White Paper

Living Systematic Reviews: Examining Excluded Full-Text Articles To Better Understand the Evidence Base on Plant-Based Treatments for Chronic Pain

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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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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

If you have comments on this White Paper, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Abstract

Living systematic reviews are a relatively new approach to keeping the evidence in systematic reviews current by frequent surveillance and updating. The Agency for Healthcare Research and Quality's Evidence-based Practice Center Program commissioned a living systematic review of plant-based treatments for chronic pain management and a series of related white papers. The first white paper described challenges and practical and methodological considerations encountered during the first year of the living review. The second white paper focused on practical considerations for adapting scope and communicating findings. This white paper examined published articles excluded after full-text review, to better understand the broader evidence base on plant-based treatments for chronic pain.

Although the literature base continues to expand, many published articles are excluded due to failure to meet eligibility criteria. The most frequent reasons for exclusion of articles at the full-text review stage were study designs that lacked comparison groups and evaluation of populations with pain conditions that were ineligible for inclusion, such as pain related to advanced cancer, multiple sclerosis, of mixed pain conditions without distinguishing patients with chronic pain. Some articles were excluded at the full-text stage because the intervention consisted of cannabis products that were not specifically identified or products that were outside the scope of the review.

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1. Background

Chronic pain is difficult to treat successfully. A series of recent systematic reviews funded by the Agency for Healthcare Research and Quality (AHRQ)[1-4] found that commonly used treatments, including opioids, nonopioid medications, and nonpharmacological interventions, are associated with limited efficacy in the long term and potential harms. In the case of opioids,[5] serious potential harms include risk of opioid use disorder and overdose. Therefore, identifying new treatments for chronic pain that are effective and safe is an important clinical and public health priority.

Plant-based compounds (PBCs) such as cannabis and kratom are a potential treatment for chronic pain; however, their effectiveness and safety is uncertain. Given increasing legal access to cannabis and clinical and research interest in PBCs for treating chronic pain, an existing evidence base was available and publication of additional research was anticipated. Therefore, in 2020, AHRQ commissioned a "living" review[6] spanning multiple years, in order to evaluate and regularly update the evidence base on cannabis and other PBCs with psychoactive properties, such as kratom, on chronic pain. Along with the living review, AHRQ commissioned a series of related white papers. The first white paper[7] drew on experience of the first year of the living review[8] and described practical and methodological considerations. The second white paper[9] was primarily based on year two of the living review[10] and focused on issues related to expanding scope and communication of findings.

For this third white paper, we sought to obtain additional insight into the larger evidence base on plant-based treatments for chronic pain, by examining articles that were selected for full-text review for potential inclusion in the living review but did not meet eligibility criteria, including the number of articles, types of studies, treatments evaluated, and reasons for exclusion.

2. Examination of Excluded Full-Text Articles

To identify eligible studies for the living review, automated searches on multiple electronic databases are run on a biweekly basis. Distiller® SR software is used to assist in managing abstract and full-text review, and EndNote™ software is used for reference management. All citations identified in the searches are screened for eligibility based on titles and abstracts against prespecified inclusion criteria by one reviewer, and all citations not relevant by the first reviewer undergo screening by a second reviewer. Any citation deemed potentially eligible by at least one reviewer is retrieved for full-text review. All articles selected for full-text review undergo dual independent review to determine eligibility for inclusion. Disagreements are resolved by consensus, or a third reviewer if needed. All articles excluded at the full-text stage are assigned a code indicating the reason for exclusion.

Articles excluded at the full-text review stage represent a subset of studies that were considered potentially eligible for inclusion based on titles and abstracts, but did not meet criteria upon examination of the full paper. Therefore, examination of excluded full-text articles may provide insight into the larger evidence base on PBCs for chronic pain beyond the studies eligible for inclusion in the living review, including the study designs utilized and the populations and interventions evaluated in this topic area. It should be noted that articles selected for full-text review do not necessarily represent a comprehensive set of relevant articles, as reviewers vary with regard to the threshold used to select articles for full-text review. Most articles are excluded at the title and abstract review stage and do not undergo full-text review; in accordance with PRISMA guidance,[11] specific reasons for exclusions at the title and abstract

stage are not recorded. It is also common for articles to have more than one reason for exclusion at the full-text stage. Although we focused on what we judged as the primary reason for exclusion, many studies had multiple reasons for exclusion. For this report, we focused on studies that were excluded at the full-text review stage for ineligible population, intervention, outcome, or comparator.

A total of 82 articles were excluded at the full-text stage for ineligible population, intervention, outcome, or comparator **(Appendix A)**. Thirty-seven studies evaluated an ineligible population, 12 studies evaluated an ineligible intervention, and 33 studies evaluated did not have a comparison group or evaluated an ineligible comparison. No study was excluded for evaluating ineligible outcomes. None of the studies excluded at the full-text stage evaluated patients with subacute pain or adolescents; the living review was expanded to include these populations in year 3.

Among the 38 studies (in 37 publications) excluded for ineligible population, 12 were excluded because they evaluated cannabis in patients with multiple sclerosis who were not clearly described as having chronic pain.[12-23] Of these, six (n=24 to 630, total N=1,985) were randomized controlled trials[12,16,18,20,22,23] and one[17] (n=191) was a post-hoc analysis of a randomized controlled trial. The living review had originally been scoped to exclude multiple sclerosis without chronic pain. Although patients with multiple sclerosis frequently have spasticity, this was considered distinct from chronic pain. As described in the second white paper, we considered expanding the scope to include multiple sclerosis with spasticity following year one of the living review.[9] However, a Technical Expert Panel did not support expanding to multiple sclerosis with spasticity, viewing pain and spasticity as distinct conditions. In addition, potential overlap was noted with existing systematic reviews of cannabis for multiple sclerosis (with or without chronic pain).[24-27]

Six studies (in 5 publications) that were excluded for evaluation of ineligible populations studied cannabis in patients with advanced cancer (patients receiving palliative care and at end-of-life were not eligible for inclusion).[28-32] In one of the studies, patients also were not required to have chronic pain.[32] Four of the studies (in 3 publications) of patients with advanced cancer and pain were randomized controlled trials (n=206 to 399; total N=1,362), each evaluating nabiximols (a comparable tetrahydrocannabinol [THC] to cannabidiol [CBD] ratio plant-extracted product).[28,29,31]

Eight studies that were excluded for evaluation of ineligible populations studied cannabis in patients with nonchronic (e.g., episodic) pain conditions or with conditions not necessarily associated with chronic pain (and were not required to have chronic pain to be enrolled).[33-40] The conditions were ulcerative colitis,[35] Huntington's disease,[36] HIV infection,[33] HIV and hepatitis C virus infection,[38] illicit opioid use,[40] ocular pain,[39] functional chest pain,[37] and inflammatory bowel disease.[34] Of these, one small study[36] (n=26) of nabiximols for Huntington's disease and one small study[37] (n=13) of dronabinol (a synthetic, high THC-to-CBD-ratio product) for functional chest pain were randomized controlled trials.

Seven studies that were excluded for evaluation of ineligible populations studied cannabis in mixed populations of chronic and nonchronic pain, without reporting results separately for patients with chronic pain.[41-47] None of these studies were randomized controlled trials. The proportion of patients with chronic pain was unreported in three studies and ranged from ~50 percent to 89 percent in the others. Of five remaining studies excluded for evaluation of ineligible population, two were animal studies,[48,49] one evaluated healthy volunteers,[50] one evaluated a population with induced/experimental pain on top of chronic pain,[51] and one evaluated patients undergoing surgery.[52]

Twelve articles were excluded at the full-text stage because they evaluated ineligible interventions.[53-64] Of these, three articles evaluated possession of a medical marijuana card, rather than use of a specific cannabis product.[53,54,63] Two of the medical marijuana card articles reported results from the same randomized controlled trial (n=186), which was not restricted to patients with pain (the study also enrolled patients with insomnia, anxiety, or depressive symptoms).[53,63] Another uncontrolled study evaluated hemp seed, a product excluded because it only contains trace amounts of THC or CBD,[59] two observational studies of cannabis for chronic pain were excluded because they did not describe the cannabis products used,[58,62] and one observational study evaluated cannabis access laws.[60] Four studies did not evaluate cannabis or other eligible PBCs.[55,57,61,64] One study evaluated integrative medicine therapies,[55] two evaluated opioids,[56,57] one evaluated olorinab,[64] and one evaluated psilocybin.[61] As described in the second white paper, we previously considered potential expansion of the scope of the living review to include psilocybin. Based on a literature scan and input from a Technical Expert Panel, however, the decision was made to not expand to include psilocybin because studies were not yet available on psilocybin for chronic pain and were not imminently expected. The excluded study of psilocybin was a randomized trial (n=16) but would also have been excluded for ineligible population, as it evaluated patients with cluster headaches, an episodic (nonchronic) pain condition.[61]

Thirty-three studies of cannabis products were excluded because they did not have an eligible comparison group.[65-97] Four studies[74,85,86,94] only compared different doses or frequencies of use and the others were uncontrolled studies (i.e., no comparison group). Among the uncontrolled studies, sample sizes ranged from 7 to 8,165 (mean 551, median 151). Most studies were conducted in patients prescribed medical cannabis for mixed chronic pain; the pain conditions and cannabis products evaluated were generally not well described.

Table 1. Characteristics of studies excluded at full-text review

Criteria for Ineligibility (Number of Studies)	Study Characteristics

Population (37)	• 12: MS[12-23] (6 RCTs[12,16,18,20,22,23])
	• 6 studies in 5 publications: advanced cancer[28-32] (4 RCTs [in 3 publications] on nabiximols[28,29,31])
	• 8: other conditions
	  ○ Ulcerative colitis[35]
	  ○ Huntington's disease (RCT, nabiximols)[36]
	  ○ HIV infection[33]
	  ○ HIV and hepatitis C virus infection[38]
	  ○ Illicit opioid use[40]
	  ○ Ocular pain[39]
	  ○ Functional chest pain (RCT, dronabinol)[37]
	  ○ Inflammatory bowel disease[34]
	• 7: mixed or acute pain conditions[41-47]
	• 4: miscellaneous (2 animal studies,[48,49] 1 in healthy volunteers,[50] 1 induced/experimental pain in addition to chronic pain[51], 1 in patients undergoing surgery[52])

Intervention (12)	• 5: product not described[53,54, 58, 62,63] (3, medical marijuana card[53,54,63]) • 1: Hemp seed[59] • 1: Cannabis access laws[60] • 1: Olorinab[64] • 1: Psilocybin[61] • 1: Integrative medicine therapies[55] • 2: Opioids[56,57]
Comparator (33)	• 4: Dose ranging studies[74,85,86,94] • 29: No comparator[65-73, 75-84, 87-93, 95-97]

Abbreviations: MS = multiple sclerosis; RCT = randomized controlled trial.

3. Conclusions

This white paper examined published articles excluded after full-text review while conducting an ongoing living review of PBCs for chronic pain. Although the literature base continues to expand, many published articles are excluded due to failure to meet eligibility criteria. We found that the most frequent reasons for exclusion of articles at full-text review were study designs that lacked comparison groups, and evaluation of populations with pain conditions that were ineligible for inclusion, such as pain related to advanced cancer, multiple sclerosis, or mixed pain conditions without distinguishing patients with chronic pain. Some articles were excluded at the full-text stage because the intervention consisted of cannabis products that were not specifically identified or products that were outside the scope of the review.

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Appendix A. Excluded Studies With Detailed Reasons

Table A-1. Excluded studies with detailed reasons

Author	Year	Title	Exclusion Code	Detailed Exclusion Reason	Randomized Controlled Trial
Abelev, S.[1]	2022	Medicinal cannabis for the treatment of chronic refractory pain: an investigation of the adverse event profile and health-related quality of life impact of an oral formulation	Ineligible comparator	No comparison group	No
Abuhasira, R.[2]	2019	Medical cannabis for older patients-treatment protocol and initial results	Ineligible population	Mixed population (57% chronic pain)	No
Aviram, J.[3]	2020	Medical cannabis treatment for chronic pain: outcomes and prediction of response	Ineligible comparator	No comparison group	No
Aviram, J.[4]	2021	Specific phytocannabinoid compositions are associated with analgesic response and adverse effects in chronic pain patients treated with Medical Cannabis	Ineligible comparator	No comparison group	No
Aviram, J.[5]	2021	Sex differences in medical cannabis-related adverse effects	Ineligible comparator	No comparison group	No
Aviram, J.[6]	2022	Long-term effectiveness and safety of medical cannabis administered through the metered-dose Syqe Inhaler	Ineligible comparator	No comparison group	Yes
Balestra, A.[7]	2023	Influence of cannabinoid treatment on trajectories of patient-related outcomes in chronic pain: pain intensity, emotional distress, tolerability and physical disability	Ineligible comparator	No comparison group	Yes
Ball, S.[8]	2015	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	Ineligible population	MS progression	Yes
Balu, A.[9]	2021	Medical cannabis certification is associated with decreased opiate use in patients with chronic pain: a retrospective cohort study in Delaware	Ineligible comparator	No comparison group	No
Becker, W.[10]	2021	Cannabis use, pain interference, and prescription opioid receipt among persons with HIV: a target trial emulation study	Ineligible population	Not chronic pain (HIV)	No
Bellnier, T.[11]	2018	Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis	Ineligible comparator	No comparison group	No
Benedict, G.[12]	2021	Medical cannabis used as an alternative treatment for chronic pain demonstrates reduction in chronic opioid use - a prospective study	Ineligible comparator	No comparison group	No

Author	Year	Title	Exclusion Code	Detailed Exclusion Reason	Randomized Controlled Trial
Boehnke, K.[13]	2020	High-frequency medical cannabis use is associated with worse pain among individuals with chronic pain	Ineligible comparator	No eligible comparison group (dose ranging study)	Yes
Bonomo, Y.[14]	2021	Pharmacokinetics, safety, and tolerability of a medicinal cannabis formulation in patients with chronic non-cancer pain on long-term high dose opioid analgesia: a pilot study	Ineligible comparator	No comparison group	No
Campbell, C.[15]	2023	Within-subject, double-blind, randomized, placebo-controlled evaluation of combining the cannabinoid dronabinol and the opioid hydromorphone in adults with chronic pain	Ineligible population	Population is induced/experimental pain on top of chronic pain	Yes
Coates, M.[16]	2022	Symptoms and extraintestinal manifestations in active cannabis users with inflammatory bowel disease	Ineligible population	Not chronic pain (inflammatory bowel disease)	Yes
Cunetti, L.[17]	2018	Chronic pain treatment with cannabidiol in kidney transplant patients in Uruguay	Ineligible comparator	No comparison group	No
Denduluri, S.[18]	2020	Cannabinoid and opioid use among total joint arthroplasty patients: a 6-year, single-institution study	Ineligible population	Preoperative	Yes
Ergisi, M.[19]	2022	An updated analysis of clinical outcome measures across patients from the UK Medical Cannabis registry	Ineligible population	Mixed population (~50% chronic or neuropathic pain)	Yes
Fallon, M.[20]	2017	Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies	Ineligible population	Not chronic pain (advanced cancer)	Yes
Flachenecker, P.[21]	2014	nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice--results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity	Ineligible population	MS spasticity	No
Flachenecker, P[22].	2014	Long-term effectiveness and safety of nabiximols (tetrahydrocannabinol/cannabidiol oromucosal spray) in clinical practice	Ineligible population	MS spasticity	No
Gambino, A.[23]	2020	Evaluating the suitability and potential efficiency of cannabis sativa oil for patients with primary burning mouth syndrome: a prospective, open-label, single-arm pilot study	Ineligible comparator	No comparison group	No
Gershoni, T.[24]	2022	Wellness of patients with chronic pain is not only about pain intensity	Ineligible comparator	No comparison group	No

Author	Year	Title	Exclusion Code	Detailed Exclusion Reason	Randomized Controlled Trial
Gilman, J.[25]	2022	Effect of medical marijuana card ownership on pain, insomnia, and affective disorder symptoms in adults: a randomized clinical trial	Ineligible intervention	Not plant-based treatment (possession of medical marijuana card)	Yes
Goedel, W.[26]	2021	Association of medical cannabis licensure with prescription opioid receipt: A population-based, individual-level retrospective cohort study	Ineligible intervention	Impact of medical cannabis licensure on opioid prescriptions	No
Greis, A.[27]	2022	Medical cannabis use reduces opioid prescriptions in patients with chronic back pain	Ineligible comparator	No comparison group	No
Greis, A.[28]	2021	Perceived efficacy, reduced prescription drug use, and minimal side effects of cannabis in patients with chronic orthopedic pain	Ineligible comparator	No comparison group	No
Gustavsen, S.[29]	2021	Safety and efficacy of low-dose medical cannabis oils in multiple sclerosis	Ineligible population	MS, not required to have chronic pain	Post-hoc analysis of RCT
Habib, G.[30]	2021	The effect of medical cannabis on pain level and quality of sleep among rheumatology clinic outpatients	Ineligible comparator	No comparison group	Yes
Harris, M.[31]	2021	UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions	Ineligible comparator	No comparison group	No
Hassan, S.[32]	2020	Does integrative medicine reduce prescribed opioid use for chronic pain? A systematic literature review	Ineligible intervention	Not plant-based treatment (combined complementary and alternative therapies)	Yes
Hefner, K.[33]	2015	Concomitant cannabis abuse/dependence in patients treated with opioids for non-cancer pain	Ineligible intervention	Opioid intervention	No
Hjorthoj, C.[34]	2021	Cannabis-based medicines and medical cannabis for patients with neuropathic pain and other pain disorders: nationwide register-based pharmacoepidemiologic comparison with propensity score matched controls	Ineligible population	Unclear population (neuropathic pain of unspecified duration)	No
Hojsted, J.[35]	2013	Addictive behaviors related to opioid use for chronic pain: a population-based study	Ineligible intervention	Not plant-based treatment (opioids)	No
Kafil, T.[36]	2018	Cannabis for the treatment of ulcerative colitis	Ineligible population	Not chronic pain (ulcerative colitis)	No
Kawka, M.[37]	2021	Clinical outcome data of first cohort of chronic pain patients treated with cannabis-based sublingual oils in the United Kingdom - analysis from the UK Medical Cannabis Registry	Ineligible comparator	No comparison group	No
Lichtman, A.[38]	2018	Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain	Ineligible population	Not chronic pain (advanced cancer pain)	Yes

Author	Year	Title	Exclusion Code	Detailed Exclusion Reason	Randomized Controlled Trial
Link, K.[39]	2023	Characterizing cannabis use in a sample of adults with multiple sclerosis and chronic pain: an observational study	Ineligible intervention	Unclear which product is being used	No
Lopez Sendoon Moreno, J.[40]	2016	A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease	Ineligible population	Not chronic pain (Huntington's disease)	Yes
Lucas, P.[41]	2020	Cannabis significantly reduces the use of prescription opioids and improves quality of life in authorized patients: results of a large prospective study	Ineligible population	Mixed population (69% chronic pain)	No
Maida, V.[42]	2008	Adjunctive nabilone in cancer pain and symptom management: a prospective observational study using propensity scoring	Ineligible population	Not chronic pain (advanced cancer)	No
Malik, Z.[43]	2017	Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial	Ineligible population	Not chronic pain (functional chest pain)	Yes
Markova, J.[44]	2019	Sativex(®) as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant Multiple Sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial	Ineligible population	Not chronic pain (MS spasticity)	Yes
Maurotti, S.[45]	2021	Hemp seeds in post-arthroplasty rehabilitation: a pilot clinical study and an in vitro investigation	Ineligible intervention	Not plant-based treatment (per inclusion criteria; hemp seeds)	No
Mazza, M.[46]	2021	Therapeutic Prospects of Cannabinoids in the Immunomodulation of Prevalent Autoimmune Diseases	Ineligible comparator	No comparison group	No
McMichael, B.[47]	2020	The impact of cannabis access laws on opioid prescribing	Ineligible intervention	Cannabis access laws	No
Meng, H.[48]	2021	Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients	Ineligible population	Mixed population (89% chronic pain)	No
Meuth, S.[49]	2020	Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: consistency of response across subgroups from the SAVANT randomized clinical trial	Ineligible population	Not chronic pain (MS spasticity)	Post-hoc analysis of RCT
Moreno-Sanz, G.[50]	2022	Sex-dependent prescription patterns and clinical outcomes associated with the use of two oral cannabis formulations in the multimodal management of chronic pain patients in Colombia	Ineligible comparator	No eligible comparison group (dose ranging study)	No
Ngyuen, T.[51]	2023	Changes in prescribed opioid dosages among patients receiving medical cannabis for chronic pain, New York State, 2017-2019	Ineligible comparator	No eligible comparison group (dose ranging study)	No

Author	Year	Title	Exclusion Code	Detailed Exclusion Reason	Randomized Controlled Trial
Novotna, A.[52]	2011	A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis	Ineligible population	MS spasticity	Yes
Nunnari, P.[53]	2022	Long-term cannabis-based oil therapy and pain medications prescribing patterns: an Italian observational study	Ineligible comparator	No comparison group	No
O'Connell, M.[54]	2019	Medical cannabis: effects on opioid and benzodiazepine requirements for pain control	Ineligible comparator	No comparison group	No
Phillips, K.[55]	2002	Chronic health conditions, acute health events, and healthcare utilization among adults over age 50 in Hawai'i who use cannabis: a matched cohort study	Ineligible population	Mixed population (% chronic pain unclear)	No
Poli, P.[56]	2022	Promising health benefits of adjuvant Acmella and Zingiber extracts combined with Coenzyme Q10 Phytosomes, supplementation in chronic pain treated with medical cannabis: a prospective and open-label clinical study	Ineligible comparator	No comparison group	No
Portenoy, R.[57]	2012	Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial	Ineligible population	Not chronic pain (advanced cancer)	Yes
Rapin, L.[58]	2021	Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic	Ineligible population	Mixed conditions	No
Renslo, B.[59]	2022	Medical cannabis use reduces opioid prescriptions in patients with osteoarthritis	Ineligible comparator	No comparison group	No
Rouhollahi, E.[60]	2020	Cannabis extract CT-921 has a high efficacy–adverse effect profile in a neuropathic pain model	Ineligible population	Animal study	No
Russo, M.[61]	2016	Evaluating Sativex in neuropathic pain management: a clinical and neurophysiological assessment in multiple sclerosis	Ineligible population	Not chronic pain (MS spasticity)	No
Sagy, I.[62]	2019	Safety and efficacy of medical cannabis in fibromyalgia	Ineligible comparator	No comparison group	No
Santos, S.[63]	2005	Management of chronic hepatitis C virus in patients with HIV	Ineligible population	Not chronic pain (co-occurring HCV + HIV)	No
Schindler, E.[64]	2022	Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: results from a randomized, double-blind, placebo-controlled trial	Ineligible intervention	Not plant-based treatment per inclusion criteria (psilocybin), cluster headaches not chronic pain	Yes
Schloss, J.[65]	2021	A phase 2 randomised clinical trial assessing the tolerability of two different ratios of medicinal cannabis in patients with high grade gliomas	Ineligible population	Not chronic pain (advanced cancer); patients not required to have chronic pain	Yes

Author	Year	Title	Exclusion Code	Detailed Exclusion Reason	Randomized Controlled Trial
Scuteri, D.[66]	2022	Is there a rational basis for cannabinoids research and development in ocular pain therapy? A systematic review of preclinical evidence	Ineligible population	Not chronic pain (ocular pain)	No
Socias, E.[67]	2020	Cannabis use is associated with reduced risk of exposure to Fentanyl among people on opioid agonist therapy during a community-wide overdose crisis	Ineligible population	Not chronic pain (illicit opioid users)	No
Sotoodeh, R.[68]	2022	Predictors of pain reduction among fibromyalgia patients using medical cannabis: a long-term prospective cohort study	Ineligible comparator	No comparison group	No
Sturgeon, J.[69]	2020	Clinical profiles of concurrent cannabis use in chronic pain: a CHOIR study	Ineligible intervention	Cannabis products not described	No
Sznitman, S.[70]	2021	Opioid and healthcare service use in medical cannabis patients with chronic pain: a prospective study	Ineligible comparator	No comparison group	No
Tervo-Clemmens, B.[71]	2022	Cannabis use and sleep quality in daily life: a daily diary study of adults starting cannabis for health concerns	Ineligible intervention	Not chronic pain (medical marijuana cardholders for mixed conditions)	No
Ueberall, M.[72]	2019	Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry	Ineligible comparator	No eligible comparison group (dose ranging study)	No
van Amerongen, G.[73]	2018	Effects on spasticity and neuropathic pain of an oral formulation of DELTA9-tetrahydrocannabinol in patients with progressive multiple sclerosis	Ineligible population	Not chronic pain (MS spasticity)	Yes
Vermersch, P.[74]	2016	Tetrahydrocannabinol: cannabidiol oromucosal spray for multiple sclerosis-related resistant spasticity in daily practice	Ineligible population	MS spasticity	No
Vicknasingham, B.[75]	2020	Kratom and pain tolerance: a randomized, placebo-controlled, double-blind study	Ineligible population	Healthy volunteers	Yes
Wade, D.[76]	2004	Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients	Ineligible population	Not chronic pain (MS spasticity)	Yes
Wang, C.[77]	2023	Assessment of clinical outcomes in patients with fibromyalgia: Analysis from the UK Medical Cannabis Registry	Ineligible comparator	No comparison group	No
Wang, Y.[78]	2021	Health outcomes among adults initiating medical cannabis for chronic pain: a 3-month prospective study incorporating ecological momentary assessment (EMA)	Ineligible comparator	No comparison group	No

Author	Year	Title	Exclusion Code	Detailed Exclusion Reason	Randomized Controlled Trial
Williams, A.[79]	2022	Adult medical cannabinoid use and changes in prescription controlled substance use	Ineligible comparator	No comparison group	No
Yacyshyn, B.[80]	2021	Safety, pharmacokinetics, and efficacy of Olorinab, a peripherally acting, highly selective, full agonist of the cannabinoid receptor 2, in a phase 2a study of patients with chronic abdominal pain associated with Crohn's disease	Ineligible intervention	Not plant-based treatment (Olorinab), also not chronic pain (Crohn's disease)	Yes
Yimam, M.[81]	2021	Antinociceptive and anti-inflammatory properties of cannabidiol alone and in combination with standardized bioflavonoid composition	Ineligible population	Animal study	No
Zajicek, J.[82]	2003	Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial	Ineligible population	Not chronic pain (MS spasticity)	Yes

Abbreviations: CAMS = cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis; CBD = cannabidiol; CHOIR = Collaborative Health Outcomes Information Registry; CUPID = Cannabinoid Use in Progressive Inflammatory brain Disease trial; EMA = ecological momentary assessment; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MS = multiple sclerosis; MOVE 2 = multicenter, non-interventional study; RCT = randomized controlled trial; SAVANT = Sativex® as add-on therapy vs. further optimized first-line ANTispastics; THC = tetrahydrocannabinol.

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