Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain – Quarterly Progress Report: December 2020

Overview

This is the first progress report for an ongoing living systematic review on plant-based treatments for chronic pain. The systematic review will synthesize evidence on the benefits and harms of plant-based compounds (PBCs) such as cannabinoids and kratom used to treat chronic pain, addressing concerns about severe 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 ones. 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 explored by patients to treat chronic pain,

but may also have serious harms, such as dependence, addiction, withdrawal potential, and developmental impacts in adolescents.

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

Detailed methods for this report can be found in the protocol. 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. We included these studies and any additional studies identified in our searches for this report. The inclusion criteria in this review are broader than the criteria in the two previous 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 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 September 14, 2020, for studies of patients with chronic pain for at least 1 month 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 pain outcomes 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

For this first progress report, literature searches identified 2,494 citations, from which we identified 17 eligible studies.[16-32] Appendix C contains a list of 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

All 17 included studies assessed the effects of cannabis-related products. No studies of kratom or other substances met inclusion criteria. Six randomized controlled trials (RCTs) evaluated products that contain a combination of THC and CBD,[19,26-28,30,31] two RCTs evaluated the effects of THC alone,[16,22] and six RCTs evaluated synthetic forms of cannabinoids.[18,20,21,24,25,29] The characteristics of these studies are listed in Table 1. Three observational studies were included.[17,23,32] Two of these were retrospective cohort studies that evaluated the effects of medical cannabis (whole plant), with one focused on safety outcomes[17] and the other focused on the effect on opioid use.[32] The third was a nonrandomized prospective study of a synthetic cannabinoid (nabilone) compared with gabapentin for treatment of neuropathic pain.[23] The characteristics of all 17 included studies are described below.

Table 1. Included randomized controlled trial characteristics

Characteristic	THC/CBD	THC	Synthetic Cannabinoids
N Studies	6	2	6
ROB % High, % Moderate, % Low	17%, 67%, 17%	100% moderate	17%, 33%, 50%
N, Randomized, Total	864	344	416
N, Range	30 to 339	65 to 279	9 to 240
N, Mean	144	172	69
Age, Mean Years	54.5	52.5	52
Female, %	64%	68.75%	55.5%
Race, % Non-White[a]	1.6% (2)	1.6% (2)	8.1% (2)
Pain Type(s)	NPP (5), RA (1)	NPP (1), visceral pain (1)	NPP (5), headache (1)
Study Duration, Range	5 to 15 weeks	7 to 12 weeks	9 to 20 weeks

Abbreviations: CBD = cannabidiol; 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

Six RCTs (N=864) evaluated products with a combination of THC and CBD compared with placebo in patients with chronic pain; five with forms of neuropathic pain (NPP) (2 multiple sclerosis [MS], 2 mixed pain patients, and 1 diabetic peripheral neuropathy [DPN]).[19,26-28,31] 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. Three of the trials allowed patients using opioids and other analgesics to enroll and continue using them during the study period.[19,26,31] The proportion of patients taking opioids was low in two studies (19% to 24% in cannabis groups and 18% to 22% in placebo groups)[19,31] and much greater in the third study (63% in the cannabis group vs. 74% in the placebo group).[26] The other three did not report baseline opioid use or use during the trials.

Three of the studies reported pain response (≥30% improvement in pain),[19,26,31] although in two of the three studies, the difference in pain response between treatment groups was not statistically significant.[19,26] The range of pain response was 25 to 50 percent in the THC/CBD

groups and 16 to 45 percent in placebo groups. All studies reported on the mean change in severity of pain, with five using the 10-point numeric rating scale and one using a 0 to 100 scale for neuropathic pain. All of the studies found the direction of effect to favor cannabis, with differences between groups ranging from −1.25 to −0.19, although the difference between groups reached statistical significance in only three studies.[26-28] Two studies reported on pain interference, with neither finding a significant difference between groups.[19,31] Four studies reported on the impact on physical function using different scales. Two studies using the 36-Item Short Form Health Survey Physical Functioning scale did not find a significant difference between groups.[19,30] The study of patients with rheumatoid arthritis found that the cannabis group improved more than the placebo group on the 28-Joint Disease Activity Score,[27] and a study of patients with mixed types of NPP found a significant improvement in the cannabis group on the Pain Disability Index.[26]

Four studies reported on quality of life, a secondary outcome for this review, with none finding a significant difference between groups.[19,26,30,31] Five studies also reported on sleep quality or sleep disturbance, with four studies reporting significantly better sleep outcomes in the cannabis groups than the placebo groups.[19,26-28,31] The studies did not report on other secondary outcomes (e.g., depression or anxiety). The three studies that allowed opioid use during the study did not report on the effect of the study medications on opioid use.[19,26,31]

Adverse events were reported in all the trials. Two reported that a higher proportion of patients in the cannabis groups experienced any adverse event compared with placebo (72% vs. 62% and 88% vs. 59%).[19,28] Serious adverse events (SAEs) were reported in four studies, with few events in most studies. One study of patients with central NPP due to MS reported that 13 percent of cannabis patients had an SAE compared with 8 percent in the placebo group[19] although this study did not define *severe* or *SAEs* a priori. Of five studies reporting on withdrawals from study due to adverse events (WAEs), two reported higher proportions in the cannabis groups, while two reported higher withdrawal in the placebo groups and one was similar between groups. Specific adverse events of dizziness (mean, 32% vs. 9.5%), nausea (32% vs. 6%), and sedation (7% vs. 2%) were reported more frequently in the cannabis groups across four RCTs.[19,26-28]

A small (n=66), high risk-of-bias retrospective cohort study found that patients prescribed opioids for chronic pain who enrolled in the New Mexico Medical Cannabis Program (MCP) were more likely to reduce their daily opioid dose than a control group not enrolled in the MCP (83.8% vs. 44.8%; odds ratio, 5.12, 95% confidence interval [CI], 1.56 to 16.88).[32] The reduction in dose was very small, but statistically significant (difference, −0.64 mg intravenous morphine equivalent, 95% CI, −1.10 to −0.18 from starting mean doses in the 2 groups of 24.4 vs. 16.2 mg, p=0.10). However, the mean amount of cannabis use per patient was not reported.

Plant-Derived Delta-9-THC

Two RCTs (N=344) evaluated THC in patients with chronic pain; one in patients with NPP from MS[22] and one in patients with chronic abdominal pain from chronic pancreatitis or postsurgical pain.[16] 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. One trial allowed patients to continue using opioids and other analgesics, with patients randomized using a stratified list based on opioid use at baseline.[16] Ninety percent in the THC group and 97 percent in the placebo group were using opioids at baseline. The other trial noted that more than half of

patients enrolled were using an analgesic at baseline, but did not report the type or whether they could continue use during the trial.[22]

A high risk-of-bias cohort study (N=431) evaluated harms of THC used to treat chronic pain for 52 weeks.[17] Patients with chronic pain for whom standard treatments were not effective were enrolled, with patients already using cannabis for pain in the treatment group and those not using cannabis as the control group. The cannabis group received herbal cannabis containing 12.5 percent (+/- 1.5%) THC. Patients were instructed to start with low doses and titrate up (maximum dosing of 5 gm per day) using the delivery system with which they were most comfortable. The median dose was reported as 2.5 gm of herbal cannabis per day; however, in terms of THC content, this is equivalent to over 300 mg per day. Clarification on the dosing has been requested from the authors of the study.

Although one of the trials reported pain response, it was not reported by percent change in pain, as specified for this report (where a 30% improvement is considered response).[22] In this study, scores of 0 to 3 on a 0 to 10 scale (0 = no pain; 10 = extreme pain) were considered a response. At week 12, the proportion with response was greater in the THC group, but it was not significant (28% vs. 18.7%). Both studies reported that the difference in pain severity at endpoint was very small and not statistically significant between groups. One of these studies stated that there were no statistically significant differences in patient global impression of change, pain-related anxiety, measures of depression and generalized anxiety, quality of life, and treatment satisfaction (data for results not presented).[16] The impact of THC on opioid use was not reported in the trial that allowed opioids and other analgesics during the study period.[16]

Both of the RCTs found the incidence of WAEs was greater in the cannabis groups (22% vs. 6.5%), and one reported that the incidence of SAEs was low, but slightly higher in the cannabis group (4.9% vs. 2.2%).[22] Both trials reported more dizziness with cannabis, with 80 percent versus 34 percent in a 7-week study and 46 percent versus 7 percent in the 12-week study. The 52-week cohort study reported lower incidence of dizziness overall, but still a higher percentage in the cannabis group (14% vs. 10%).[17] The 3-week trial and the 52-week cohort study also reported higher incidences of nausea and sedation with cannabis. The long-term cohort study found the incidence of any adverse event and of SAEs was similar between groups but slightly higher in the usual-care group. The cannabis group in this study was a self-selected group of prior cannabis users and may represent patients who were already known to tolerate it. The study reported 4.7 percent of those using cannabis withdrew from the study due to adverse events but did not clearly report on WAEs in the usual-care group. While the study conducted neurocognitive testing and found both groups improved to a similar degree over the study period, almost 3 percent of those in the cannabis group experienced a “cognitive disorder,” compared with none in the usual-care group. While effects on pulmonary function are not a specified adverse event for this review, the study also conducted pulmonary function tests throughout the study and did not find a decline in the cannabis group.

Synthetic Delta-9-THC

Six RCTs (N= 416)[18,20,21,24,25,29] and one moderate risk-of-bias cohort study[23] evaluated synthetic THC in patients with chronic pain: one in chronic medication overuse headache and the others in a variety of types of neuropathic pain (1 spinal cord injury, 2 MS, 1 DPN, 1 mixed, 1 unclear). Two of the studies used dronabinol,[24,29] and the others used nabilone. 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 the synthetic THC with placebo, with durations of 5, 9, and 14 weeks.[18,21,29] 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).[18] The other three trials were crossover design studies, with one using diphenhydramine as an active control (47 weeks),[24] another using ibuprofen (8 weeks),[20] and the third using dihydrocodeine (6 weeks).[25] A small moderate risk-of-bias cohort study (N=156) evaluated nabilone and gabapentin in patients with NPP of various types for six months.[23] Prospectively, patients presenting with NPP were allowed to initiate nabilone or gabapentin, or to add one of these 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. Two studies allowed patients to continue taking their current medication for pain, not specifically excluding opioids or requiring their discontinuation.[21,29] The 14-week study of dronabinol specifically allowed tramadol as rescue medication for acute pain during the trial, but did not report on its use during the study period.[29] One additional study reported that no other pain medications could be initiated during the trial.[18]

Of the three placebo-controlled trials, only a small study (N=26) of patients with DPN reported on pain response (≥30% improvement from baseline). At 5 weeks, 85 percent of nabilone patients had improved pain response, compared with 38 percent in the placebo group (calculated relative risk, 2.20, 95% CI, 1.07 to 4.55).[21] Pain intensity did not differ significantly between dronabinol and placebo in a trial of 240 patients with MS after 14 weeks of treatment,[29] but was significantly lower at endpoint with nabilone than placebo in a small (N=26) 5-week trial of patients with painful diabetic neuropathy.[21] This trial also reported that pain interference was significantly lower at 5 weeks with nabilone (mean difference, −1.1, 95% CI, −2.15 to −0.50).[21] There was no difference in depression scores, but anxiety, quality of life, and sleep improved more in the nabilone group versus the placebo group. The other placebo-controlled trials did not report the secondary outcomes. Adverse events were reported in all three placebo-controlled trials, but heterogeneously. In two trials reporting incidence or frequency of any adverse event, the synthetic THC groups (dronabinol in one, nabilone in the other) had higher proportions than the placebo groups (88% vs. 73% and 54% vs. 46%, respectively).[21,29] SAEs were reported in no patients in one study.[18] In another trial, SAEs were not reported, but more patients in the dronabinol group than the placebo group experienced an adverse event that was rated as severe (12% vs. 7%).[29] WAEs were reported in more patients in the THC groups than placebo, but the difference was largest in a small study of nabilone (13% vs. 0%)[18] and smaller in the study of dronabinol (15% vs. 10%).[29] Specific adverse events were reported for both groups in one trial, with dronabinol-treated patients reporting more dizziness (20% vs. 4.3%) and sedation (8.1% vs. 4.3%), and similar proportions with nausea (4.8% vs. 3.4%).[29]

None of the crossover trials reported pain response. In an RCT of patients with NPP (N=96 randomized, 73 analyzed) comparing nabilone and dihydrocodeine (30 to 240 mg per day), after 6 weeks of treatment, the opioid resulted in greater reduction in pain severity (VAS 0 to 100 scale; −5.7, 95% CI, −10.9 to −0.5; P=0.03, as reported by study authors).[25] There were no statistically significant differences in secondary outcomes measured (depression, anxiety, quality of life, or sleep). While the study indicates patients could continue other drugs for pain, it is not clear which those were or if new drugs were started outside of the protocol (including other opioids). An 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.[20] There were no statistically significant differences in secondary outcomes measured (depression, anxiety, and quality of life). There

were no differences in incidence 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 taken was "combination medications." Two weeks post-study endpoint, treatment with nabilone resulted in lower daily analgesic intake than after ibuprofen (0.89/d vs. 1.34/d; p=0.03).[20] While the incidence rates were low, dizziness (7.7% vs. 0%) and cognitive deficits (3.8% vs. 0%) occurred more frequently when taking nabilone, while nausea (7.7% vs. 3.8%) and sedation (3.8% vs. 0%) 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.[24] 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 on either treatment.

The observational study of nabilone, gabapentin, or the combination found no differences in pain severity between the groups at 3 months, but at 6 months nabilone reduced pain intensity more than gabapentin (0 to 100 VAS, mean difference, −5.8, 95% CI, −10.18 to −1.42).[23] There was not a difference in pain interference at 6 months between nabilone and gabapentin or the combination. Quality of life, depression, and anxiety were not different between groups at 6 months. Using the Medical Outcomes Study Sleep Scale measured at 6 months,[18,29] patients assigned to nabilone monotherapy had better sleep scores than those assigned to gabapentin monotherapy or the combination (scale range, 0 to 60; mean difference, −3.1, 95% CI, −7.57 to 1.37 vs. gabapentin; mean difference, −7.3, 95% CI, −11.86 to −2.74 vs. combination therapy). The proportion of patients reporting any adverse event was 35 percent with nabilone and 47 percent with gabapentin, but not reported for the combination. No SAEs were reported. WAEs were similar in the nabilone and combination groups (10% and 9%) but higher in the gabapentin monotherapy group (23%). At 6 months, more patients in the gabapentin group reported sedation (60%) than in the other two groups (35% and 36%). Dizziness was reported in similar proportions of patients across groups (33% vs. 39% vs. 33%).

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

No evidence was identified.

Summary

In this first progress report, 17 studies were included. Table 2 provides a summary of the findings of the evidence in this report. This summary also includes two RCTs[29,31] and one cohort study,[32] each assessing a different cannabis product that was included in previous systematic reviews on treatments for chronic pain. 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

Outcome	Plant-Derived THC/CBD	Plant-Derived THC	Synthetic THC
Count of Studies and Patients	k=6 trials (N=864) / k=1 observational study (N=66)	k=2 trials (N=344) / k=1 observational study (N=431)	k=6 trials (N=416) / k=1 observational (N=156)
Strength of Body of Evidence	Pending	Pending	Pending
Included Studies Risk of Bias: RCTs/Observational Studies	Moderate/high	Moderate/high	Low/moderate
Study Duration Category	Short (1 to <6 mos)	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)	Difference not statistically significant, but large absolute difference (1 RCT)	Large difference, favoring synthetic THC over placebo (1 RCT)
Pain Severity (change)	Small difference, favoring THC/CBD (6 RCTs; 3 statistically significant)	Small difference, not statistically significant (2 RCTs)	Moderate difference, favoring nabilone (1 RCT); Small difference, not statistically significant with dronabinol (1 RCT)
Pain Interference	Small difference, not statistically significant (2 RCTs)	Not reported	Moderate difference, favoring nabilone over placebo (1 RCT)
Function/Disability	Inconsistent findings according to scale and population (2 RCTs)	Not reported	Not reported
Secondary Outcomes	Sleep improved in THC/CBD groups (5 RCTs; 4 statistically significant), QoL not improved (4 RCTs)	Small difference, not statistically significant (1 RCT)	QoL and sleep improved with nabilone vs. placebo, other outcomes: small difference, not statistically significant (1 RCT)
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).	Greater WAEs and SAEs in THC groups (2 RCTs)	Higher incidence of AEs (3 RCTs), SAEs (2 RCTs), WAEs (2 RCTs) in THC groups vs. placebo
Specific Adverse Events	Dizziness, nausea, sedation greater with THC/CBD (4 RCTs)	Dizziness, nausea, sedation greater with THC (2 RCTs, 1 cohort study)	Dizziness, sedation greater with THC vs. placebo (1 RCT)

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.

Next Quarterly Progress Report

The next Quarterly Progress Report update is scheduled to be available in late February 2021.

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22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

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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.

AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

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DOI: https://doi.org/10.23970/AHRQEPCCERPLANTPAIN1. Posted final reports are located on the Effective Health Care Program search page.

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 update 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 (1 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 September 14, 2020
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 August 2020
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 September 10, 2020
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 September Week 1 2020
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 September 15, 2020
('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 September 15, 2020
(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. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

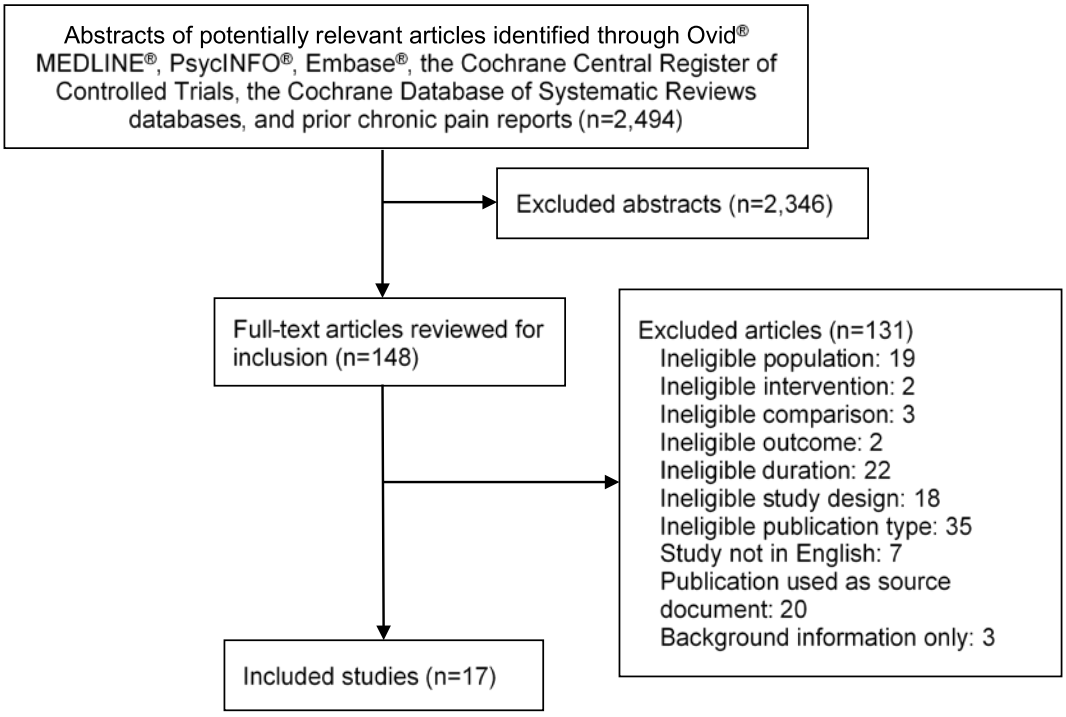
15. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS ONE. 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795. PMID: 29145417.

16. 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.

17. 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. Aboud T, Schuster NM. Pain Management in Multiple Sclerosis: a Review of Available Treatment Options. Current Treatment Options in Neurology. 2019 Nov 27;21(12):62. doi: https://dx.doi.org/10.1007/s11940-019-0601-2. PMID: 31773455. **Exclusion reason:** Systematic review used as source document

2. 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 Network Open. 2020 Jul 01;3(7):e2010874. doi: https://dx.doi.org/10.1001/jamanetworkopen.2020.10874. PMID: 32678452. **Exclusion reason:** Inadequate duration

3. 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 reason:** Inadequate duration

4. Abuhasira R, Ron A, Sikorin I, et al. Medical Cannabis for Older Patients-Treatment Protocol and Initial Results. Journal of Clinical Medicine. 2019 Nov 01;8(11):01. doi: https://dx.doi.org/10.3390/jcm8111819. PMID: 31683817. **Exclusion reason:** Ineligible population

5. Abuhasira R, Ron A, Sikorin I, et al. Medical cannabis for older patients—treatment protocol and initial results. Journal of Clinical Medicine. 2019;8(11)doi: 10.3390/jcm8111819. **Exclusion reason:** Ineligible population

6. Akgün K, Essner U, Seydel C, et al. Daily Practice Managing Resistant Multiple Sclerosis Spasticity With Delta-9-Tetrahydrocannabinol: Cannabidiol Oromucosal Spray: A Systematic Review of Observational Studies. Journal of Central Nervous System Disease. 2019;11doi: 10.1177/1179573519831997. **Exclusion reason:** Systematic review used as source document

7. Allan GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Canadian Family Physician. 2018 02;64(2):e78-e94. PMID: 29449262. **Exclusion reason:** Ineligible publication type

8. Almog S, Aharon-Peretz J, Vulfsons S, et al. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial. European Journal of Pain. 2020 May 23;23:23. doi: https://dx.doi.org/10.1002/ejp.1605. PMID: 32445190. **Exclusion reason:** Inadequate duration

9. Amato L, Minozzi S, Mitrova Z, et al. Systematic review of safeness and therapeutic efficacy of cannabis in patients with multiple sclerosis, neuropathic pain, and in oncological patients treated with chemotherapy. Epidemiologia e Prevenzione. 2017;41(5-6)doi: 10.19191/EP17.5-6.AD01.069. **Exclusion reason:** Ineligible publication type

10. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. Journal of Pain. 2015 Dec;16(12):1221-32. doi: https://dx.doi.org/10.1016/j.jpain.2015.07.009. PMID: 26362106. **Exclusion reason:** Inadequate duration

11. Aviram J, Samuelly-Leichtag G. Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain Physician. 2017 09;20(6):E755-E96. PMID: 28934780. **Exclusion reason:** Systematic review used as source document

12. Ball S, Vickery J, Hobart J, et al. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health technology assessment. 2015;19(12):1-187. **Exclusion reason:** Ineligible outcome

13. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opinion on Pharmacotherapy. 2006 Apr;7(5):607-15. PMID: 16553576. **Exclusion reason:** Ineligible publication type

14. Bellnier T, Brown GW, Ortega TR. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. The Mental Health Clinician. 2018 May;8(3):110-5. doi: https://dx.doi.org/10.9740/mhc.2018.05.110. PMID: 29955555. **Exclusion reason:** Ineligible study design

15. Berger AA, Keefe J, Winnick A, et al. Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia. Best Practice and Research: Clinical Anaesthesiology. 2020doi: 10.1016/j.bpa.2020.08.010. **Exclusion reason:** Ineligible publication type

16. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004 Dec;112(3):299-306. PMID: 15561385. **Exclusion reason:** Inadequate duration

17. Blake A, Wan BA, Malek L, et al. A selective review of medical cannabis in cancer pain management. Annals of Palliative Medicine. 2017 Dec;6(Suppl 2):S215-S22. doi: https://dx.doi.org/10.21037/apm.2017.08.05. PMID: 28866904. **Exclusion reason:** Ineligible population

18. Boehnke KF, Scott JR, Litinas E, et al. High-Frequency Medical Cannabis Use Is Associated With Worse Pain Among Individuals With Chronic Pain. Journal of Pain. 2020 May - Jun;21(5-6):570-81. doi: https://dx.doi.org/10.1016/j.jpain.2019.09.006. PMID: 31560957. **Exclusion reason:** Ineligible study design

19. Boychuk DG, Goddard G, Mauro G, et al. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. Journal of Oral & Facial Pain and Headache. 2015;29(1):7-14. doi: https://dx.doi.org/10.11607/ofph.1274. PMID: 25635955. **Exclusion reason:** Ineligible publication type

20. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA. 2018 12 18;320(23):2448-60. doi: https://dx.doi.org/10.1001/jama.2018.18472. PMID: 30561481. **Exclusion reason:** Systematic review used as source document

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Appendix F. Evidence Tables

Shown in associated Excel files.

Appendix G. Risk of Bias Assessment

Shown in associated Excel files.