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Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: Annual Update #1

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This report is based on research conducted by the <EPC> Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. XXX-20XX-XXXXX). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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/reference/purpose.cfm

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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 reviewed the report will be added in the final version.

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 does not necessarily represent the views of individual reviewers.

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 non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers who reviewed the report will be added in the final version.

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: Annual Update #1

Structured Abstract

Objectives. To update the evidence on benefits and harms of cannabinoids and similar plant-based compounds to treat chronic pain.

Data sources. Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases, reference lists of included studies, submissions received after Federal Register request were searched to February 2022 (updated from July 2021).

Review methods. Using dual review, we screened search results for randomized controlled trials (RCTs) and observational studies of patients with chronic pain evaluating cannabis, kratom, and similar compounds with any comparison group and at least 1 month of treatment or followup. Dual review was used to abstract study data, assess study-level risk of bias, and rate the strength of evidence. Prioritized outcomes included pain, overall function, and adverse events. We grouped studies that assessed tetrahydrocannabinol (THC) and/or cannabidiol (CBD) based on their THC to CBD ratio and categorized them as high-THC to CBD ratio, comparable THC to CBD ratio, and low-THC to CBD ratio. We also grouped studies by whether the product was a *whole-plant* product (cannabis), cannabinoids *extracted or purified* from a whole plant, or a *synthetic* product. We conducted meta-analyses using the profile likelihood random effects model and assessed between-study heterogeneity using Cochran's Q statistic chi square test and the I^2 statistic. Magnitude of benefit was categorized as no effect or small, moderate, and large effects.

Results. From 3,172 abstracts (original report plus update), 21 RCTs (N=1,905) and 8 observational studies (N=13,769) assessing different cannabinoids were included; none evaluated kratom. One new RCT evaluated oral CBD, and one new observational study compared different cannabis-related products. Studies were primarily short term, and 59 percent enrolled patients with neuropathic pain. Comparators were primarily placebo or usual care. The strength of evidence (SOE) was low, unless otherwise noted. Compared with placebo, comparable THC to CBD ratio oral spray was associated with a small benefit in change in pain severity (7 RCTs, N=632, 0 to10 scale, mean difference [MD] −0.54, 95% confidence interval [CI] −0.95 to −0.19, I^2=39%; SOE: moderate) and overall function (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI −0.73 to −0.16, I^2=32%). There was no effect on study withdrawals due to adverse events. There was a large increased risk of dizziness and sedation and a moderate increased risk of nausea (dizziness: 6 RCTs, N=866, 30% vs. 8%, relative risk [RR] 3.57, 95% CI 2.42 to 5.60, I^2=0%; sedation: 6 RCTs, N=866, 22% vs. 16%, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%; and nausea: 6 RCTs, N=866, 13% vs. 7.5%, RR 1.79, 95% CI 1.19 to 2.77, I^2=0%). Synthetic products with high-THC to CBD ratios were associated with a moderate improvement in pain severity, a moderate increase in sedation, and a large increase in nausea (pain: 6 RCTs, N=390 to 10 scale, MD −1.15, 95% CI −1.99 to −0.54, I^2=48%; sedation: 3 RCTs, N=335, 19% vs. 10%, RR 1.73, 95% CI 1.03 to 4.63, I^2=28%; nausea: 2 RCTs, N=302, 12% vs. 6%, RR 2.19, 95% CI

0.77 to 5.39; I^2=0%). We found moderate SOE for a large increased risk of dizziness (2 RCTs, 32% vs. 11%, RR 2.74, 95% CI 1.47 to 6.86, I^2=40%). Extracted whole-plant products with high-THC to CBD ratios (oral) were associated with a large increased risk of study withdrawal due to adverse events (1 RCT, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33) and dizziness (1 RCT, 62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34). We observed a moderate improvement in pain severity when combining all studies of high-THC to CBD ratio (8 RCTs, N=684, MD −1.25, 95% CI −2.09 to −0.71, I^2=58%; SOE: moderate). Evidence (including observational studies) on whole-plant cannabis, topical or oral CBD, low-THC to CBD, other cannabinoids, comparisons with active products or between cannabis-related products, and impact on use of opioids was insufficient to draw conclusions. Other important harms (psychosis, cannabis use disorder, and cognitive effects) were not reported.

Conclusions. Low to moderate strength evidence suggests small to moderate improvements in pain (mostly neuropathic), and moderate to large increases in common adverse events (dizziness, sedation, nausea) with high- and comparable THC to CBD ratio extracted cannabinoids and synthetic products in short-term treatment (1 to 6 months); high-THC to CBD ratio products were also associated with increased risk of withdrawal due to adverse events. Evidence for whole-plant cannabis, and other comparisons, outcomes, and PBCs were unavailable or insufficient to draw conclusions, despite some new evidence for oral CBD and comparing cannabis-based products. Small sample sizes, lack of evidence for moderate and long-term use and other key outcomes, such as other adverse events and impact on use of opioids during treatment, indicate that more research is needed.

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Evidence Summary

Main Points

This is the first annual update of an ongoing living systematic review on cannabis and other plant-based treatments for chronic pain. 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 (including CBD only). Since the original systematic review, 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, no effect on overall function and increased risk of sedation, and large 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.
- Evidence on whole-plant cannabis (including patient's choice of products), low THC to CBD ratio products (topical or oral [***one new RCT***] CBD), other cannabinoids (cannabidivarin), and comparisons with other active interventions or different cannabis-related products (***one new observational study***) 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.

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 psychoactive 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. These may also have serious harms including dependence, addiction, and physiological withdrawal potential.[17]

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.[9,18] The purpose of this living 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.

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), as described in the full report. Searches for this update covered publication dates from database inception to February 2022 (updated from 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.[19,20]

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 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.

Results

The included randomized controlled trials (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	High	High	Low	NA - other cannabinoids
Source	Plant-extracted	Plant-extracted	Synthetic Nabilone Dronabinol Dronabinol/Namisol®[a]	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 (2)
Route of Administration, Formulation	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 (k =1) Oral capsule, 2.5 mg THC/0.8 – 1.8 mg CBD extract (k =1)	Nabilone oral 0.25 mg capsule (k=1); Nabilone oral 0.5 mg capsule (k=5); Dronabinol 2.5 mg oral capsule (k =1); Dronabinol 5 mg oral capsule (k=1); Namisol®[a] 3 mg oral tablet (k =1)	Topical oil, 83 mg CBD/fluid ounce (k =1), Oral tablet, 10 mg CBD (k =1)	Oral oil, 50 mg/ml 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,[b] %	1.6% (2)	1% (1)	5.4% (3)	NR	NR
Primary Pain Type (n Studies)	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)

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
Baseline Pain Score, Mean (Range)[c]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.46 (4 to 8.1)[d]	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] Namisol® is a purified, plant-based product, but grouped with synthetic dronabinol because they are chemically identical.
[b] (n) = number of studies reporting this characteristic at baseline.
[c] Scores were standardized to a 0 to 10 scale.
[d] Weighted mean includes median scores for 1 study (6 vs. 6).

Table 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)
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	Insufficient (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 (2) [+]	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

This first annual update for a living systematic review on cannabis and other PBCs identified one new RCT and one new observational study on cannabis-related products which did not change the overall conclusions of the original report. Therefore, the implications of the updated findings for clinical practice remain 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.[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.

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 addition, the unavailability or unclear availability of studied cannabis products in specific settings may reduce the generalizability of findings. 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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Introduction

Background

Chronic pain, defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,[1,2] is a serious public health issue in the United States, affecting approximately 100 million people[3] and resulting in over $560 billion annually in costs.[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.[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.[7] This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[7-9] involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdoses related to prescription opioids in the United States,[1] with an estimated 17,087 prescription opioid overdose deaths in 2016.[7] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[10]

While opioids are often prescribed for chronic pain, they are associated with small to moderate effects on pain and overall function with frequent adverse effects,[11] 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] Recent systematic reviews found that several nonopioid drugs,[12] and some nonpharmacologic treatments[13] 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.[12]

The challenges of treating chronic pain in light of the limited benefits of commonly prescribed prescription medications and the ongoing opioid crisis drive a search for alternative pain treatments, including cannabis. The goals of current research are to identify alternative treatments with 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.[14] Tetrahydrocannabinol (THC), one of many cannabinoids in cannabis, has demonstrated analgesic properties,[15,16] though its psychoactive effects and abuse potential increase its risk and 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 psychoactive or addictive,[17,18] but may not be as potent as THC. Observational studies indicate that some patients use cannabis and related compounds as a substitute for opioids.[19-22]

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.[23,24] They may also have serious harms, such as dependence, addiction, and physiological withdrawal potential.[25] 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.[26] Recent legalization of cannabis by several states[27] may

lead to more, and higher quality research on PBCs with potential for treating chronic pain.[28] 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.[28,29]

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.

Purpose and Scope of the Systematic Review

This is the first update of a "living systematic review" which assesses the effectiveness and harms of plant-based treatments for chronic pain conditions. The review is living in the sense that it uses methods to identify and synthesize recently published literature on an ongoing basis. The original systematic review was based on searches conducted through July 2021; this update includes new evidence published to February 2022. For the purposes of this review, PBCs included are those that are similar to opioids in effect and that have 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 chronic pain, and clinicians who treat chronic 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").[30] All methods were determined a priori, and a protocol was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol) and on the PROSPERO systematic reviews registry (registration no. CRD42021229579). Below is a summary of the specific methods used in this review. Search strategies appear in Appendix A, and a complete description of methods are presented in Appendix B.

Key Questions

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

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

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through February 4, 2022, with ongoing, automated monthly searches to identify newly published studies. Searches for the original systematic review were run in September 2020 and updated through July 5, 2021. Search strategies are available in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and reviewing the two prior AHRQ pain reports[11,12] for studies that met the inclusion criteria for this review. For the original 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).[30] 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

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults (including pregnant or breastfeeding women) 18 years and older with chronic pain (>12 weeks or pain persisting past the time for normal tissue healing). See categorization of specifically included pain populations below.	**All KQs:** Children and adolescents <18 years old; adults with acute or subacute pain; patients at end of life or in palliative care (e.g., with late stage cancer-related pain)
Interventions	**KQs 1 and 2:** Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes **KQs 3 and 4 :** Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids **All KQs**: Co-use of other drugs for pain	**All KQs:** Non-plant-based interventions, capsaicin, herbal supplements
Comparators	**All KQs:** Any comparator, or usual care	**All KQs:** No comparison
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, overall function or disability, including pain interference[a]); 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)	**All KQs:** Other outcomes
Time of followup	**All KQs:** short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year)	**All KQs:** studies with <1-month (4 weeks) of treatment or followup after treatment
Setting	**All KQs:** Any nonhospital setting or setting of self-directed care	**All KQs**: Hospital care, hospice care, emergency department care
Study design	**All KQs:** RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits	**All KQs:** Other study designs

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

[a] The degree to which pain directly interferes with patients' ability to participate in their daily activities.

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. Quarterly surveillance reports describing recently published studies as they were newly identified are available at: https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review

The risk of bias of individual studies was assessed using methods consistent with the AHRQ Methods Guide.[30] 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).[11-13,31,32]

Based on input from a Technical Expert Panel, 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. This category was further stratified based on whether interventions consisted of synthetic THC or were derived from whole-plant cannabis. Whole plant-based products can be either extracted or purified, depending on the process used to isolate higher concentrations of THC or CBD. Extracted 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. Purified products are pharmaceutical grade and considered free of contaminants (i.e., consist of only THC or THC and CBD combinations). Namisol® presented a challenge for categorization because it is a purified plant-based product, but chemically identical to synthetic dronabinol.[33] Therefore, we grouped Namisol® (purified plant-based dronabinol) together with synthetic dronabinol, but also performed sensitivity analyses without Namisol®.

The second category, low-THC, contains a ratio of THC to CBD of less than one (i.e., higher CBD than THC, at least 1 to 2 ratio). These may similarly be 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), and these may also be extracted or purified products.

Interventions consisting of whole-plant cannabis products (not extracted, purified, or synthetic) were categorized according to any 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 were analyzed together with oral and oromucosal products.

Table 2. Organizing principle of cannabis-related studies based on ratios of THC to CBD

Intervention Category	Definition	Possible Derivatives	Example Products	U.S. Availability
High-THC[a]	THC to CBD ratio equals ≥2:1 ratio	Synthetic, extracted or purified from whole-plant, whole-plant	Synthetic: dronabinol/Marinol®, nabilone/Cesamet® Extracted: THC oil (oral) Purified: dronabinol/ Namisol®[b]	Synthetic dronabinol (Marinol®) and nabilone (Cisamet®) available via prescription.[c] Purified dronabinol (Namisol®) availability currently unknown.[d] High-THC extracted and whole-plant products available in U.S. where allowed, none FDA-approved. Availability of specific products unknown.
Low-THC	THC to CBD ratio equals 1:≥2 ratio	Extracted or purified from whole-plant, whole-plant	CBD topical cream or ointment; cannabis flowers, buds, leaves	Multiple CBD products available in U.S. states, where allowed, none FDA-approved. Availability of specific products unknown.
Comparable THC to CBD	THC to CBD ratio is between threshold for high-THC and low-THC categories	Extracted or purified from whole-plant, whole-plant	Nabiximols (Sativex®)	Availability of nabiximols (Sativex®), currently unknown.[e] Multiple other comparable THC/CBD ratio products available in U.S., where allowed, none FDA-approved. Availability of specific products unknown.
Whole-Plant Cannabis Products	Potentially unknown THC to CBD ratio; categorized based on information provided	Whole-plant or parts/materials from the plant, not extracted, purified, or synthetic	Cannabis flowers, resins, buds, leaves, hashish	Multiple whole-plant cannabis CBD products available in U.S., where allowed, none FDA-approved. Availability of specific products unknown.
Other Cannabinoids	Interventions testing cannabinoids other than THC and/or CBD	Extracted or purified from whole-plant	Extracted oils (oral)	Availability of this specific cannabinoid in the U.S. is unknown.

Abbreviations: CBD = cannabidiol; THC = tetrahydrocannabinol.
[a] Nabilone included in this category.
[b] Namisol® is chemically identical to dronabinol, and is therefore grouped together with synthetic dronabinol.
[c] FDA approved for nonpain indications; HIV associated cachexia, chemotherapy-related nausea.
[d] Manufactured in The Netherlands, may be available in some European countries. Not currently FDA-approved.
[e] 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.[34] 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 χ^2 test and the I^2 statistic.[35] Pain scales were converted to a

standardized 0 to 10 scale and the mean difference was used as the effect measure for change in pain. A similar approach was used for other primary continuous outcomes (e.g. overall function). 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[36] to combine interventions with comparable THC to CBD ratios and high-THC trials. The primary analysis for high-THC trials was stratified by the type of derivative used in the intervention (synthetic vs. whole-plant extracts). Sensitivity analysis was conducted by excluding studies rated as high risk of bias, excluding a trial of Namisol®[37] (purified plant-based dronabinol) that was grouped with synthetic dronabinol, and by repeating analyses using a random effects model based on the profile likelihood method with the Bartlett's correction to reduce potential deviation from the null distribution when the number of studies is small.[38] Although the Bartlett's correction resulted in greater imprecision in pooled estimates (wider confidence intervals), findings regarding statistical significance of findings were unchanged, with one exception (high-THC for sedation). Therefore, it is not discussed further, except for that analysis. All meta-analyses were conducted using command *metan* and *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 using the same system used in other recent AHRQ reviews conducted on chronic pain[11-13,31,32] to provide a consistent benchmark for comparing results of pain interventions across reviews. The findings were categorized as small, moderate, and large magnitudes of effect based on the ranges of effect shown in Table 3. 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.

Table 3. 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.

Small effects using this system may be below published thresholds for clinically meaningful effects; however, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or 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 type of product (synthetic vs. extracted from whole-plant), duration (short-, medium-, long-term followup), and type of pain (e.g. neuropathic, visceral, joint).

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 is initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.[30,39] To ensure consistency and validity of the evaluation, the strength of evidence is reviewed by the entire team of investigators prior to assigning a final grade on the following factors:

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

For description of overall grade, please 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.[40-42] 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 simply described as having an effect.

Living Systematic Review Methods

This is the first annual update of an ongoing living systematic review. Previous quarterly surveillance reports that were conducted prior to this full update, describing new evidence as it became available, can be found at: https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review. Future quarterly surveillance reports and updates will also be posted at this location.

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 (CDB) ratio interventions, high-THC to CBD ratio interventions (stratified into synthetic, extracted from whole-plant, and whole-plant cannabis products), low-THC to CBD ratio interventions (topical CBD), and other cannabinoids. No studies meeting inclusion criteria were identified for KQs 3 and 4.

After screening 3,172 abstracts, 273 full-text publications of studies were dually reviewed, resulting in 21 randomized controlled trials (RCTs) and 8 observational studies being included in this review. One new RCT[43] of synthetic oral CBD (low-THC to CBD ratio) and one new observational study[44] comparing plant-based comparable THC to CBD ratio versus synthetic THC (high-THC to CBD ratio) were added for this update. All included studies assessed cannabinoid interventions; no studies of kratom or other plant-based compounds met inclusion criteria.

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 RCTs evaluated products that contain a combination of THC and CBD (comparable THC to CBD ratio).[45-51] Two RCTs evaluated the effects of high-THC to CBD ratio, whole-plant derived extracts.[52,53] Nine RCTs evaluated synthetic forms of THC (high-THC to CBD ratio).[37,54-61] Two trials evaluated CBD (low-THC to CBD ratio): one trial assessed topical CBD[62] and one trial synthetic oral CBD.[43] One trial evaluated the phytocannabinoid, cannabidivarin (CBDV).[63]

Appendix D contains individual study-level data and additional results for pooled data from studies where data were available. 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

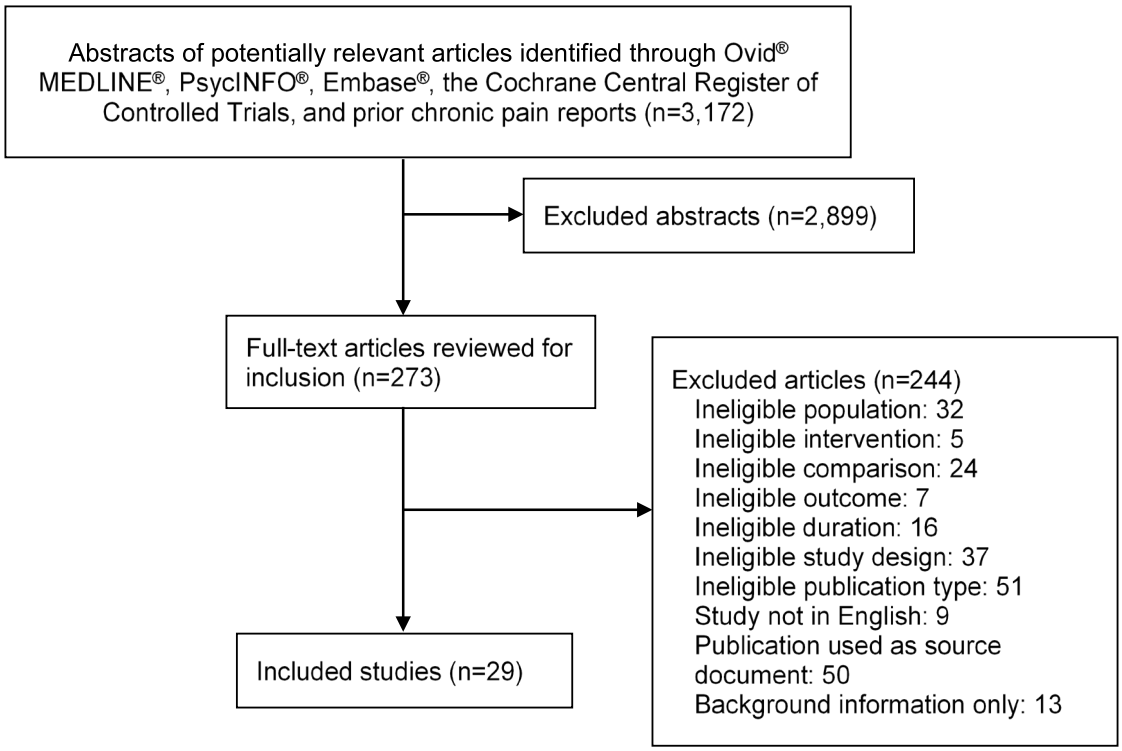


Table 4 summarizes the characteristics of the included trials, and Table 5 provides details on included observational studies.

Table 4. Characteristics of included randomized controlled trials of cannabinoids

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 Nabilone Dronabinol Dronabinol/Namisol®[a]	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 (2)
Route of Administration, Formulation	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 (k =1) Oral capsule, 2.5 mg THC/0.8 – 1.8 mg CBD extract (k =1)	Nabilone oral 0.25 mg capsule (k=1); Nabilone oral 0.5 mg capsule (k=5); Dronabinol 2.5 mg oral capsule (k =1); Dronabinol 5 mg oral capsule (k=1); Namisol®[a] 3 mg oral tablet (k =1)	Topical oil, 83 mg CBD/fluid ounce (k =1), Oral tablet, 10 mg CBD (k =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 to 2 mg twice daily, titrated. Final mean dose 1.84 Dronabinol capsules: 2.5 to 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,[b] %	1.6% (2)	1% (1)	5.4% (3)	NR	NR
Primary Pain Type (n Studies)	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)[c]	6.59 (5.3 to 7.3)	8.47 (8.25 to 8.67)	6.46 (4 to 8.1)[d]	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.

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

[b] (n) = number of studies reporting this characteristic at baseline.

[c] Scores were standardized to a 0 to 10 scale.

[d] Weighted mean includes median scores for 1 study (6 vs. 6).

Table 5. Characteristics of included observational studies of cannabinoids

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

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD vs. Synthetic THC
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)
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.

KQ 1 and KQ 2. In adults with chronic pain, what are the benefits (KQ 1) and harms (KQ 2) of cannabinoids for treatment of chronic pain?

Key Points for Comparable THC to CBD Ratio

- No new studies evaluated comparable THC to CBD ratio products.
- All results are short-term (4 weeks to <6 months) in duration.
- Based on previously included evidence, comparable THC to CBD ratio products were 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, I^2=39%) and overall function (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI –0.73 to −0.16) (strength of evidence [SOE]: moderate). While more patients had a response (≥30% improvement from baseline), 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, I^2=0%) (SOE: low).
- Compared with placebo, comparable THC to CBD was associated with a large increase in risk of dizziness (6 RCTs, N=866, 30% vs. 8%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%) and sedation (6 RCTs, N=866, 22% vs. 16%, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%), 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, I^2=0%). There was no effect on study withdrawal due to adverse events (SOE: low).

Summary of Findings for Comparable THC to CBD Ratio

No new studies evaluated comparable THC to CBD ratio products. Seven RCTs (N=882, range 18 to 339)[45-51] included in the original report compared products containing a combination of extracted THC and CBD (THC/CBD; comparable THC to CBD ratio) with placebo in patients experiencing chronic pain. All used nabiximols, 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 6 studies). Overall availability of nabiximols is unknown. 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,[45-49,51] while the other study 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.[47] Two trials were high risk of bias: one a small (n=16), 4-week, crossover trial, and the other a small (n=29), 12-week, parallel design trial.[47,50] The rest were parallel design trials, four moderate risk of bias,[45,48,49,51] and one low risk of bias.[46] The mean age of participants 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.[46-48,51] The proportion of patients taking opioids was low in two studies (11% to 24%)[46,51] and much greater in the third study (63% in the cannabis group vs. 74% in the placebo group).[48] The other three trials did not report opioid use. All of the RCTs of

comparable THC to CBD ratio products allowed prior cannabis use, with a range of 5 percent to 64 percent of enrolled patients having used cannabis previously. None of the studies 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.

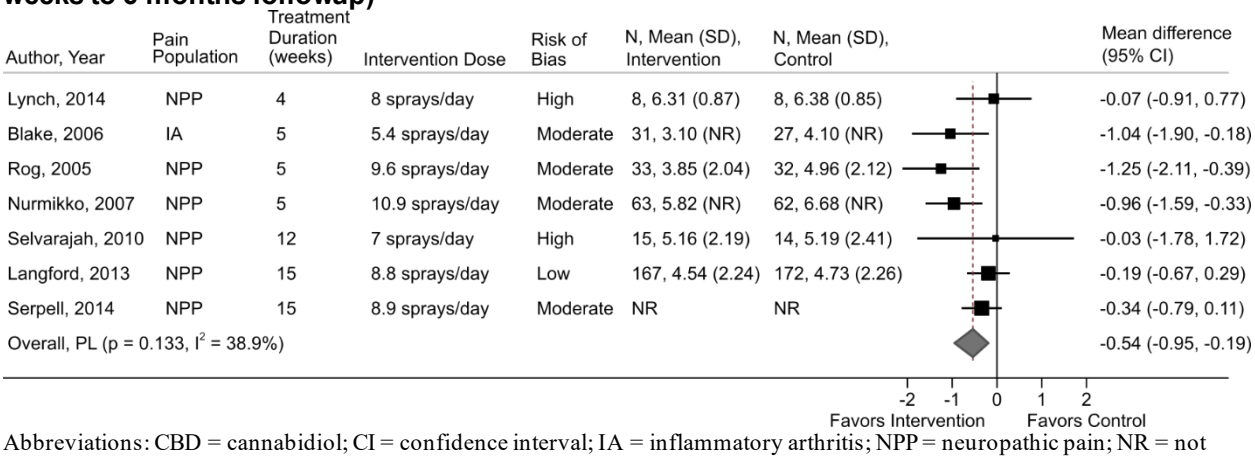
For pain response (≥30% reduction in pain) pooled analysis of four RCTs[46,48,50,51] found a statistically nonsignificant increase with combination THC/CBD treatment (4 RCTs, 38% vs. 31%, RR 1.18, 95% CI 0.93 to 1.71, I^2=36%; Appendix D, Figure D-1). Based on pooled analysis of all seven RCTs, pain severity showed a small, statistically significant improvement with combination THC/CBD treatment (7 RCTs, 0 to 10 scale, MD −0.54, 95% CI −0.95 to −0.19, I^2=39%; Figure 2).[45-51] Figure 2 shows that, except for the small, high risk of bias, crossover study, the size of effect was larger and statistically significant in the shorter studies (4 to 5 weeks) compared with the longer studies (12 to 15 weeks). Subgroup analysis was not conducted because all of the studies are of short duration (1 to <6 months). Sensitivity analysis excluding two high risk of bias studies[47,50] did not alter the findings (0 to 10 scale, MD −0.63, 95% CI −1.15 to −0.24, I^2=52%).[46,51]

Six studies (N=616) with 5 to 15 weeks followup reported on overall function or disability (including measures of pain interference).[45,46,48-51] 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 not 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.[46,50,51] One used the Short General Health Questionnaire (GHQ-12; 0 to 36 scale), and found a small, but not statistically significant, difference between groups.[48] Three of the studies reported on the Short Form-36 (SF-36) Physical and Mental scales (0 to 100).[46,47,50] 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 stayed similar in the THC/CBD group and decreased (worsened) in the placebo group.[47] Five studies 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.[45,46,48,49,51] The studies did not report on other secondary outcomes (e.g., depression or anxiety).

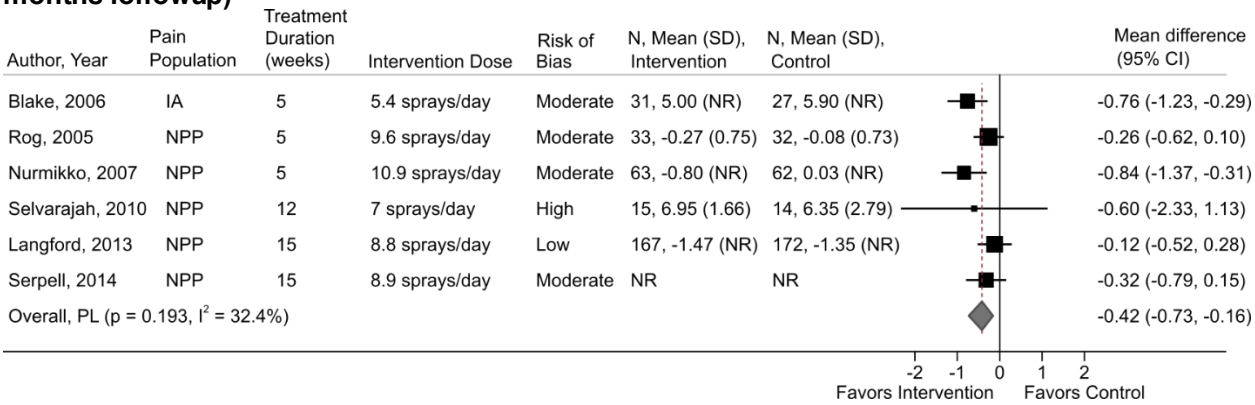
The four RCTs that allowed opioid use during the study period did not report on changes in opioid used during the study period.[46,48,51]

Figure 2. Change in pain severity with comparable THC to CBD ratio versus placebo (short term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; SD = standard deviation; THC = tetrahydrocannabinol.

Figure 3. Overall function: comparable THC to CBD ratio versus placebo (short term, 4 weeks to 6 months followup)



Abbreviations: BPI-SF = Brief Pain Inventory- Short Form; CBD = cannabidiol; CI = confidence interval; DAS28 = 28-Joint Disease Activity Scale; GNDS = Guy's Neurological Disability Scale; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PDI = Pain Disability Index; SD = standard deviation; SF-36 = 36 Item Short Form Survey; SF-36 PF = 36 Item Short Form Survey Physical Functioning; THC = tetrahydrocannabinol.

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, I^2=0%, Appendix D, Figure D-2).[46,49]

Serious adverse events (SAEs) were reported in four studies, with two reporting that none occurred.[47,49] Pooling results from the other two studies found no effect on SAEs with comparable THC/CBD products (2 RCTs, 1.1% vs. 2.2%, RR 0.68, 95% CI 0.04 to 10.85, I^2=38%, Appendix D, Figure D-3).[45,48]

Five RCTs reported on study withdrawals due to adverse events (WAEs). Pooled analysis of these results found no difference between comparable THC to CBD ratio products versus placebo in risk of WAEs, though the estimate was imprecise (5 RCTs, 12.5% vs. 10.2%, RR 1.14, 95% CI 0.65 to 3.02, I^2=51%, Appendix D, Figure D-4).[45,46,48,49,51]

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).[50] Dizziness occurred significantly more in the THC/CBD groups than placebo groups (6 RCTs, 30% vs. 8%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%, Appendix D, Figure D-5).[45-49,51]

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, I^2=0%, Appendix D, Figure D-6).[45-49,51] 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, I^2=0%, Appendix D, Figure D-7).[45-49,51]

Key Points for High-THC to CBD Ratio

- No new RCTs evaluated high-THC to CBD ratio products.
- All RCT results are short-term (4 weeks to <6 months) in duration
- Based on previously included studies, synthetic high-THC to CBD ratio (100% THC) products were associated with a moderate improvement in pain severity (6 RCTs, N=390, 0 to 10 scale, MD −1.15, 95% CI −1.99 to −0.54, I^2=48%) and no effect on overall function or disability (2 RCTs, N=unclear, 0 to 10 scale, MD −0.35, 95% CI −1.9 to 0.94, I^2=72%) (SOE: low).
- Synthetic high-THC to CBD ratio (100% THC) products were associated with a moderate increase in risk of sedation (3 RCTs, N=335, 19% vs. 10%, RR 1.73, 95% CI 1.03 to 4.63, I^2=28%) (SOE: low), and dizziness (2 RCTs, N=132, 32% vs. 11%, RR 2.74, 95% CI 1.47 to 6.86, I^2=40%) (SOE: moderate).
- Synthetic high-THC to CBD ratio (100% THC) products were associated with a moderate increased risk of study withdrawal due to adverse events (4 RCTs, N=357, 13% vs. 9%, RR 1.72, 95% CI 0.90 to 4.13, I^2=0%) and a large increased risk of nausea (2 RCTs, N=302, 12% vs. 6%, RR 2.19, 95% CI 0.77 to 5.39; I^2=0%), but the differences did not reach statistical significance.
- Plant-based, extracted high-THC to CBD ratio products were associated with a large increased risk of study withdrawal due to adverse events (1 RCT, N=277, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33), 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 insufficient.
- The combined evidence for extracted and synthetic high-THC to CBD ratio products found a moderate improvement in pain severity (8 RCTs, N=684, −1.25, 95% CI −2.09 to −0.71, I^2=58%) (SOE: moderate).

Summary of Findings for High-THC to CBD Ratio

No new RCTs evaluated high-THC to CBD ratio products. Eleven RCTs included in the original report studied products with a high-THC to CBD ratio,[37,52-61] with nine RCTs of synthetic THC (100% THC: 3 dronabinol, 100% THC analog: 6 nabilone),[37,54-61] and two products extracted from whole-plant cannabis (one with a 48:1 and the other with a 2:1 THC to CBD ratio).[52,53] Synthetic dronabinol and nabilone are available by prescription and are FDA-approved for nonpain indications. The availability of Namisol® is unclear though it is manufactured in The Netherlands and may be available in some European countries. Other extracted and high-THC whole-plant products are available in the United States, where allowed, though the availability of specific products is unclear.

Six of the synthetic THC RCTs were placebo-controlled,[37,57-61] and three were active-controlled crossover trials.[54-56] Both studies of THC extracted from whole-plant were placebo-controlled. All of the RCTs were short duration (4 weeks to 6 months followup). Additionally, two short duration observational studies,[44,64] including a new study[44] comparing a synthetic THC

versus plant-based comparable THC to CBD ratio product, were included. The evidence for synthetic and plant-derived products are presented below separately. Where meta-analyses could be conducted for placebo-controlled trials, the data for both types of products are presented on one plot, stratified by type, with subgroup analyses conducted when possible.

Synthetic THC

Nine RCTs (N=467; 3 dronabinol [including one trial[37] of plant-derived dronabinol, Namisol®] and 6 nabilone)[37,54-61] evaluated synthetic THC for treating chronic pain. Six of the trials enrolled patients with neuropathic pain (3 multiple sclerosis [MS], 1 each painful diabetic neuropathy, spinal cord injury, and mixed neuropathic pain conditions),[54,56,57,59-61] and one each in patients with chronic abdominal pain,[37] medication overuse headache,[55] and fibromyalgia.[58] All studies were of short-duration followup, ranging from 4 to 14 weeks of active treatment. Both medications were titrated upward, with a maximum dose of 15 to 20 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 period prior to randomization.[59] 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 treatment or placebo. Thirty percent of patients (11/37) were withdrawn from the study during the run-in period.

Six trials were parallel design 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).[60] The other three RCTs were crossover trials with an active control arm; one using diphenhydramine as an active control (47 weeks),[56] another using ibuprofen (8 weeks),[55] and the third using dihydrocodeine (6 weeks).[54] Risk of bias was high in two trials,[56,61] moderate in four,[37,54,58,60] and low in three.[55,57,59] The mean age of participants was 50 years, and 61 percent were female. Race was poorly reported, with only three trials reporting 5.4 percent of participants being non-White. Three studies allowed patients to continue taking their current medication for pain, not specifically excluding opioids or requiring their discontinuation,[37,57,58] with one specifically allowing tramadol as rescue medication for acute pain during the trial.[57] The other studies required patients to discontinue opioid use before the study[54,56] or did not report baseline opioid use or use during the study period.[55,59-61] Five parallel design placebo-controlled trials (2 dronabinol, 3 nabilone) excluded patients with prior cannabis use.[37,57-60] One crossover designed trial (nabilone vs. dihydrocodeine) excluded patients with prior cannabis use.[54]

A small (n=156), moderate risk of bias cohort study evaluated nabilone and gabapentin in patients with neuropathic pain of various types for six months.[64] Patients were prospectively allowed to initiate nabilone or gabapentin, or to add one of them to pre-existing treatment with the other. The mean dose at 6 months was 3 mg per day for nabilone and 2,296 mg per day for gabapentin.

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 THC

Based on pooled analysis of six RCTs, synthetic high-THC to CBD ratio products were associated with moderate improvements in pain severity (6 RCTs, 0 to 10 scale, MD −1.15, 95%

CI −1.99 to −0.54, I^2=48%; Figure 4).[37,57-61] Results were similar when the trial of Namisol® was excluded (5 RCTs, MD −1.20, 95% CI −2.51 to −0.24, I^2=48%). Stratified analysis showed that the pooled effect estimate for nabilone (MD −1.59, 95% CI −2.49 to −0.82, I^2=0%) was somewhat larger than with dronabinol (MD −0.52, 95% CI −1.43 to 0.07, I^2=0%; Appendix D, Figure D-8, Table D-6), but the difference was not statistically significant (p=0.08).[37,57-61] A single, low risk of bias RCT (n=26) of patients with diabetic neuropathy reported on pain response (≥30% improvement from baseline), finding a large effect with nabilone (85% vs. 38%, RR 2.20, 95% CI 1.06 to 4.55).[59]

Three RCTs reported on overall function (including pain interference) or disability.[59-61] Pooled analysis of two RCTs of nabilone (N=41) did not find a statistically significant difference between synthetic high-THC and placebo (0 to 10 scale, MD −0.35, 95% CI −1.9 to 0.94, I^2=72%; Appendix D, Figure D-9). The third RCT (n=13) reported that neither group had a change in disability, measured with the Bartell Index (no data reported).[61]

Few synthetic THC studies reported on secondary outcomes. A small (n=26), low risk of bias RCT of patients with diabetic neuropathy reported no difference in depression using the Hospital Anxiety and Depression-D [HADS-D] scale (0 to 10, MD −0.4, 95% CI −1.26 to 1.46), but statistically significantly improved anxiety (HADS-A, 0 to 10 scale, MD −2.9, 95% CI −3.80 to −2.0) with nabilone after five weeks.[59] Quality of life findings were mixed, with a statistically nonsignificant difference between groups using the 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 four weeks with nabilone than with placebo (MD −12.07, p<0.02). Using the anxiety questions on the FIQ, anxiety was significantly improved in the nabilone group after 4 weeks (FIQ anxiety questions, 0 to 10 scale, MD −2.2, p<0.01).[58] Depression was not significantly improved using the FIQ. The three RCTs that allowed opioid use during the study period did not report on the effect of the study medications on opioid use.[54,57,58]

Adverse events were poorly reported. The most commonly reported was WAEs. Pooled analysis of WAEs in four trials showed a statistically nonsignificant increase with synthetic THC (13% vs. 9%, RR 1.72, 95% CI 0.90 to 4.13, I^2=0%, Appendix D, Figure D-10). Of these four studies, two evaluated nabilone[58,60] (7% vs. 4%, RR 1.54, 95% CI 0.14 to 17.71, I^2=0%) and two evaluated dronabinol[37,57] (17% vs. 9%, RR 1.73, 95% CI 0.79 to 5.87, I^2=18%, Appendix D, Figure D-11), with no statistically significant differences between subgroups (p=0.91). 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-12).[57,59] A single study reported SAEs and found a non-statistically significant increased risk with dronabinol (n=240, 10% vs. 6%, RR 1.60, 95% CI 0.65 to 3.93).[57]

Specific adverse events of interest were reported more often in the synthetic THC groups, reaching statistically significant differences with dizziness (2 dronabinol RCTs, 32% vs. 11%, RR 2.74, 95% CI 1.47 to 6.86, I^2=40%, Appendix D, Figure D-13)[37,57] and sedation (3 RCTs, 1 nabilone, 2 dronabinol, 19% vs. 10%, RR 1.73, 95% CI 1.03 to 4.63, I^2=28%, Appendix D, Figure D-14).[37,57,58] A sensitivity analysis using the Bartlett's correction resulted in a more imprecise pooled estimate for sedation that was no longer statistically significant (3 RCTs, RR 1.73, 95% CI 0.44 to 15.71, I^2=28%, Figure D-15). In stratified analyses for sedation, the study

of nabilone (n=33) reported a greater magnitude of effect (RR 8.40, 95% CI, 1.16 to 60.84, Figure D-14) than the trials of dronabinol (N=302, RR 1.55, 95% CI 0.84 to 3.07, I^2=0%, Figure D-14) with no statistically significant subgroup differences (p=0.10). Synthetic THC (dronabinol) was also associated with increased risk of nausea, but the estimate was imprecise, and the difference was not statistically significant (2 RCTs, 12% vs. 6%, RR 2.19, 95% CI 0.77 to 5.39, I^2=0%, Appendix D, Figure D-14).[37,57]

Active-Control Studies of Synthetic THC

Three previously included crossover RCTs[54-56] and one observational study,[65] compared a synthetic cannabinoid with active-controls. One high risk of bias trial used diphenhydramine as the control (47 weeks),[56] another low risk of bias trial used ibuprofen (8 weeks),[55] and the third moderate risk of bias trial used dihydrocodeine (6 weeks).[54] None of the crossover trials reported pain response (≥30% reduction in pain from baseline). In a 6-week RCT of patients with neuropathic pain (n=96 randomized, 73 analyzed) comparing nabilone versus dihydrocodeine (30 to 240 mg per day), dihydrocodeine resulted in greater reduction in pain severity (VAS 0 to 100 scale; MD −5.7, 95% CI −10.9 to −0.5, p=0.03).[54] There were no statistically significant differences in secondary outcome measures (depression, anxiety, quality of life, or sleep). While the study indicated patients could continue to use other drugs for pain, it was not clear what those were or if new drugs (including other opioids) were started outside of the protocol.

A low risk of bias RCT of nabilone and ibuprofen (400 mg per day) in patients with medication overuse headache (n=60) found that after 8 weeks of treatment, there was not a significant difference in pain severity between treatments.[55] There were no statistically significant differences in secondary outcomes measured (depression, anxiety, and quality of life). There were no differences in rates of any adverse events or WAEs (SAEs were not reported). Analgesic intake and dependence for headache control were measured at baseline and 2 weeks after the end of study, but the specific medications were not reported, except that the most common form of analgesic consisted of "combination medications." At two weeks post-study, treatment with nabilone resulted in lower daily analgesic intake than after ibuprofen (0.89/d vs. 1.34/d; p=0.03).[55] Although overall rates were low, dizziness (7.7% vs. 0%) and cognitive deficits (3.8% vs. 0%) occurred more frequently when taking nabilone, while nausea (3.8% vs. 7.7%) and sedation (0% vs. 3.8%) occurred more frequently with ibuprofen.

In the very small (n=7), high risk of bias RCT comparing dronabinol with diphenhydramine in patients with spinal cord injury, pain intensity did not differ between treatments.[56] No other outcomes were reported for efficacy. More patients withdrew from the study when assigned to nabilone (2 of 7 patients), and dry mouth, constipation, fatigue, and drowsiness were reported in similar numbers of patients for both groups.

A moderate risk of bias, prospective observational study of nabilone and gabapentin (or the combination, not reported here) among patients with mixed neuropathic pain found no difference in pain severity between groups at 3 months. 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.[64] There were no differences in pain interference, quality of life, depression, or anxiety at 6 months. Overall adverse events were lower in the nabilone group (47% vs. 35%), and no SAEs were reported. WAEs were also lower in the nabilone group (10% vs. 23%). More patients in the gabapentin group reported sedation (60%) than in the nabilone

group (35%). Dizziness was reported in similar proportions of patients in the groups (33% vs. 39%).

Head-To-Head Comparisons Of Cannabis-Based Products

One new retrospective cohort study (n=774) compared nabiximols oromucosal spray (plant-based comparable THC to CBD ratio) versus oral dronabinol (synthetic 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), using a propensity matched analysis.[44] 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, pain intensity improved more in the nabiximols group than the dronabinol group, though 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]). Nabiximols were also associated with greater percent improvement in function versus dronabinol (76.0% vs. 68.3% on the modified Pain Disability Index, $p<0.001$), though the difference was small. Nabiximols were also associated with greater percent improvements in quality of life, anxiety, and depression, and higher likelihood of discontinuing all rescue analgesics (75.6% vs. 45.9%, RR 1.7, $p<0.001$). Nabiximols were associated with 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) than dronabinol. 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 placebo-controlled RCTs (N=294) included in the original report studied THC extracted from whole-plant cannabis, with different ratios of THC to CBD.[52,53] A 12-week, moderate risk of bias RCT of 277 patients with pain due to MS studied a product described as an extract from *Cannabis sativa* L. using an extraction medium of ethanol 96 percent. The product contained 2.5 mg of THC and CBD in the range of 0.8 to 1.8 mg per soft gelatine capsule.[53] Dosing was THC 2.5 mg twice daily titrated to a maximum daily dose of 25 mg/day or placebo (mean not reported). More than half of patients enrolled were using an analgesic at baseline, but the type or whether they could continue use during the trial was not reported; patients using cannabis within 30 days of study enrollment were excluded.[53] An 8-week, low risk of bias RCT of 17 patients with fibromyalgia studied low-dose, sublingual THC oil.[52] The product contained 24.44 mg/mL of THC and 0.51 mg/mL of CBD; a 48 to 1 THC to CBD ratio, and small quantities of other cannabinoids, but the extraction process was not described. Dosing was described as starting with THC 1.2mg/CBD 0.02 mg oil per dropper-full (a 60 to 1 ratio) given as a single daily dose. The mean daily dose was 4.4 mg THC/0.08 mg CBD in the active treatment group. The dose of CBD in this preparation was described as so low as to not contribute meaningfully to outcomes. Twenty five percent of patients had used an opioid prior to the study, but did not report on opioid use during the trial.

In pooled analysis, pain severity was improved with the extracted 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, I^2=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

specific pain condition (fibromyalgia vs. multiple sclerosis), resulting in 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 (MD −3.92, 95% CI −5.98 to −1.86)[52,53] on pain than the larger (n=277) 12-week study of a much higher dose of extracted cannabis (MD −0.90, 95% CI −1.49 to −0.31).[52,53] Pain response was not reported.

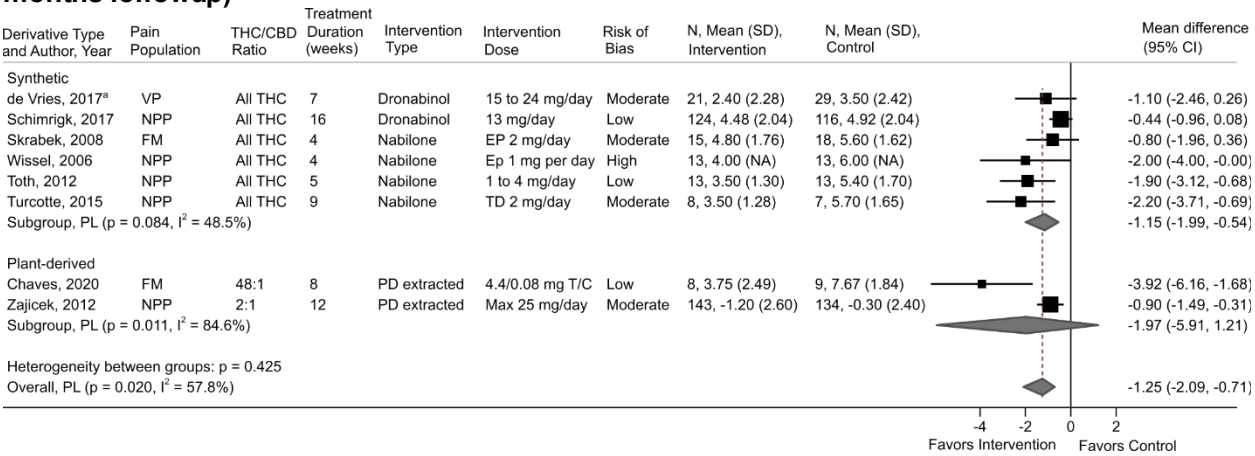
In patients with fibromyalgia, physical functioning was not improved (1 RCT, FIQ subscale 0 to 10, MD 1.75, 95% CI −0.46 to 3.98) compared with placebo.[52] Quality of life was improved with extracted THC (1 RCT, FIQ scale 0 to 100 scale, MD 36.0, p=0.005).[52] These analyses did not adjust for potentially important differences in baseline scores between groups. Differences in depression and anxiety were not found between groups.

In patients with MS there was a higher risk of WAEs, (1 RCT, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33), and dizziness (1 RCT, 62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34) with extracted THC compared with placebo.[53] An increased risk of SAEs was also found, but the difference did not reach statistical significance (1 RCT, 4.9% vs. 2.2%, RR 2.19, 95% CI 0.58 to 8.28). In patients with fibromyalgia, there was a large increased risk of somnolence with extracted THC (1 RCT, 88% vs 11%, RR 7.9, 95% CI 1.2 to 50.9).[52] No other adverse events of interest were 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 or extracted), we combined results from all studies of high-THC to CBD ratio interventions (Figure 4). The overall combined mean difference is −1.25 (95% CI −2.09 to −0.71, I^2=50%). Although there is substantial statistical heterogeneity in the overall pooled estimate, subgroup analysis of synthetic versus plant-extracted forms of high-THC (Appendix D, Table D-7) did not find statistically significant differences in estimates of effect (p=0.42). This analysis allowed evaluation of publication (small-study size) bias (≥8 studies). Both the funnel plot and the Egger test (p=0.006) indicated potential publication bias, with smaller studies with small effect sizes missing (Appendix I, Figure I-1).

Figure 4. Change in pain severity with high-THC ratio versus placebo (short term, 4 weeks to 6 months followup)



Abbreviations: CBD = cannabidiol; CI = confidence interval; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; THC = tetrahydrocannabinol; VP = visceral pain; WP = whole plant.

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

Key Points for Low-THC to CBD Ratio

- In the *short-term,* one new RCT (n=129) of synthetic oral CBD (low-THC to CBD ratio) had insufficient evidence to draw conclusions.
- In the *short-term*, one previously included RCT (n=29) of topical CBD (low-THC to CBD ratio) had insufficient evidence to draw conclusions.

Summary of Findings for Low-THC to CBD Ratio

Two trials (N=158) evaluated CBD (low-THC to CBD) products versus placebo.[43,62] One new RCT assessed a synthetic oral CBD product (cannabidiol)[43] and one previously included RCT assessed topical CBD oil.[62]

A moderate risk of bias RCT (n=129) assessed synthetic oral CBD versus placebo in patients with hand osteoarthritis and psoriatic arthritis over a period of 12 weeks (median age 62, 44% female).[43] Patients received 10 mg CBD tablets twice daily; if a 20 percent reduction in pain was not achieved in the first 4 weeks, patients increased their dose to 30 mg day. There were no differences between CBD and placebo in likelihood of pain improvement (≥30%; RR 1.01, 95% CI 0.66 to 1.55), pain severity (VAS, 0 to 100 scale, MD 0.23, 95% CI −9.41 to 9.90), or physical function (Health Assessment Questionnaire-Disability Index, 0 to 3 scale; MD 0.03, 95% CI −0.11 to 0.18). There were also no differences in depression, anxiety, or sleep quality. More patients receiving CBD reported any adverse event (56.9% vs. 42.6%; RR 1.33, 95% CI 0.92 to 1.93); the proportion of patients with serious adverse events was similar (3.4% vs. 3.3%, RR 1.05, 95% CI 0.15 to 7.22) and there were few withdrawals due to adverse events (0% vs. 3%, RR 0.19, 95% CI 0.01 to 3.86).

A small (n=29), high risk of bias RCT evaluated topical CBD oil in patients with neuropathic pain (mean age 68 years, 38% female).[62] Patients were randomized to four weeks of CBD cream (250 mg/3 oz) applied to symptomatic areas up to 4 times daily or placebo; the total daily dose received was not reported. Improvement in pain intensity was statistically significantly greater in the CBD group versus the placebo group (−1.34 vs. −0.59, p=0.009 by ANCOVA). It was not clear if the analysis also included a crossover extension phase wherein patients initially randomized to placebo were given CBD. A planned analysis taking baseline score into account

was not reported. This study did not report pain response, pain interference, overall function/disability, or secondary outcomes. No adverse events were reported. In addition, this study was not registered in an online repository, and there were serious ethical concerns, as the study authors reported that they were unable to obtain institutional review board approval yet proceeded with conducting the trial.

Key Points for Other Cannabinoids

- In the *short-term*, evidence on cannabinoids other than THC and CBD was insufficient to draw conclusions (1 RCT, N=31)

Summary of Findings for Other Cannabinoids

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").[63] 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 Points for Whole-Plant Cannabis and Mixed (Patient-Choice) Cannabis Products

- No new studies evaluated whole-plant cannabis or mixed (patient-choice) cannabis products.
- Based on previously included studies, 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,[66-68] or self-reported use of cannabis,[69,70] and one moderate risk of bias study evaluating a specific whole-plant cannabis product.[65] 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),[68] and the other five were long duration (1 to 4 years observation).[65-

[67,69,70] 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).[65-67] Two of the studies are retrospective analyses of larger prospective cohort studies of patients with chronic pain taking opioids,[69,70] 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.[65] Total daily doses received were reported in two studies with one reporting 93 mg of THC per week (mean) in a medical cannabis program,[68] and the other reporting 2.5 grams per day of a whole-pant cannabis product (dose confirmed with study authors).[65]

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.[68] A moderate risk of bias study of opioid users also reported no statistically significant differences on pain or pain interference outcomes between frequent cannabis users (daily or near-daily)[69] 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.[65] 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 serious adverse events 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 withdrawal due to adverse events was 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.[66,67,69,70] 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 odds ratio [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 opioid users with chronic pain, a statistically nonsignificant difference in OME use at one year was found between patients reporting daily or near daily cannabis use (type and dose reported) and those reporting no use.[69] 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.[70] 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).[67] 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 with chronic pain, what are the benefits (KQ 3) and harms (KQ 4) of kratom or other plant-based substances for treatment of chronic pain?

Key Points

- 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 pain with plant-based compounds include their effectiveness and safety in treating chronic pain 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 is the first annual update for a living review on cannabis and other plant-based compounds for chronic pain. As in the original report, no studies of plant-based compounds other than cannabis were identified. Although two new studies were added for this update (one placebo-controlled trial RCT of an oral low-THC to CBD ratio product[43] and one observational study comparing different cannabis-related products[44]), they did not impact overall findings because they were the sole study to evaluate these comparisons and had methodological limitations and imprecision.

Overall, including previously reviewed evidence, our findings are applicable to the *short-term* treatment (1 to <6 months), in patients with chronic pain (mainly neuropathic pain) compared with placebo. Change in pain severity was reported across all studies, but other pain-related and overall functional outcomes (including pain interference) were reported sporadically.

Comparable tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio oromucosal spray is probably associated with small improvements in pain severity (strength of evidence [SOE]: moderate) and overall functioning (SOE: low) versus placebo in the short-term. Combined THC/CBD may also be associated with a moderate to large increased risk of dizziness, sedation and nausea versus placebo, with no effect on serious adverse events or WAEs. There was a small increase in the proportion of patients with at least 30 percent improvement in pain (pain response) versus placebo; while the SOE was low, the finding was not statistically significant due to imprecision. For secondary outcomes, sleep quality was improved in the treatment groups, and quality of life was not different between groups.

Synthetic oral THC (which had high-THC to CBD ratios) products may be associated with moderate improvement in pain severity and no effect on overall function (SOE: low). They are probably associated with a large increase in risk of dizziness (SOE: moderate) and may be associated with large increased risk of nausea and moderate increased risk of sedation (SOE: low). There was a moderate increase in the proportion of patients that withdrew from studies due to adverse events; the SOE was low, but the finding was not statistically significant due to inadequate sample size (imprecision). For secondary outcomes, evidence was very limited with no clear effect on quality of life or depression, and inconsistent results for anxiety and global disease improvement for patients with fibromyalgia treated with synthetic high-THC to CBD ratio products.

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 (SOE: low). For secondary outcomes, a single study found no difference between groups in depression or anxiety. Combining the evidence for all high-THC to CBD ratio products resulted in a moderate improvement in pain severity, with a low SOE.

Evidence on whole-plant cannabis, mixed forms of cannabis (patient-choice), low-THC to CBD ratio products (topical or synthetic oral CBD), other cannabinoids (cannabidivarin

[CBDV]), and comparisons with other active interventions or between cannabis-based products were insufficient to draw conclusions. Similarly, evidence for other outcomes reported for comparable THC to CBD and high-THC to CBD ratio products was insufficient. See Appendix G for details.

Other adverse events (psychosis, CUD, cognitive deficits) and secondary outcomes were not reported for any product.

While there are no applicable clinical practice guidelines with which to compare these results, 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.[16,71-73] 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. These prior reviews combined all forms of cannabinoids in meta-analyses. Our review has more stratified results based on the pre-specified THC to CBD ratio categories, leading to a higher strength of evidence rating in some cases.[16] Although these were high-quality reviews, they are not current and may be missing newer evidence. An additional four unrelated systematic reviews examining utility of cannabis for chronic pain were published in 2020; overall, these findings are also consistent with our findings.[74-77] One of the reviews conducted meta-regression, finding that the impact on pain was similar between neuropathic and non-neuropathic pain populations[76] 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.[23,24] 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 five 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%).[24]

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)

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	Insufficient (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 7. 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 (2) [+]	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.

Strengths and Limitations

The evidence base on cannabis and other plant-based treatments for chronic pain has multiple important limitations. Seventy-one percent of trials enrolled patients with chronic pain due to a

neuropathic cause (6 in patients with multiple sclerosis, 4 with a mix of conditions or not specified, 2 with diabetic neuropathy, and 1 each with chemotherapy, HIV, 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. In terms of age, there is limited evidence on younger and older populations, with most patients being middle-aged (mean age 52 years). 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 detailing the interventions and products studied. For example, products are described as extracted 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 did not consistently report the ratio of THC to CBD in the products, particularly outside of the products that are close to a 1 to 1 ratio (oromucosal spray, Sativex). Other limitations include the complete lack of evidence on other plant-based compounds like kratom, no randomized controlled trial (RCT) evidence on whole-plant cannabis products, and only a single, small study each for topical 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 7 of 29 studies (24%); 19 of 28 studies (68%) reported on overall function (including pain interference) or disability. The studies poorly reported baseline use of opioids for pain, and only observational studies (5 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, 48 percent did not report serious adverse events, and 59 percent did not report the overall adverse events, particularly by group. When serious adverse events 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); 42 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 serious adverse events may take time to develop and longer studies are required to capture such

events. 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. Also, using an organizational framework that categorizes cannabis-related products by both their THC and CBD ratios and their origin (plant-based versus synthetic) allows 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 *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 the findings to chronic pain.

There are also some limitations to our review process. We excluded non-English language publications and study results published only as abstracts. We categorized nabilone as a synthetic high-THC product though it is more accurately described as a synthetic cannabinoid – a chemical analog to THC, and could have differing effects to THC. 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 Namisol® with synthetic dronabinol, even though Namisol® is a purified plant product, because they are chemically identical (delta-9-THC). However, results for synthetic high-THC to CBD ratio products were similar when the Namisol® trial was excluded. Meta-analyses were based on small numbers of trials, which can result in overly precise estimates using the profile likelihood model. Therefore, we conducted sensitivity analyses using the Bartlett's correction. Although the Bartlett's correction resulted in wider confidence intervals 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 no longer statistically significant using the Bartlett's correction. However, the Bartlett's correction may result in overly conservative (wide) confidence intervals when the number of studies is small; additional studies examining sedation would help increase precision. Our inclusion criteria required that the study population have chronic pain, or have subgroup analyses for this group, which may be why we did not find evidence related to kratom. We were unable to assess publication bias (small sample size bias) for most outcomes, as most meta-analyses included fewer than eight studies. The exception was the analysis of change in pain severity with high-THC interventions, where we were unable to rule out important publication bias. Additional studies are needed to clarify the effect size estimates and our confidence in the findings. Since this is a living systematic review, new evidence will be incorporated into the review and findings updated on a regular basis. 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.[11,12] 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.

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 6.4 on a 0 to 10 scale, with a range of 4.4 to 8.1). 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.

The evidence base is generally applicable to women with around 56 percent of enrolled participants being female across all studies. 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 52 years). Currently, the evidence is poorly applicable to patients of non-White race. 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 applicable to comparable THC to CBD ratio oromucosal spray and to high-THC synthetic medications. 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 drugs applies to dosing that was titrated upward, with a maximum dose of 15 to 24 mg per day of dronabinol and 0.25 to 2 mg per day of nabilone (mean doses not reported). For high-THC to CBD products extracted from whole-plants, the evidence was too heterogeneous and limited (2 RCTs) to describe an applicable dose. Applicability to other products including 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, Namisol® is manufactured in the Netherlands and may be available in some European countries, but is not FDA-approved at this time. Nabiximols are manufactured and available in Canada and some European countries, but are not FDA-approved. 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). None of the studies reported other information relevant for assessing applicability, such as the description of the source of potential study participants or the number of women randomized relative to the number of women enrolled.

Only 17 percent of studies were conducted in the United States, with the majority being from Europe (52%), and 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 interventions, whole-plant cannabis, and kratom.

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

The implications of the present findings for clinical practice are mixed. Our results suggest that select individuals with chronic neuropathic pain may experience moderate short-term improvements in pain when using cannabis products (synthetic or extracted from whole-plant) that have a high-THC to CBD ratio. The impact of this intervention on moderate or long-term outcomes is unknown. Cannabis products with a comparable THC to CBD ratio may also result in small improvements in pain severity. Those who take products containing comparable or high ratios of THC are also at increased risk for adverse events, including dizziness, sedation and nausea. The expected benefit of this treatment appears comparable to those observed with prescription opioids, several nonopioid medications, and nonpharmacological interventions.[11-13] 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 appears to be larger with opioids and the antidepressant duloxetine than with cannabis-related products. However, these comparisons are qualitative and indirect and 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 cannabis products' adverse event profiles 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.

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 address the opioid epidemic, 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 leads to several important additional questions that could be addressed most effectively in a clinical practice guideline. Examples of questions that could be best 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? And finally, what are the comparative effects on costs of care?

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 pain

PICOTS Element	Gap in Evidence	Suggested Future Research
Populations	• Non-White populations, older adults, women • Pain conditions other than neuropathic pain	• Studies to assess possible differential effects in different races or ethnicities • Stratified analyses according to sex, including effects in pregnant and lactating persons • Studies to assess effects based on age differences • Pain populations expanded to include persons with non-neuropathic chronic pain, specifically back pain, other musculoskeletal pain, and fibromyalgia
Interventions	• High THC to CBD ratio from plant origin (not synthetic) • Comparable THC to CBD ratio formulations other than oromucosal spray • Low THC to CBD ratios, whole-plant cannabis, and other cannabinoids • Kratom	• Studies of high THC to CBD ratio products derived from whole-plant cannabis, with clear description of extraction or purification process and consistent nomenclature regarding the final product • Studies to compare different routes of administration (e.g., oromucosal spray, oral oil, oral capsule, smoked, etc.) • Studies should include and compare standardized treatment plans • Exploration of effects of different cannabinoids • Studies to asses kratom and/or other plant-based treatments
Comparators	• Head-to-head comparisons	• 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
Outcomes	• Pain response (>30% improvement in pain severity) • Overall function, quality of life • Depression, anxiety, sleep, opioid use • Adverse event outcomes	• Outcomes should be consistently defined and reported across studies; ideally a core set of outcomes should be developed for future 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., QOL, 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	• Considering the chronic nature of the conditions, studies should provide followup assessments at longer timepoints, e.g., ≥3, 6 or 12 months

PICOTS Element	Gap in Evidence	Suggested Future Research
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	• All Designs: o Studies with larger sample sizes to adequately power statistical analyses for key outcomes are needed across all interventions except the synthetic medications o 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: o Should be conducted prospectively where possible, and conduct and report on ascertainment and validation of exposure and outcomes following best-practice guidance[78] o 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: o Should not use run-in periods, or enriched enrollment randomized withdrawal designs that may overestimate effects and limit the generalizability of the findings[79] o Should be conducted using the parallel design (not crossover) • Systematic Reviews o 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

As in the original report, the first annual update to our living systematic review found that 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.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ANCOVA	analysis of covariance
BPI-SF	Brief Pain Inventory – Short Form
CBC	cannabichromene
CBD	cannabidiol
CBDV	cannabidivarin
CBG	cannabigerol
CI	confidence interval
CUD	cannabis use disorder
DAS28	28-Joiny Disease Activity Scale
EPC	Evidence-based Practice Center
FIQ	Fibromyalgia Impact Questionnaire
FM	fibromyalgia
GHQ-12	Short General Health Questionnaire
GNDS	Guy's Neurological Disability Scale
HADS-D	Hospital Anxiety and Depression Scale
IA	inflammatory arthritis
KQ	Key Question
MCID	minimal clinically important difference
MCP	New Mexico Medical Cannabis Program
MD	mean difference
MS	multiple sclerosis
NA	not applicable
NPP	neuropathic pain
NR	not reported
NRS	numerical rating scale
ODI	Oswestry Disability Index
OME	oral morphine equivalent
OR	odds ratio
PBC	plant-based compound
PDI	Pain Disability Index
PICOTS	populations, interventions, comparators, outcomes, timing, and settings
PL	profile likelihood
QOL	quality of life
RA	rheumatoid arthritis
RCT	randomized controlled trial

RDQ	Roland-Morris Disability Questionnaire
ROB	risk of bias
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SEADS	Supplemental Evidence and Data for Systematic review
SF-36	Short Form-36
SMD	standardized mean difference
SOE	strength of evidence
SRDR+	Systematic Review Data Repository Plus
THC	tetrahydrocannabinol
TOO	Task Order Officer
VAS	visual analogue scale
VP	visceral pain
WAE	withdrawal due to adverse events
WP	whole plant