Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain – Quarterly Progress Report: February 2021

Overview

This is the second progress report for an ongoing living systematic review on plant-based treatments for chronic pain. The ensuing systematic review will synthesize evidence on the benefits and harms of cannabinoids and other plant-based compounds (PBCs) such as kratom used to treat chronic pain, addressing the impact on pain and function, as well as concerns about adverse effects, abuse, misuse, dependence, and addiction.

The purpose of this progress report is to describe the body of literature identified thus far. This report will be periodically updated with new studies as they are published and identified, culminating in a systematic review that provides a synthesis of the accumulated evidence.

Background

Chronic pain is defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,[1,2] and it affects approximately 100 million people in the United States.[3] Chronic pain adversely affects physical and mental functioning, productivity, and quality of life, and is often refractory to treatment and associated with substantial costs.[4-6]

While opioids are often prescribed for chronic pain, a recent series of systematic reviews found that opioids,[7] several nonopioid drugs,[8] and some nonpharmacologic treatments[9] have small to moderate effects on pain and function, with some frequent adverse effects and some less frequent but serious adverse effects. The 2016 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends that nonopioid therapy is preferred for treatment of chronic pain.[1,2] The limited efficacy of opioids and the ongoing opioid crisis drive a search for alternative pain treatments, including PBCs such as cannabis and related compounds, as some data suggest they may have analgesic properties.[10]

The term *cannabinoid* refers to a group of closely related compounds that are active in cannabis, with the two main cannabinoid compounds being tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has demonstrated analgesic properties,[11,12] although its psychoactive effects and abuse potential may limit its suitability as an analgesic. CBD and other cannabinoids may also have some analgesic or anti-inflammatory properties and are not thought to be psychoactive or addictive.[13,14] While not derived from plants, two synthetic THC drug products, dronabinol and nabilone, are approved for use in the United States by the Food and Drug Administration. Their approvals are not for treating pain, but for treating nausea and vomiting associated with chemotherapy and for anorexia associated with HIV. However, because they contain THC, they have also been studied for treating chronic pain. Other PBCs with effects similar to opioids or cannabis, such as kratom, may be considered to treat chronic pain. These may also have serious harms, such as dependence, addiction, and withdrawal potential.

Four Key Questions (KQs) guide the review:

KQ1: In adults with chronic pain, what are the benefits of cannabinoids for treatment of chronic pain?

KQ2: In adults with chronic pain, what are the harms of cannabinoids for treatment of chronic pain?

KQ3: In adults with chronic pain, what are the benefits of kratom or other plant-based substances for treatment of chronic pain?

KQ4: In adults with chronic pain, what are the harms of kratom or other plant-based substances for treatment of chronic pain?

The protocol for the systematic review can be found at: https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/protocol.

Methods

This report builds and expands on two prior systematic reviews on treatments for chronic pain (one on opioids[7] and one on nonopioid treatments[8]), which included a small number of trials on cannabinoids. The inclusion criteria in this review are broader than the criteria in the two previous systematic reviews in that we now include any comparator instead of only head-to-head comparators and have reduced the minimum study duration to 1 month (or 4 weeks) instead of 3 months. The full inclusion and exclusion criteria for this report are in Appendix A.

In brief, we searched Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through February 1, 2021, for studies of patients with chronic pain for at least 4 weeks of treatment or followup. We selected studies of cannabis, kratom, and similar PBCs compared with a placebo, no treatment, each other, or another treatment. Pain is the primary outcome for this review; details on included primary and secondary outcomes are in Appendix A and search strategies are in Appendix B.

We followed the methods guidance in the Agency for Healthcare Research and Quality Methods Guide,[15] and we abstracted key information and conducted risk of bias assessments for each included study. Our methods include categorizing the duration of studies as short-, intermediate-, and long-term, and the magnitude of effects as small, moderate, and large.

A more detailed discussion of methods can be found in the protocol.

Results to Date

Results Overview

Across the monthly literature searches, 2,632 citations were screened, from which we identified a total of 23 eligible studies,[16-38] 6 of which are new to this second progress report.[18,20,23,31,36,37] Appendix C contains a list of all 23 included studies, and a literature flow diagram can be found in Appendix D. A list of studies excluded after reviewing the full manuscripts can be found in Appendix E along with reasons for their exclusion. Appendix F contains detailed evidence tables of included studies, and Appendix G contains risk of bias assessments.

Description of the Evidence

Overview

The first progress report summarized the evidence on 14 randomized controlled trials (RCTs) of cannabis-related products and 3 observational studies.[16,17,19,21,22,24-30,32-35,38] In this second progress report, 6 additional RCTs were added,[18,20,23,31,36,37] for a total of 23 included studies assessing the effects of cannabis-related products. (Study characteristics of RCTs are in Table 1.) In total, seven RCTs evaluated products that contain a combination of THC and CBD.[17,22-24,27,29,30] Three RCTs evaluated the effects of plant-derived THC alone.[18,19,38] Eight RCTs evaluated synthetic forms of THC.[21,25,26,28,31-33,36] Also in this progress report is a newly included study that assessed the effect of topical CBD alone[37] and another that evaluated cannabidivarin (CBDV), a phytocannabinoid.[20] No new observational studies were identified.

No studies of kratom or other substances met inclusion criteria.

Table 1. Characteristics of included randomized controlled trials

Characteristic	THC/CBD	THC	Synthetic THC	CBD	CBDV
N Studies	7	3	8	1	1
ROB % High, % Moderate, % Low	29%, 57%, 14%	0%, 67%, 33%	25%, 37.5%, 37.5%	100% high	100% moderate
N, Randomized, Total	882	362	469	29	34
N, Range	18 to 339	18 to 279	9 to 240	NA	NA
N, Mean	126	121	59	NA	NA
Age, Mean Years	56	52	51	68	50
Female, %	67%	79%	62%	38%	3%
Race, % Non-White[a]	1.6% (2)	1.6% (2)	8.1% (2)	NA	NA
Pain Type(s)	NPP (6), RA (1)	NPP (1), visceral pain (1), fibromyalgia (1)	NPP (6), headache (1), fibromyalgia (1)	NPP	NPP
Study Duration, Range	4 to 15 weeks	7 to 12 weeks	4 to 47 weeks	4 weeks	4 weeks

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; NA = not applicable; NPP = neuropathic pain; RA = rheumatoid arthritis; ROB = risk of bias; THC = tetrahydrocannabinol.

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

KQs 1 and 2: Benefits and Harms of Cannabis

Plant-Derived THC and CBD Combination

In the first progress report (published in January 2021),[39] six RCTs (N=864)[18,20,23,31,36,37] evaluated products with a combination of THC and CBD compared with placebo in patients with chronic pain (5 in patients with neuropathic pain).[17,22,24,27,30] All of the RCTs used an oromucosal spray product with 2.7 mg of THC and 2.5 mg of CBD per 100 mcl spray (specified as the product Sativex® in 5 studies). Studies ranged from 5 to 16 weeks in duration of active treatment; the weighted mean daily dose received was 8.4 sprays (21 mg THC/23 mg CBD) for patients assigned to cannabis and 12.7 sprays for those assigned to placebo. The findings are summarized in Table 2. In summary, two trials reported that significantly more patients achieved response (>30% reduction in pain) with cannabis, three reported a significantly lower pain severity, and two reported small but not statistically significant reductions in pain interference. Sleep was

significantly improved in four trials, but function or disability and quality of life were not clearly improved. The THC/CBD groups reported more adverse events than placebo groups in two trials. Specific adverse events of dizziness, nausea, and sedation were most frequently reported and occurred more often in the THC/CBD groups in four trials.

In this progress report, one additional crossover trial (n=16 analyzed; 18 enrolled) of a THC/CBD combination oromucosal spray in patients with neuropathic pain caused by chemotherapy was included.[23] This study had a moderate risk of bias. Although dosing instructions and final number of sprays used per day (8 THC/CBD and 11 placebo) were similar to the other RCTs, the strength of the solution used in the spray was not reported. Attempts to contact the author were unsuccessful. After dose stabilization (days to achieve not reported), patients were treated for 4 weeks. The mean age was 56 years and 83 percent were female. Medications used previously for pain included opioids (n=2), cannabis (n=5), anticonvulsants (n=10), antidepressants (n=1), and nonsteroidal anti-inflammatory drugs (n=2). Use of these medications during the trial was not reported.

Using the Neuropathic Rating Scale (NRS)-Pain Intensity (range 0 to10), pain intensity did not differ between groups at 4 weeks (6.00 vs. 6.38), with the change from baseline less than one point in both groups. The Short Form-36 Physical scale improved more with placebo (increased 13.82 points on a 0 to 100 scale) compared with THC/CBD (increased 2.82 points). Although the study authors reported this as "not statistically significant," our analysis finds the difference to be statistically significant (mean difference −11, 95% confidence interval [CI] −20.49 to −1.51). Adverse event reporting was sparse. Dizziness was reported in six patients while using THC/CBD and none when using placebo, nausea occurred in six while using THC/CBD and one when using placebo, and fatigue occurred in seven while using THC/CBD and none while using placebo. The denominators for these numbers were not clear, as two randomized patients were not included in the analyses, and reasons for this, or the timing of their discontinuation from the trial, were not provided. No other included outcomes were reported.

Plant-Derived Delta-9-THC

In the first progress report,[39] two RCTs (N=344) evaluated THC in patients with chronic pain.[19,38] The RCTs used oral forms of THC, one in tablet form and the other in capsule form, with final total daily doses (after titration) of 15 mg to 24 mg in one study and 25 mg in the other. All of the trials were short in duration, ranging from 7 to 15 weeks. Pain outcomes (response in 1 RCT, severity in 2 RCTs) did not differ statistically, and both RCTs reported more withdrawals due to adverse events (WAEs), serious adverse events (SAEs), dizziness, nausea, and sedation with oral plant-derived THC than with placebo (Table 3).

In this second progress report, one additional RCT evaluated oral plant-derived THC in 17 patients with fibromyalgia (mean age 52 years, 100% female).[18] This was a low risk of bias, 8-week study of low-dose, sublingual THC oil.[18] Study authors described the product as containing 24.44 mg/mL of THC and 0.51 mg/mL of CBD, a 48 to 1 THC/CBD ratio, and small quantities of other cannabinoids. However, dosing is 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 3.6 drops (4.4 mg THC/0.08 mg CBD) in the active treatment group, and 4.3 drops in the placebo group. The dose of CBD in this preparation was considered so low as to not contribute meaningfully to outcomes. Additionally, the THC dose in this study is much lower than in other included studies (4.4 mg/day vs. 15 to 28 mg/day). The authors reported that 25 percent of patients had used an opioid prior to the study, but did not report on opioid use during the study.

This study used the Fibromyalgia Impact Questionnaire (FIQ) to assess outcomes, with individual items of "pain" and "physical function" (0 to 10), which we report below.

Improvement in pain severity was statistically significantly better with THC versus placebo, with a moderate size difference (mean difference −3.92, 95% CI −6.17 to −1.68). Pain response and pain interference, specifically, were not reported. The overall FIQ score scale, which includes some elements on pain interference, improved significantly more in the THC group. Physical functioning, assessed with a subscale of the FIQ (10-point scale), also improved more with THC, but this difference was small and not significant (mean difference 1.75, 95% CI −0.46 to 3.98). Also using subscales of the FIQ, depression and anxiety were assessed and were not different between groups at the study endpoint. Adverse events were poorly reported, with study authors noting that no patients withdrew due to adverse events and that patients assigned to THC reported somnolence (88%) and dizziness (25%), while one (11%) placebo patient reported somnolence.

Synthetic Delta-9-THC

In the first progress report,[39] six RCTs (N= 416)[21,25,26,28,32,33] evaluated synthetic THC (2 dronabinol, 4 nabilone) in patients with chronic pain. Both drugs 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.) Three RCTs compared synthetic THC with placebo, with durations of 5, 9, and 14 weeks.[28,32,33] One of these added nabilone or placebo to gabapentin treatment in patients who had not achieved pain relief (visual analog scale [VAS] score for pain >50).[33] The other three trials were crossover design studies, comparing to diphenhydramine, ibuprofen, and dihydrocodeine.[21,25,26] For the comparisons with placebo, one trial found that synthetic THC was significantly better than placebo in response (≥30% improvement, large difference),[32] while the others did not report this outcome. For improvement in pain severity, two trials reported differing results according to the specific drug: dronabinol was not significantly better,[28] while nabilone was significantly better (moderate difference).[32] This trial also reported that pain interference was significantly better with nabilone than placebo (moderate difference),[32] and that sleep and quality of life were more improved with nabilone, but the difference was not significant. Across the trials, there was a greater incidence of adverse events of any kind with synthetic THC in three RCTs,[25,28,32] WAEs in three,[26,28,33,36] and SAEs in one.[28] Dizziness and sedation were reported more frequently with synthetic THC than placebo in one trial.[28] The findings are summarized in Table 4.

In this second progress report, two additional RCTs (N=51) evaluated synthetic THC, both using nabilone. In a moderate risk of bias RCT, 40 patients with fibromyalgia (mean age 49, 93% women)[31] were randomized to nabilone, titrated up to 1 mg twice daily, or placebo for 4 weeks. The authors noted that the use of opioids at baseline did not differ between groups, but no other information about opioid use was reported. Pain was measured on a 0 to 10 VAS. The other RCT was a high risk of bias crossover trial of 13 patients with pain from multiple sclerosis (mean age 45, 70% female), randomized initially to nabilone (titrated to 1 mg daily) or placebo for 4 weeks.[36] This study reported that three patients had previously or were currently using an opioid for pain. The pain scale was an 11-point scale used to measure spasticity-related pain.

Neither study reported pain response (≥30% improvement in pain). Both studies found that mean pain severity improved more with nabilone than placebo (mean differences of 1.43 to 2.0 on 11-point scales, $p<0.05$). Both differences are considered moderate magnitude of effect. Pain interference, specifically, was not reported in either study. The overall change in the FIQ, which

has some elements of pain interference, was significantly greater in the nabilone group (−12.07, p<0.02) in the study of patients with fibromyalgia.[31] In the RCT of patients with multiple sclerosis, function did not improve with either nabilone or placebo using the Barthel Index.[36] The study of patients with fibromyalgia reported that anxiety improved more with nabilone than placebo (mean difference −1.67, p<0.02 on the FIQ subscale); however, other subscale items such as depression were not reported.[31] Although both trials reported on adverse events, not all included outcomes were addressed. The study of patients with fibromyalgia reported no SAEs and no difference in WAEs (5% vs. 5%). The trial of patients with multiple sclerosis, using a lower dose, found greater WAEs with nabilone (15% vs. 0%) and did not report on SAEs. Drowsiness was reported more frequently with nabilone than placebo in both trials (15% to 47% vs. 6% to 8%). Other adverse events of interest were not reported.

Cannabidiol (CBD)

This second progress report includes a single, small, high risk of bias RCT (n=29) of topical CBD oil in patients with neuropathic pain (mean age 68 years, 38% female).[37] Patients were randomized to 4 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.

The change in pain intensity was statistically significantly greater in the CBD group versus the placebo group (−1.34 vs. −0.59, p=0.009 by analysis of covariance). It was not clear if the analysis also included a crossover extension phase in which 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, function/disability, or secondary outcomes. No adverse events were reported. These findings are summarized in Table 5.

Other Cannabinoids

In this second progress report, a single, small (n=31), moderate risk of bias trial of oral CBDV (described as "a novel phytocannabinoid derived from the *Cannabis* sativa L. plant") was included.[20] 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 NRS pain scale (10-point scale), statistically significantly fewer patients achieved response (≥30% pain reduction) with CBDV compared with placebo (38% vs. 81%, relative risk 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 (mean difference 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). These findings are summarized in Table 5.

KQs 3 and 4: Kratom and Other Plant-Based Compounds

No evidence was identified.

Summary

The first progress report[39] included 17 studies, and 6 studies[18,20,23,31,36,37] have been added in this second progress report. To date, all included studies evaluated cannabinoids and were short term (12 weeks or less in duration). Tables 2 through 5 summarize the current evidence for cannabis-related interventions. No studies of kratom or other substances have been identified thus far. Other adverse events of interest (e.g., emergence of cannabis use disorder, psychosis, opioid use) were not reported in these studies; most of the studies were underpowered and too short to determine these outcomes.

Table 2. Summary of current evidence for plant-derived THC/CBD

Outcome	First Progress Report	Second Progress Report
Count of Studies and Patients	k=6 trials (N=864) / k=1 observational study (N=66)	k=1 trial (N=16)
Strength of Body of Evidence	Pending	Pending
Included Studies Risk of Bias: RCTs/Observational Studies	Moderate/high	High
Study Duration Category	Short (1 to <6 mos)	Short (1 to <6 mos)
Pain Response (≥30% reduction in pain)	Small difference, favoring THC/CBD (3 RCTs; 2 statistically significant)	Not reported
Pain Severity (change)	Small difference, favoring THC/CBD (6 RCTs; 3 statistically significant)	No difference
Pain Interference	Small difference, not statistically significant (2 RCTs)	Not reported
Function/Disability	Inconsistent findings according to scale and population (2 RCTs)	Small difference, favoring placebo
Secondary Outcomes	Sleep improved in THC/CBD groups (5 RCTs; 4 statistically significant), QoL not improved (4 RCTs)	Not assessed
Adverse Events (Any, SAE, WAE)	Higher incidence of AEs in THC/CBD groups (2 RCTs), no clear difference in SAEs or WAEs (4 and 5 RCTs).	Higher incidence of AEs in THC/CBD group, No reported SAEs or WAEs
Specific Adverse Events	Dizziness, nausea, sedation greater with THC/CBD (4 RCTs)	Dizziness, nausea, sedation greater with THC/CBD

Abbreviations: AE = adverse event; CBD = cannabidiol; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse events.

Table 3. Summary of current evidence for plant-derived THC

Outcome	First Progress Report	Second Progress Report
Count of Studies and Patients	k=2 trials (N=344) / k=1 observational study (N=431)	k=1 trials (N=17)
Strength of Body of Evidence	Pending	Pending
Included Studies Risk of Bias: RCTs/Observational Studies	Moderate/high	Low
Study Duration Category	Short (1 to <6 mos)	Short (1 to <6 mos)
Pain Response (≥30% reduction in pain)	Difference not statistically significant, but large absolute difference favoring THC (1 RCT)	Not reported
Pain Severity (change)	Small difference, not statistically significant (2 RCTs)	Moderate difference, statistically significant favoring THC
Pain Interference	Not reported	Not reported
Function/Disability	Not reported	Small difference, not statistically significant

Outcome	First Progress Report	Second Progress Report
Secondary Outcomes	Small difference, not statistically significant (1 RCT)	Small difference in depression, no difference in anxiety, not statistically significant
Adverse Events (Any, SAE, WAE)	Greater WAEs and SAEs in THC groups (2 RCTs)	0 WAEs, other outcomes not reported
Specific Adverse Events	Dizziness, nausea, sedation greater with THC (2 RCTs, 1 cohort study)	Dizziness, sedation greater with THC

Abbreviations: AE = adverse event; CBD = cannabidiol; RCT = randomized controlled trial; SAE = serious adverse event; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse events.

Table 4. Summary of current evidence for synthetic THC

Outcome	First Progress Report	Second Progress Report
Count of Studies and Patients	k=6 trials (N=416) / k=1 observational (N=156)	k=2 trials (N=51)
Strength of Body of Evidence	Pending	Pending
Included Studies Risk of Bias: RCTs/Observational Studies	Low/moderate	Moderate (1 RCT), high (1 RCT)
Study Duration Category	Short (1 to <6 mos)	Short (1 to <6 mos)
Pain Response (≥30% reduction in pain)	Large difference, favoring synthetic THC over placebo (1 RCT)	Not reported
Pain Severity (change)	Moderate difference, favoring nabilone (1 RCT); Small difference, not statistically significant with dronabinol (1 RCT)	Moderate difference, favoring nabilone (2 RCTs)
Pain Interference	Moderate difference, favoring nabilone over placebo (1 RCT)	Not reported
Function/Disability	Not reported	No change from baseline in either group (1 RCT)
Secondary Outcomes	QoL and sleep improved with nabilone vs. placebo, other outcomes: small difference, not statistically significant (1 RCT)	Moderate difference favoring nabilone in anxiety (1 RCT)
Adverse Events (Any, SAE, WAE)	Higher incidence of AEs (3 RCTs), SAEs (2 RCTs), WAEs (2 RCTs) in THC groups vs. placebo	Any AEs not reported; No reported SAEs (1 RCT), higher incidence of WAEs in 1 RCT, no difference in the other (lower dose study)
Specific Adverse Events	Dizziness, sedation greater with THC vs. placebo (1 RCT)	Sedation greater with THC vs. placebo (2 RCTs)

Abbreviations: AE = adverse event; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse events.

Table 5. Summary of current evidence for other cannabinoids newly identified for second quarterly progress report

Outcome	CBD	CBDV
Count of Studies and Patients	k=1 trial (N=29)	k=1 trial (N=32)
Strength of Body of Evidence	Pending	Pending
Included Studies Risk of Bias: RCTs/Observational Studies	High	Moderate
Study Duration Category	Short (1 to <6 mos)	Short (1 to <6 mos)
Pain Response (≥30% reduction in pain)	Not reported	Large difference favoring placebo
Pain Severity (change)	Small difference favoring CBD	Small difference, not statistically significant
Pain Interference	Not reported	Not reported
Function/Disability	Not reported	Not reported
Secondary Outcomes	Not reported	Small differences in anxiety, depression, sleep; not statistically significant

Outcome	CBD	CBDV
Adverse Events (Any, SAE, WAE)	Reported no AEs, no SAEs, or WAEs	Very small differences in any AE, WAEs, SAEs, more frequent with CBDV, but not statistically significant
Specific Adverse Events	Not reported	Not reported

Abbreviations: AE = adverse event; CBD = cannabidiol; CBDV = cannabidivarin; RCT = randomized controlled trial; SAE = serious adverse event; WAE = withdrawal due to adverse events.

Next Reports

A draft systematic review of the evidence is scheduled to be available for public comment in late March 2021. The next (third) quarterly progress report update is scheduled for late May 2021.

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22. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97. doi: https://dx.doi.org/10.1007/s00415-012-6739-4. PMID: 23180178.

23. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014 Jan;47(1):166-73. doi: https://dx.doi.org/10.1016/j.jpainsymman.2013.02.018. PMID: 23742737.

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25. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012 Nov;13(8):677-84. doi: https://dx.doi.org/10.1007/s10194-012-0490-1. PMID: 23070400.

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27. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9. PMID: 16186518.

28. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. Eur Neurol. 2017;78(5-6):320-9. doi: 10.1159/000481089. PMID: 29073592.

29. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.

30. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.

31. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008 Feb;9(2):164-73. PMID: 17974490.

32. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82. doi: https://dx.doi.org/10.1016/j.pain.2012.06.024. PMID: 22921260.

33. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59. doi: https://dx.doi.org/10.1111/pme.12569. PMID: 25288189.

34. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS ONE. 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795. PMID: 29145417.

35. Ware MA, Wang T, Shapiro S, et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015 Dec;16(12):1233-42. doi: https://dx.doi.org/10.1016/j.jpain.2015.07.014. PMID: 26385201.

36. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. J Neurol. 2006 Oct;253(10):1337-41. PMID: 16988792.

37. Xu DH, Cullen BD, Tang M, et al. The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. Curr Pharm Biotechnol. 2020;21(5):390-402. doi: https://dx.doi.org/10.2174/1389201020666191202111534. PMID: 31793418.

38. Zajicek JP, Hobart JC, Slade A, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32. doi: https://dx.doi.org/10.1136/jnnp-2012-302468. PMID: 22791906.

39. McDonagh MS, Wagner J, Ahmed AY, et al. Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain—Quarterly Progress Report: December 2020. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.). 2021 January. AHRQ Publication No. 21-EHC013. doi: 10.23970/AHRQEPCCERPLANTPAIN1

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Disclaimers

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00006). 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 decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care 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.

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Afterword

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 https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

These quarterly progress reports will provide up-to-date information about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this report, 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. They will be considered in the next version of the report.

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Appendix A. Inclusion and Exclusion Criteria

Inclusion criteria for the systematic review are briefly summarized below. Full details on other systematic review methods are available in the protocol at https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/protocol.

Table A-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, function, disability, pain interference); harms and adverse effects; secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, health care 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 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 = population, interventions, comparators, outcomes, timing, setting; RCT = randomized controlled trial

Appendix B. Literature Search Strategies

Database: Ovid MEDLINE(R) ALL 1946 to February 1, 2021
1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab,kw.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8 1 or 2 or 5 or 6 or 7
9 Cannabis/
10 exp Cannabinoids/
11 Medical Marijuana/
12 Mitragyna/
13 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,kf.
14 or/9-13
15 8 and 14
16 limit 15 to english language
17 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
18 ((animal or animals or avian or bird or birds or bovine or canine or cow* or dog or dogs or cat or cats or feline or hamster* or horse* or lamb or lamb* or mouse or mice or monkey or monkeys or murine or pig or piglet* or pigs or porcine or primate* or rabbit* or rat or rats or rodent* or songbird* or veterinar*) not (human* or patient*)).ti,kf,jw.
19 or/17-18
20 16 not 19

Database: EBM Reviews - Cochrane Central Register of Controlled Trials February 2021
1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab,hw.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,hw.
8 1 or 2 or 5 or 6 or 7
9 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,hw.
10 8 and 9

11 conference abstract.pt.
12 "journal: conference abstract".pt.
13 "journal: conference review".pt.
14 "http://.www.who.int/trialsearch*".so.
15 "https://clinicaltrials.gov*".so.
16 11 or 12 or 13 or 14 or 15
17 10 not 16

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 1, 2021
1 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab.
2 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
3 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab.
4 (1 or 2) and 3

Database: APA PsycInfo 1806 to Februrary Week 1 2021
1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic.ti,ab.
5 3 and 4
6 ((chronic or persistent or intractable or refractory) adj3 pain).ti,ab.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
8 1 or 2 or 5 or 6 or 7
9 Cannabis/
10 exp Cannabinoids/
11 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab.
12 or/9-11
13 8 and 12
14 limit 13 to english language

Database: Elsevier Embase to February 1, 2021
('cannabis'/exp OR cannabis OR cannabinoid* OR 'cannabinol'/exp OR cannabinol OR 'marijuana'/exp OR marijuana OR 'cannabidiol'/exp OR cannabidiol OR phytocannabinoid* OR 'tetrahydrocannabinol'/exp OR tetrahydrocannabinol OR 'dronabinol'/exp OR dronabinol OR 'nabilone'/exp OR nabilone OR 'sativex'/exp OR sativex OR 'cbd' OR 'thc' OR 'kratom'/exp OR kratom OR 'khat'/exp OR khat OR 'qat'/exp OR qat OR 'psilocybin'/exp OR psilocybin OR 'hemp'/exp OR hemp OR hydroxymitragynine) AND ('chronic pain'/exp OR arthralgia OR 'back pain' OR headache OR 'musculoskeletal pain' OR 'neck pain' OR neuralgia OR 'nociceptive pain'

OR 'intractable pain' OR fibromyalgia OR myalgia OR arthritis OR osteoarthrtis) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Database: Elsevier Scopus to February 1, 2021
(TITLE (cannabis OR cannabinoid* OR cannabinol OR marijuana OR cannabidiol OR phytocannabinoid* OR tetrahydrocannabinol OR dronabinol OR nabilone OR sativex OR "CBD" OR "THC" OR kratom OR khat OR qat OR psilocybin OR hemp OR hydroxymitragynine)) AND (TITLE ("chronic pain" OR arthralgia OR "back pain" OR headache OR "musculoskeletal pain" OR "neck pain" OR neuralgia OR "nociceptive pain" OR "intractable pain" OR fibromyalgia OR myalgia OR arthritis OR osteoarthritis OR "neuropathic pain"))

Appendix C. Included Studies List

1. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011 Jul-Aug;11(4):353-68. doi: https://dx.doi.org/10.1111/j.1533-2500.2010.00427.x. PMID: 21087411.
2. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006 Jan;45(1):50-2. PMID: 16282192.
3. Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Pain Med. 2020;21(10):2212-8. doi: https://dx.doi.org/10.1093/pm/pnaa303. PMID: 33118602
4. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. Clin Gastroenterol Hepatol. 2017 Jul;15(7):1079-86.e4. doi: https://dx.doi.org/10.1016/j.cgh.2016.09.147. PMID: 27720917.
5. Eibach L, Scheffel S, Cardebring M, et al. Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial. Clin Pharmacol Ther. 2020 Aug 08;08:08. doi: https://dx.doi.org/10.1002/cpt.2016. PMID: 32770831.
6. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ. 2008 Jan 26;336(7637):199-201. doi: https://dx.doi.org/10.1136/bmj.39429.619653.80. PMID: 18182416.
7. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97. doi: https://dx.doi.org/10.1007/s00415-012-6739-4. PMID: 23180178.
8. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014 Jan;47(1):166-73. doi: https://dx.doi.org/10.1016/j.jpainsymman.2013.02.018. PMID: 23742737.
9. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007 Dec 15;133(1-3):210-20. PMID: 17997224.
10. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012 Nov;13(8):677-84. doi: https://dx.doi.org/10.1007/s10194-012-0490-1. PMID: 23070400.
11. Rintala DH, Fiess RN, Tan G, et al. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil. 2010 Oct;89(10):840-8. doi: https://dx.doi.org/10.1097/PHM.0b013e3181f1c4ec. PMID: 20855984.
12. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9. PMID: 16186518.
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14. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010 Jan;33(1):128-30. doi: 10.2337/dc09-1029. PMID: 19808912.

15. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014 Aug;18(7):999-1012. doi: 10.1002/j.1532-2149.2013.00445.x. PMID: 24420962.

16. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008 Feb;9(2):164-73. PMID: 17974490.

17. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82. doi: https://dx.doi.org/10.1016/j.pain.2012.06.024. PMID: 22921260.

18. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59. doi: https://dx.doi.org/10.1111/pme.12569. PMID: 25288189.

19. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS ONE. 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795. PMID: 29145417.

20. Ware MA, Wang T, Shapiro S, et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015 Dec;16(12):1233-42. doi: https://dx.doi.org/10.1016/j.jpain.2015.07.014. PMID: 26385201.

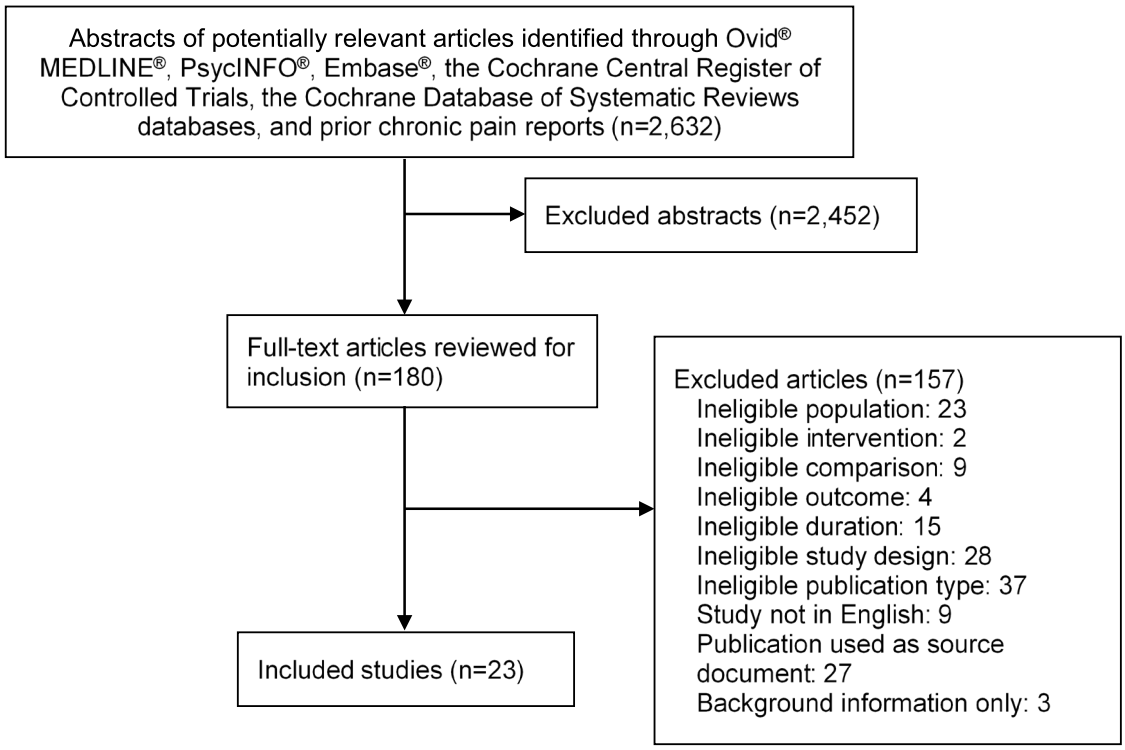
21. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. J Neurol. 2006 Oct;253(10):1337-41. PMID: 16988792.

22. Xu DH, Cullen BD, Tang M, et al. The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. Curr Pharm Biotechnol. 2020;21(5):390-402. doi: https://dx.doi.org/10.2174/1389201020666191202111534. PMID: 31793418.

23. Zajicek JP, Hobart JC, Slade A, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32. doi: https://dx.doi.org/10.1136/jnnp-2012-302468. PMID: 22791906.

Appendix D. Literature Flow Diagram

Figure D-1. Literature flow diagram



Abbreviations: KQ = Key Question

Appendix E. Excluded Studies List

1. Abo Ziad R, Grynbaum MB, Peleg R, et al. The Attitudes and Beliefs of Family Physicians Regarding the Use of Medical Cannabis, Knowledge of Side Effects, and Barriers to Use: A Comparison Between Residents and Specialists. Am J Ther. 2020;Publish Ahead of Print. doi: https://dx.doi.org/10.1097/MJT.0000000000001236. PMID: 33416237. **Exclusion:** Ineligible study design
2. Aboud T, Schuster NM. Pain Management in Multiple Sclerosis: a Review of Available Treatment Options. Curr Treat Options Neurol. 2019 Nov 27;21(12):62. doi: https://dx.doi.org/10.1007/s11940-019-0601-2. PMID: 31773455. **Exclusion:** Systematic review used as source document
3. Abrams DI, Couey P, Dixit N, et al. Effect of Inhaled Cannabis for Pain in Adults With Sickle Cell Disease: A Randomized Clinical Trial. JAMA netw. 2020 Jul 01;3(7):e2010874. doi: https://dx.doi.org/10.1001/jamanetworkopen.2020.10874. PMID: 32678452. **Exclusion:** Inadequate duration
4. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007 Feb 13;68(7):515-21. PMID: 17296917. **Exclusion:** Inadequate duration
5. Abuhasira R, Ron A, Sikorin I, et al. Medical Cannabis for Older Patients-Treatment Protocol and Initial Results. J Clin Med. 2019 Nov 01;8(11):01. doi: https://dx.doi.org/10.3390/jcm8111819. PMID: 31683817. **Exclusion:** Ineligible population
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Appendix F. Evidence Tables

Shown in associated Excel files.

Appendix G. Risk of Bias Assessment

Shown in associated Excel files.