonopioid drugs,[8] and some nonpharmacologic treatments[9] 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.[8]

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,[10,11] 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 psychoactive or addictive.[12,13] While not derived from plants, two synthetic cannabinoid products, dronabinol (synthetic THC) and nabilone (a THC analog), have also been studied for treating chronic pain. Other plant-based compounds with effects similar to opioids or cannabis, such as kratom, have been considered to treat chronic pain. These may also have serious harms including dependence, addiction, and physiological withdrawal potential.[14]

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.[7,15] The purpose of this systematic review was to evaluate the evidence on benefits and harms of cannabinoids and similar plant-based substances (e.g., kratom) to treat chronic pain

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Effective Healthcare Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), and we describe these in the full report. Our searches covered publication dates from database inception to July 2021. 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 benefit or harm, but were not so wide that they included the potential for both meaningful benefits and harms.[16,17]

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 randomized controlled trials (RCTs) are described in Table B. Seven 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	High	High	Low	NA - other cannabinoids
Source	Plant-extracted	Plant-extracted	Synthetic	Plant-extracted	Plant-extracted
N Studies	7	2	9	1	1
Comparator (Study Count)	Placebo (7)	Placebo (2)	Placebo (6); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1)	Placebo (1)	Placebo (1)
Risk of Bias % High, % Moderate, % Low	29%, 57%, 14%	0%, 50%, 50%	22%, 44%, 33%	100% high	100% moderate
Total Randomized	882	297	534	29	34
Age, Mean Years	53	52	50	68	50
Female, %	66%	89%	61%	38%	3%
% Non-White[a] (Study Count)	1.6% (2)	1% (1)	5.4% (3)	NA	NA
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)	NPP (1)
Baseline Pain Score, Mean (Range)[b]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.46 (4 to 8.1)[c]	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	4 weeks

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

[a] (Study count) = number of studies reporting this characteristic at baseline.

[b] Scores were standardized to a 0 to 10 scale.
[c] Weighted mean includes median scores for one study (6 vs. 6).

Table C. Characteristics of included observational studies

Characteristic	THC/CBD	THC	Synthetic THC
THC to CBD Ratio	Unclear	High	High
Source	Any cannabis product (patient's choice)	Plant-based	Synthetic (nabilone)
N Studies	5	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)
ROB % High, % Moderate, % Low	60% high, 40% moderate	100% high	100% moderate
N Total	12,508	431	156
Age, Mean Years	53	49	61
Female, %	55%	57%	59%
% Non-white (study count)	54% (1); NR (4)	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic non-cancer pain	Chronic non-cancer pain	NPP
Baseline Pain Score, Mean (Range)[a]	5.35 (4.56 to 8.00)	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)
Study Duration, Weeks (Range)	12 to 208	52	26

Abbreviations: CBD = cannabidiol; NPP = neuropathic pain; NR = not reported; ROB = risk of bias; THC = tetrahydrocannabinol.

[a] 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)

THC to CBD Ratio	Pain Response Effect Size (N Studies) [SOE][a]	Pain Severity Effect Size (N Studies) [SOE][a]	Overall Function Effect Size (N Studies) [SOE][a]
Comparable THC/CBD Oromucosal Spray	Potential effect (4)[b] [+]	Small effect (7) [++]	Small effect (6) [++]
High-THC – Synthetic, Oral	Insufficient (1)	Moderate effect (5) [+]	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
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC, Smoked)	No evidence	Insufficient (1)	No evidence

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

[a] Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: + = low, ++ = moderate, +++ = high.
[b] Findings with small or larger magnitude of effect, not statistically significant; but with SOE rating of Low or higher (downgraded mainly for imprecision).

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

THC to CBD Ratio	WAE Effect Size (N Studies) [SOE][a]	SAE Effect Size (N Studies) [SOE][a]	Dizziness Effect Size (N Studies) [SOE][a]	Nausea Effect Size (N Studies) [SOE][a]	Sedation Effect Size (N Studies) [SOE][a]
Comparable THC/CBD Oromucosal Spray	Insufficient (5)	No effect (2) [+]	Large effect (6) [+]	Moderate effect (6) [+]	Large effect (6) [+]
High-THC – Synthetic, Oral	Potential effect[b] (4) [+]	Insufficient (1)	Large effect (2) [++]	Potential effect[b] (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
Other Cannabinoids – CBDV, oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC, smoked)	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] Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: + = low, ++ = moderate, +++ = high.
[b] Findings with small or larger magnitude of effect, not statistically significant; but with SOE rating of Low or higher (downgraded mainly for imprecision).

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 adequate 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), 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. These limitations affect both the stability and applicability of the findings.

Implications and Conclusions

The implications of the present findings for clinical practice are mixed. 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.7,8 These qualitative and indirect comparisons with very limited evidence on cannabis products relative to the other drugs however need confirmation. The comparisons of effects on serious and long-term harms are however not possible, 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.

In the short term (4 weeks to <6 months), small magnitude improvements in pain severity and overall functioning or disability were found with comparable THC to CBD ratio oral sprays, with large increased risk of dizziness and sedation, and moderate increased risk of nausea compared with placebo. In the short term, moderate improvements in pain severity and no effect on overall function were found with high-THC to CBD synthetic oral products, with moderate increased risk of withdrawal from studies due to adverse events, serious adverse events, and sedation, and a large increased risk of dizziness compared with placebo. In the short-term, moderate improvements in pain severity were found with whole-plant extracted, high-THC to CBD oral products, with large increased risk of study withdrawal due to adverse events and dizziness, and moderate increased risk of serious adverse events. The strength of these findings are low to moderate. Evidence on whole-plant cannabis, topical CBD, and other cannabinoids was insufficient to draw conclusions. 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 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.

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Full Report

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