



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Living Systematic Review on Plant-Based Treatment for Chronic Pain*

Initial Publication Date: November 3, 2020

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(Amendment Details-see Section V)

I. Background and Objectives for the Systematic Review

Chronic pain, defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,^{1,2} is a serious public health issue in the United States, affecting approximately 100 million people,³ and resulting in over \$560 billion annually in costs.⁴ Chronic pain substantially impacts physical and mental functioning, reducing productivity and quality of life; it is the leading cause of disability and is often refractory to treatment.^{5,6} Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015.⁷ This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality⁷⁻⁹ involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdose related to prescription opioids in the United States,¹ with an estimated 17,087 prescription opioid overdose deaths in 2016.⁷ In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.¹⁰

A recent series of related systematic reviews found that opioids,¹¹ several nonopioid drugs,¹² and some nonpharmacologic treatments¹³ 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 *Guidelines for Prescribing Opioids for Chronic Pain* recommend that non-opioid therapy is preferred for treatment of chronic pain.¹² The challenges of treating chronic pain in light of the lackluster evidence on opioids, the ongoing opioid crisis, and difficulty in safely prescribing opioids drive a search for alternative pain treatments, including cannabis.

In an effort to address the opioid epidemic, a prominent goal of current research is to identify alternative treatments with equal or better benefits for pain while avoiding potential unintended consequences that could result in harms. Plants have historically been evaluated for medicinal properties, with some being developed into drug therapies (i.e., the field of pharmacognosy). These include analgesic compounds, such as aspirin being developed from willow bark.¹⁴ Some data suggest that cannabinoids may have analgesic properties, though research in this area is mixed.¹⁵ Tetrahydrocannabinol (THC), one of many cannabinoids in cannabis, has demonstrated analgesic properties,^{16,17} though its psychoactive effects and abuse potential increase its risk and suitability as an analgesic. Other cannabinoids (e.g., cannabidiol [CBD], cannabigerol [CBG], and cannabichromene [CBC]) may also have some analgesic or anti-inflammatory properties and are not thought to be psychoactive or addictive,^{18,19} but these cannabinoids may not be as potent

as THC. The aforementioned recent reviews on chronic pain included evidence on cannabis and related compounds, but found too little evidence to draw meaningful conclusions on either benefits or harms. Other plant-based compounds (PBCs) with effects similar to opioids or cannabis, such as kratom, were not included in these reviews. These additional compounds may also have serious harms, such as dependence, addiction, withdrawal potential, and developmental impacts in adolescents.²⁰ Although some PBCs thought to reduce pain are currently classified as Schedule I by the Drug Enforcement Administration, the recent legalization of cannabis by several states may lead to more, and higher quality, research on them. Initiatives to develop and study alternative interventions for chronic pain are expected to contribute to this increase in research on PBCs, specifically for pain.

The key decisional dilemmas for treating chronic pain with PBCs include the effectiveness in treating chronic pain and the effect of specific formulations, doses or potencies, routes of administration, types of pain, and other patient characteristics on outcomes. Similarly, it is important to identify harms and adverse effects of PBCs. These may include risks of frequent or daily use, risk of developing dependence or addiction (e.g., cannabis use disorder), mental health effects and impact on harms of co-prescribed opioids. It is also unclear what impact PBC use for pain has on opioid use, and, if PBCs are effective, how they compare to other interventions. Although we expect the evidence base to grow substantially, the current evidence on benefits of cannabis and some other PBCs for chronic pain may be too limited to support recommendations for their use.^{11,12,21,22} Hence, the initial best use of the current evidence may be to clearly delineate potential harms of PBCs as well as potential benefits, such as reduced opioid use or improved pain.

Purpose of the Review

This is a “living systematic review” (LSR), which will assess the effectiveness and harms of plant-based treatments for chronic pain conditions. The review will be living in the sense that it will use methods to identify and synthesize recently published literature on an ongoing basis. For the purposes of this review, PBCs included are those that are similar to opioids in effect and that have the potential for addiction, misuse, and serious adverse effects; other PBCs, such as herbal treatments are not included. The intended audience includes policy and decisionmakers, funders and researchers of treatments for chronic pain, and clinicians who treat chronic pain.

II. The Key Questions

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

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

Table 1 outlines the inclusion and exclusion criteria related to Populations, Interventions, Comparators, Outcomes, Timing, Settings (PICOTS), and study designs of interest for each KQ.

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	All KQs: Adults (including pregnant or breastfeeding women) 18 years and older with chronic pain (>12 weeks or pain persisting past the time for normal tissue healing). See categorization of specifically included pain populations below.	All KQs: Children and adolescents <18 years old; adults with acute or subacute pain; patients at end of life or in palliative care (e.g. with late stage cancer-related pain)
Interventions	KQs 1 and 2: Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes KQs 3 and 4 : Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids All KQs: Co-use of other drugs for pain	All KQs: Non-plant-based interventions, capsaicin, herbal supplements
Comparators	All KQs: Any comparator, or usual care	All KQs: No comparison
Outcomes	All KQs: Primary efficacy outcomes (i.e., pain, function, disability, pain interference); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder); 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

III. Methods

Living Systematic Reviews are an innovative way to approach evidence synthesis for topics where research is “emerging rapidly, current evidence is uncertain, and new research may change policy or practice decisions.”^{23,24} Over the past few years, interest has expanded in exploring issues such as selection of appropriate topics, developing specific methods, and end-user engagement in LSRs.²⁴⁻²⁷ At the end of the review, we will create a summary methods document detailing the methods developed for this LSR and providing recommendations for future developments.

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies will be based on the KQs and are described in the previous PICOTS section.

Important subgroups to consider in evaluating this evidence are:

- Specific types of pain: neuropathic pain (including nociceptive and centralized; patients with multiple sclerosis and painful skin disorders are included in this category), musculoskeletal pain (including low-back pain), visceral pain, fibromyalgia, inflammatory arthritis, headache disorders, sickle cell disease, and cancer pain (non-end of life)
- Degree of nociplasticity/central sensitization
- Patient demographics (e.g., age, race, ethnicity, sex, socioeconomic status)
- Comorbidities including past or current substance use disorders, mental health disorders, medical comorbidities, and high risk for opioid use disorder)
- PBC characteristics: route of administration, frequency of administration, potency of product, dose or estimated dose, specific compounds (e.g. THC, CBD, terpenes, flavonoids), and specific formulations used
- Co-use of other interventions for pain: opioids, nonopioids (e.g. nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentin, pregabalin)

Below are additional details on the scope of this project:

Study Design: For all KQs, we will include randomized controlled trials (RCTs) of at least one-month duration. Initially, in the base-year of this LSR, we will include observational studies for both benefits (to address gaps in evidence where RCTs are not available) and harms. Eligible observational studies must assess a mean duration of treatment of one month, and have concurrent controls (e.g., cohort and case-control studies). Those that control for potential confounders will be prioritized. As the evidence grows, and more RCTs become available throughout the project, we will reassess the need to include observational studies, specifically to address benefits. A decision to discontinue including them will be made based on the strength of the RCT evidence. When the RCT evidence on a given KQ and outcome is insufficient, we will include observational studies that meet inclusion criteria. When the strength of evidence is low, moderate, or high based on RCTs, we will update our protocol to exclude observational studies. We do not anticipate excluding observational studies assessing harms. For all KQs, we will exclude uncontrolled observational studies, case series, and case reports, but will keep a list of studies excluded for this reason. Systematic reviews will be used to identify primary studies and

to summarize harms of PBCs in other populations or other study designs if there is no evidence identified that meets our criteria.

Non-English Language Studies: We will restrict to English-language articles, but will review English-language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria in order to help assess for the likelihood of language bias.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Publication Date Range: Electronic searches for evidence on cannabinoids will be conducted starting from the dates of the last searches in each of the prior pain reports^{11,12} (August and September 2019), and then monthly thereafter using automated searches created by our research librarian. Searches for other PBCs (e.g., kratom) and for observational studies will be conducted from the inception of each database, and then monthly thereafter.

Literature Databases: Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases will be searched to capture published literature. Search strategies for MEDLINE are available in **Appendix 1**.

Supplementing Searches: A Supplemental Evidence And Data for Systematic review (SEADS) portal will be available, and a Federal Register Notice will be posted for this review annually.

Hand Searching: Reference lists of included articles will also be reviewed for includable literature.

Process for Selecting Studies: Pre-established criteria will be used to determine eligibility for inclusion and exclusion of abstracts in accordance with the Agency for Healthcare Research and Quality (AHRQ) Methods Guide, based on the KQs and PICOTS.²⁸ We will use DistillerSR® software to assist with screening abstracts. While the review team conducts manual assessment of study citations, the Distiller® AI feature will be training in the background. When the Distiller® AI decisions reach a level of 95 percent accuracy, we will deploy the system to assist with dual review (this typically takes 2000 citations, but varies by topic).²⁹ To ensure accuracy, any citation deemed not relevant for full-text review (manually or using machine learning) will be reviewed by a second researcher. All citations deemed potentially relevant by at least one of the reviewers or DistillerSR® will be retrieved. Each full-text article will be independently reviewed for eligibility by two team members, including any articles suggested by peer reviewers or that arise from the public posting process. Any disagreements will be resolved by consensus. A record of studies excluded at the full-text level with reasons for exclusion will be maintained. As part of our LSR methods, these procedures will be used to screen the results of searches conducted monthly.

Data Abstraction and Data Management

After studies are selected for inclusion, data will be abstracted into categories that include but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results relevant to each KQ as outlined in the previous PICOTS section. Information that will be abstracted that is relevant for assessing applicability will include the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention,

and care settings. All study data will be verified for accuracy and completeness by a second team member. On a quarterly basis, any newly identified studies will be abstracted and evidence tables uploaded to AHRQ's Systematic Review Data Repository Plus (SRDR+).

Assessment of Methodological Risk of Bias of Individual Studies

Predefined criteria will be used to assess the risk of bias of individual controlled trials, systematic reviews, and observational studies. Randomized trials will be evaluated using criteria and methods developed by the Cochrane Back Review Group,³⁰ and cohort and case-control studies will be evaluated using criteria developed by the U.S. Preventive Services Task Force.³¹ These criteria and methods will be used in accordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews developed by the Agency for Healthcare Research and Quality.³² Studies will be given an overall rating of “low,” “medium,” or “high” risk of bias. We will use DistillerSR® software to conduct these assessments, using dual review by two independent reviewers. Disagreements identified by DistillerSR® will be resolved through consensus. Assessments and final ratings will be converted to evidence tables, and uploaded on a quarterly basis to SRDR+.

Data Synthesis

We will construct evidence tables showing study characteristics (as discussed above), results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. Data will be qualitatively summarized in tables, using ranges and descriptive analysis and interpretation of the results. Studies identified in prior AHRQ chronic pain reports^{11,12} that meet inclusion criteria will be included in this review. We will evaluate the persistence of benefits or harms by evaluating the three periods identified in prior AHRQ pain reports (3 to 6 months, 6 to 12 months, and ≥ 12 months).^{11-13,33,34}

Meta-analyses will be conducted to summarize data and obtain more precise estimates on outcomes for which studies are homogeneous enough to provide a meaningful combined estimate.³⁵ The decision to conduct quantitative synthesis will depend on presence of at least two studies, completeness of reported outcomes and a lack of heterogeneity among the reported results. To determine whether meta-analyses are indicated, we will consider the risk of bias of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Meta-analyses will be conducted using a random effects model, and statistical heterogeneity will be assessed using the I^2 method. Publication bias (small sample size bias) will be assessed using funnel plots when there are eight or more studies in meta-analyses. To evaluate subgroup effects, we will summarize within-study analyses of subgroup differences and perform study-level analyses on key demographic and clinical factors. Sensitivity analyses will be conducted on study risk of bias.

The magnitude of effects for pain and function will be classified using the same system used in other recent AHRQ EPC reviews conducted on chronic pain^{11-13,33,34} to provide a consistent benchmark for comparing results of pain interventions across reviews. A small/slight effect is defined for pain as a mean between-group difference following treatment of 5 to 10 points on a 0- to 100-point visual analog scale (VAS), 0.5 to 1.0 points on a 0- to 10-point numeric rating scale, or equivalent; for function as a mean difference of 5 to 10 points on the 0- to 100-point

Oswestry Disability Index (ODI) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A moderate effect is defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large/substantial effects are defined as greater than moderate. We will apply similar thresholds to other outcomes measures. Small effects using this system may be below published thresholds for clinically meaningful effects; however, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or function using a treatment with low cost or no serious harms may be important. When data are available we will also evaluate the proportion of patients meeting thresholds for clinically important differences (e.g., >30% or >50% pain relief or improvement in function).

Grading the Strength of Evidence for Major Comparisons and Outcomes

We will assess the strength of evidence for all primary comparisons and outcomes listed above in Table 1. Regardless of whether evidence is synthesized quantitatively or qualitatively, the strength of evidence for each KQ/body of evidence will be initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.³² To ensure consistency and validity of the evaluation, the strength of evidence will be reviewed by the entire team of investigators prior to assigning a final grade on the following factors:

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

The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Quarterly Reports

We will create quarterly reports to identify evidence from studies published since the last full systematic review or quarterly report. We will evaluate how the new evidence may alter the findings of the systematic review and will make a note of when and how conclusions will be changed. We will use the following thresholds to determine if the new evidence will alter the findings of the systematic review:

- The Strength of Evidence for a primary outcome changes levels (insufficient, low, moderate, large), or
- The magnitude of effect changes categories (small/slight, moderate, large), or
- The direction of effect changes

Assessing Applicability

Applicability will be assessed in accordance with the AHRQ Methods Guide,³⁶ which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies. For example, exclusion of chronic pain patients with psychiatric comorbidities reduces applicability to clinical practice since many patients with chronic pain have such comorbidities, and may respond more poorly to treatment. Similarly, trials that use active run-in periods evaluate highly selected populations who tolerated and responded well to the study intervention, rather than the general population of chronic pain patients being considered for the intervention. Factors that may affect applicability which we have identified a priori include eligibility criteria and patient factors (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical and psychiatric comorbidities, event rates and symptom severity in treatment and control groups), intervention factors (e.g., dose and duration of therapy, intensity and frequency of monitoring, level of adherence, use of co-interventions), comparisons (e.g., type and dosing of comparison), outcomes (e.g., use of unvalidated or nonstandardized outcomes, measurement of short-term or surrogate outcomes), settings (e.g., primary care vs. specialty setting, country), and study design features (e.g., use of run-in periods) relevant to applicability. We will use this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

IV. References

1. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *JAMA*. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464. PMID: 26977696.
2. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep*. 2016 Mar 18;65(1):1-49. doi: 10.15585/mmwr.rr6501e1. PMID: 26987082.
3. Dahlhamer JJJ, Zelaya, C, et al. . Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018. doi: 10.15585/mmwr.mm6736a2.
4. Institute of Medicine Committee on Advancing Pain Research. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: National Academies Press; National Academy of Sciences; 2011.
5. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain*. 2008 Jul-Aug;24(6):469-78. doi: 10.1097/AJP.0b013e31816b2f26. PMID: 18574357.

6. Eriksen J, Sjogren P, Bruera E, et al. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006 Nov;125(1-2):172-9. doi: 10.1016/j.pain.2006.06.009. PMID: 16842922.
7. U.S. Centers for Disease Control and Prevention. Annual Surveillance Report of Drug-Related Risks and Outcomes--United States, 2017. Special Surveillance Special Report 1. Atlanta, GA: 2018. <https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf>.
8. Vital signs: overdoses of prescription opioid pain relievers--United States, 1999-2008. *MMWR. Morbidity and mortality weekly report*. 2011;60(43):1487-92. PMID: 22048730.
9. Drug Abuse Warning Network. The DAWN Report: Highlights of the 2010 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. Rockville, MD: Substance Abuse and Mental Health Services Administration; Center for Behavioral Health Statistics and Quality; 2012. <https://www.samhsa.gov/data/sites/default/files/DAWN096/DAWN096/SR096EDHighlights2010.htm>.
10. U.S. Department of Health and Human Services. HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis. HHS Press Office; 2017. <https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html>. Accessed Jul 30 2020.
11. Chou R, Hartung D, Turner J, et al. Opioid Treatments for Chronic Pain. Comparative Effectiveness Review No. 229. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC011. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. PMID: 32338848.
12. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid Pharmacologic Treatments for Chronic Pain. Comparative Effectiveness Review No. 228. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC010. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. PMID: 32338847.
13. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Comparative Effectiveness Review No. 227. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC009. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. PMID: 32338846.
14. Desborough MJR, Keeling DM. The aspirin story - from willow to wonder drug. *Br J Haematol*. 2017 Jun;177(5):674-83. doi: 10.1111/bjh.14520. PMID: 28106908.
15. Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain*. 2018 Oct;159(10):1932-54. doi: 10.1097/j.pain.0000000000001293. PMID: 29847469.
16. Elikkottil J, Gupta P, Gupta K. The analgesic potential of cannabinoids. *J Opioid Manag*. 2009 Nov-Dec;5(6):341-57. PMID: 20073408.
17. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA*. 2015;313(24):2456-73. doi: 10.1001/jama.2015.6358.
18. Vučković S, Srebro D, Vujović KS, et al. Cannabinoids and Pain: New Insights From Old Molecules. *Front Pharmacol*. 2018;9:1259-. doi: 10.3389/fphar.2018.01259. PMID: 30542280.
19. Morales P, Hurst DP, Reggio PH. Molecular Targets of the Phytocannabinoids: A Complex Picture. *Prog Chem Org Nat Prod*. 2017;103:103-31. doi: 10.1007/978-3-319-45541-9_4. PMID: 28120232.
20. Risks of Adolescent Marijuana Use. U.S. Department of Health & Human Services; Office of Population Affairs. <https://www.hhs.gov/ash/oah/adolescent-development/substance-use/marijuana/risks/index.html>. Accessed May 25, 2020.
21. Kansagara D, O'Neil M, Nugent S, et al. Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review. VA Evidence-based Synthesis Program Reports. Washington, DC: Department of Veterans Affairs; 2017. PMID: 29369568.
22. Nugent SM, Morasco BJ, O'Neil ME, et al. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. *Ann Intern Med*. 2017 Sep 5;167(5):319-31. doi: 10.7326/M17-0155. PMID: 28806817.
23. Elliott J, DeJean D, Clifford T, et al. Cannabis for pediatric epilepsy: protocol for a living systematic review. *Syst Rev*. 2018 Jul 18;7(1):95. doi: 10.1186/s13643-018-0761-2. PMID: 30021618.
24. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction-the why, what, when, and how. *J Clin Epidemiol*. 2017 Nov;91:23-30. doi: 10.1016/j.jclinepi.2017.08.010. PMID: 28912002.
25. Akl EA, Meerpohl JJ, Elliott J, et al. Living systematic reviews: 4. Living guideline recommendations. *J Clin Epidemiol*. 2017 Nov;91:47-53. doi: 10.1016/j.jclinepi.2017.08.009. PMID: 28911999.

26. Simmonds M, Salanti G, McKenzie J, et al. Living systematic reviews: 3. Statistical methods for updating meta-analyses. *J Clin Epidemiol*. 2017 Nov;91:38-46. doi: 10.1016/j.jclinepi.2017.08.008. PMID: 28912004.
27. Thomas J, Noel-Storr A, Marshall I, et al. Living systematic reviews: 2. Combining human and machine effort. *J Clin Epidemiol*. 2017 Nov;91:31-7. doi: 10.1016/j.jclinepi.2017.08.011. PMID: 28912003.
28. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015 Nov;68(11):1312-24. doi: 10.1016/j.jclinepi.2014.11.023. PMID: 25721570.
29. Taieb V, Smela-Lipińska B, O'Brien P, et al. Use of Artificial Intelligence with DistillerSR Software for a Systematic Literature Review of Utilities in Infectious Disease. *Value in Health*. 2018;21:S387.
30. Furlan AD, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine*. 2009 Aug 15;34(18):1929-41. doi: 10.1097/BRS.0b013e3181b1c99f. PMID: 19680101.
31. U.S. Preventive Services Task Force. Methods and processes. 2018. <https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes>. Accessed December 17, 2018.
32. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2017. <https://effectivehealthcare.ahrq.gov/topics/ceer-methods-guide/overview>. Accessed June 1, 2019.
33. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatment for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. HHSA 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2016. PMID: 26985522
34. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No 18-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2018. <https://effectivehealthcare.ahrq.gov/topics/nonpharma-treatment-pain/research-2018> PMID: 30179389.
35. Morton SC, Murad MH, O'Connor E, et al. Quantitative Synthesis—An Update. Methods Guide for Comparative Effectiveness Reviews. (Prepared by the Scientific Resource Center under Contract No. 290-2012-0004-C.) AHRQ Publication No. 18-EHC007-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2018. Posted final reports are located on the Effective Health Care Program search page (<https://effectivehealthcare.ahrq.gov/>). <https://doi.org/10.23970/AHROEPCMETHGUIDE3>.
36. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.
37. Chou R, Ahmed AY, Iyer S, et al. Living Systematic Reviews: Practical Considerations for Adapting Scope and Communicating the Evolving Evidence. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) Rockville, MD: Agency for Healthcare Research and Quality; December 2022 (article in press).

V. Summary of Protocol Amendments

Date	Section	Original Protocol	Revision	Rationale
March 29, 2023	II. The Key Questions	Limited to chronic pain in adults	Added adolescents and subacute pain	Scope was expanded; detailed in methods paper ³⁷
March 29, 2023	III. Methods	Included use of Distiller AI to assist with citation review	Will not use AI	The study yield did not warrant the use of AI for citation review
March 29, 2023	Table 1: Population	Excluded adolescents	Added adolescents	Adolescents also experience chronic

Date	Section	Original Protocol	Revision	Rationale
				pain and have a high prevalence of cannabis use (recreational or medical).
March 29, 2023	Table 1: Population	Excluded subacute pain	Added subacute pain	Subacute pain, often defined as pain lasting for 4 to 12 weeks, represents a transitional state between acute (<4 weeks) pain, which often resolves, and chronic pain, which is more likely to persist. Effective treatments for reducing the likelihood of subacute pain becoming chronic are also needed.
March 29, 2023	Section XI: Registration	Stated that protocol will be registered in PROSPERO	Updated that protocol has been registered	

Abbreviations: AI = artificial intelligence.

VI. Definition of Terms

Not applicable.

VII. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given

the opportunity to do so through the peer or public review mechanism. In this review, we will convene two groups of experts; one relating to clinical and technical expertise in PBCs and/or chronic pain, and another relating to technical and experiential expertise in LSRs.

Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

IX. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

X. Role of the Funder

This project was funded under Contract No. 75Q80120D00006 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XI. Registration

This protocol is registered in the international prospective register of systematic reviews (PROSPERO).

Appendix 1. 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 cannabitol 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