White Paper

Living Systematic Reviews: Practical Considerations for Adapting Scope and Communicating the Evolving Evidence

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Prepared by:
Pacific Northwest Evidence-based Practice Center
Portland, OR

Investigators:
Roger Chou, M.D.
Azrah Y. Ahmed, B.A.
Suchitra Iyer, Ph.D., M.Sc.
Benjamin J. Morasco, Ph.D.
Christina Bougatsos, M.P.H.
Devan Kansagara, M.D., M.C.R.

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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.

Robert Otto Valdez, Ph.D., M.H.S.A.
Director
Agency for Healthcare Research and Quality

Therese Miller, Dr.P.H.
Acting Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Craig A. Umscheid, M.D., M.S.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.
Task Order Officer
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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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. A prior white paper described challenges and practical and methodological considerations encountered during the first year of the living review. The current report builds and expands upon the prior white paper, with additional observations and experiences from the second year. This white paper focuses on four key issues encountered in year two of the living systematic review: (1) adapting or expanding review scope; (2) optimizing living review reports' frequency and format; (3) utilizing ongoing input from experts; and (4) using data visualization and innovative methods to complement the living review reports.

Contents

Tables

Figures

Appendixes

1. Background

In 2020, the Agency for Healthcare Research and Quality (AHRQ) commissioned a "living" review[1] spanning multiple years, in order to evaluate and update the evidence-base on cannabis and other plant based compounds (PBCs) with psychoactive properties, such as kratom, on chronic pain. A prior white paper[2] drew on experience of the first year of the living review[3] and described practical and methodological considerations. This white paper focuses on four key issues encountered in year two of the living systematic review: (1) adapting or expanding review scope; (2) optimizing frequency and format of living updates; (3) utilizing ongoing input from experts; and (4) using data visualization and innovative methods to complement the living review reports.

Chronic pain is difficult to treat successfully. A series of recent systematic reviews conducted by AHRQ[4-7] found that commonly used treatments, including opioids, nonopioid medications, and nonpharmacological interventions, are associated with limited efficacy and potential harms. In the case of opioids,[8] 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. PBCs such as cannabis and kratom are a potential treatment for chronic pain; however, it is unclear whether PBCs are effective and/or safe. Given increasing legal access to cannabis and research interest in PBCs for treating chronic pain, it was anticipated that additional research would be published in the coming months and years, so a living review was initiated.

2. Revisiting Review Scope

The clinical, policy, and regulatory context in which living reviews are conducted changes over time. In addition, conducting the living review provides insight into areas for which the evidence is changing more rapidly but which may not have been the primary focus of the original key questions/scope of the review. Therefore, an important practical consideration for maintaining the relevance of living reviews is to consider adapting or expanding the scope on an ongoing or periodic basis.[1,9]

The topic for this living review was originally nominated by the United States Congress, reflecting their priority to improve public health by identifying new treatments for chronic pain. The scope (inclusion/exclusion criteria) was developed with input from a Technical Expert Panel (TEP) with expertise in cannabis, chronic pain, and living review methods.[10] The scope focused on two PBCs, cannabis and kratom, based on widespread and/or increasing use for chronic pain, potential trade-offs between benefits and harms (including potential for substance use disorder or misuse), and need for evidence to inform regulatory and policy decisions. The review focused on adults with chronic pain conditions, based on initial scoping and the anticipated volume of literature.

During year two of the living review, several factors were noted which prompted us to consider an expansion of the scope. The relatively low rate of new eligible studies of cannabis for chronic pain (**Table 1**) and (to date) no eligible studies of kratom indicated that an expansion of scope could be accommodated within the allocated resources.

Table 1. Update report schedule with numbers of new studies added

Report	Abstracts Reviewed	Full-Text Reviewed	New Studies	Publication Date
Systematic review	2,850	214	27 total	October 2021
Quarterly surveillance report 1	32	3	0	October 2021
Quarterly surveillance report 2	102	27	1	January 2022
Quarterly surveillance report 3	170	22	0	May 2022
Systematic review update 1 (draft version)	18	7	2 (29 total)[a]	March–April 2022
Quarterly surveillance report 4	106	18	1 (29 total)[b]	June 2022
Systematic review update 1 (final version)	5	0	2 (29 total)[a]	September 2022

[a]Two new studies since the prior year's full systematic review.
[b]New study was included in the systematic review update 1 (draft version).

To better inform decisions about adapting or expanding the scope, we performed a horizon scan by searching for in-progress trials on clinicaltrials.gov, and conducted additional searches of the published literature. Recognizing the need to incorporate additional perspectives in policy and living review methods that were earlier limited, we invited additional new members to the TEP for the second year of the review. Additional experts were recruited to address policy and methods issues as well as address attrition (due to new conflicts of interest, unavailability, or other factors affecting original TEP members) and offer fresh insights. Formal, semi-structured TEP calls to obtain input on various issues were organized so as to inform the next cycle of surveillance and updates. The TEP provided input on potential scope changes and optimal frequency and format of the reviews. The discussion centered on related "natural" compounds not originally included, such as psilocybin; use of PBCs in non-adult (e.g., adolescent) persons; use of PBCs for non-chronic (e.g., subacute) pain; and use of cannabis for spasticity without pain.

- Adolescents: The TEP members generally felt that adolescents are an important, yet understudied population for cannabis and chronic pain. Use of cannabis is widespread among adolescents.[11] Although data on the use of cannabis in adolescents for chronic pain is limited, some evidence indicates that it is the most commonly reported reason for medical cannabis use in this age group,[12] raising concerns about long-term impacts of cannabis use on the developing brain. Therefore, the TEP recommended considering expanding the scope to include adolescents while acknowledging that there are likely few eligible studies of adolescents, but noting that this was an important research gap that could inform future research. A literature search identified no eligible published randomized trials, non-randomized (controlled) studies, or in-progress studies of cannabis or kratom for chronic pain in adolescents, though uncontrolled studies of cannabis were identified.[13,14]
- Subacute pain: We received mixed input about expanding the scope from only chronic pain (greater than 3 months duration) to also addressing subacute pain (4 weeks to 3 months duration). While some of the TEP members felt that cannabis may

be used to treat subacute pain, other members noted that subacute pain represents a relatively short transition period between acute and chronic pain and that systematically reviewing the evidence may be of limited clinical utility. To further inform the feasibility of including studies that address subacute pain, we conducted a search on MEDLINE, CCRCT, Embase, and PsycINFO to identify published studies and identified none.

- Psilocybin: Most TEP members felt that psilocybin is a compound with growing interest and knowledge base. They acknowledged that psilocybin is technically not "plant-based," but suggested that the living review could be re-framed to address plant-based and other "natural" compounds. However, it was noted that no trials or controlled studies of psilocybin are likely to be published at this time, suggesting that it may be premature to add psilocybin to the scope now, but that the decision should be re-visited in the next one to two years. To further inform whether to expand the scope to include psilocybin, we searched clinicaltrials.gov for in-progress trials. We identified four such trials, with anticipated completion dates ranging from July 2023 to August 2024 (**Table 2**). Although one small (n=14) randomized trial evaluated low-dose psilocybin for cluster headaches, it did not meet inclusion criteria because the condition is characterized by recurrent but brief (minutes to hours) episodes and not considered chronic pain.[15] Due to the lack of evidence examining psilocybin and chronic or subacute pain, the decision was made to not include psilocybin for this year, but revisit the decision next year.

Table 2. Upcoming clinicaltrials.gov studies on psilocybin for treatment of chronic and subacute pain

Title	ClinicalTrials.gov Identifier	Comparison	Enrollment	Anticipated Completion Date
Psilocybin-assisted Therapy for Phantom Limb Pain	NCT05224336	Psilocybin; Placebo (Niacin)	20	July 2023
Open-label Study to Assess the Safety and Efficacy of TRP-8802 With Psychotherapy in Adult Participants With Fibromyalgia	NCT05128162	TRP-8802 (Psilocybin); Psychotherapy	20 (estimated)	May 2024
Psilocybin-facilitated Treatment for Chronic Pain	NCT05068791	Psilocybin; Dextromethorphan	30	July 2024
Psilocybin in Patients With Fibromyalgia: EEG-measured Brain Biomarkers of Action	NCT05548075	Psilocybin; Behavioral Therapeutic Support	20	August 2024

Abbreviations: EEG = electroencephalogram.

- Spasticity: We also discussed the appropriateness of including spasticity not associated with chronic pain. Spasticity is commonly experienced post-stroke and by patients with multiple sclerosis and cerebral palsy. Spasticity refers to an abnormal increase in muscle tone and contraction, usually caused by damage to the nerve pathways in the brain or spinal cord. Although spasticity is often associated with pain, this is not always the case. While some TEP members felt that reviewing the evidence on spasticity without chronic pain may provide useful complementary information, others noted that spasticity is a distinct condition not reflective of typical chronic pain and expanding the scope to include a non-pain condition would be confusing. In

addition, they noted that the living review already includes patients with spasticity and chronic pain (though studies of patients with spasticity without chronic pain or with unclear chronic pain are excluded). Further, expanding the scope to include spasticity could be duplicative, given the recent publication of a Cochrane systematic review on cannabis for multiple sclerosis (including spasticity)[16] and other published reviews on cannabis for spasticity and associated neurological conditions.[17-19] Therefore, the decision was made to not expand the scope to include spasticity.

Based on the considerations described above, we plan to prospectively expand the scope of the living review to include adolescents and subacute pain. The original protocol was posted on the PROSPERO international prospective register of systematic reviews (registration: CRD42021229579); we will post an updated protocol on PROSPERO that will reflect these changes in scope. We will continue to revisit scoping issues on an annual basis, utilizing input from experts and scans of the published literature and in-progress studies to inform decisions to adapt or expand the scope (e.g., for psilocybin, with anticipated completion of the first trial of psilocybin for chronic pain in July 2023).

3. Utilizing Ongoing Input From Experts

For a standard AHRQ systematic review, a panel of individuals (i.e., Key Informants) with expertise in the topic is typically engaged early in the review process primarily to assist in refining the scope of the review; once the review is under way a TEP is convened to provide technical and expert input on the protocol. Ongoing involvement of the TEP is usually not anticipated or required given the "one-off" nature of a standard (non-living) review. For a living systematic review, however, given the ongoing nature of the review and the need to reassess the scope and methods periodically, we have maintained a continually engaged TEP, consisting of persons with expertise in pharmacology, pain, addiction medicine, cannabis, behavioral health, and cannabis-related policy. We obtained input from the TEP as methodological or technical issues arose (such as classifying new interventions); unlike a typical (non-living) systematic review, where the TEP may be asked to provide similar input prior to completion of the report, for this living review we utilized the TEP on a periodic basis while conducting multiple quarterly and annual reports. For example, we continue to consult with the TEP on an ongoing basis about how to classify new products identified during surveillance within our categorization scheme.[20]We also obtained input from the TEP on how to handle a new study that evaluated a topical cannabis product, as it was unclear whether it was intended to produce systemic or only localized effects.[21]

Our experience highlights the value of reevaluating TEP expertise, recruiting new perspectives, and ongoing TEP engagement. We plan to maintain the TEP and will seek input from them on methodological or technical issues that arise, and will engage the TEP following the third annual review to obtain input on key issues that arise during year 3.

4. Living Review Report Frequency and Format

An important practical consideration for conducting living reviews is the optimal frequency and format of updates, and level of detail, to inform users of new evidence without causing reader fatigue or burnout.

We produced four quarterly reports in the interim between the cumulative annual updates. The annual reports presented detailed findings, similar to a "standard" systematic review.(**Table 1**). The quarterly surveillance reports in the interim were briefer (7 to 10 pages), and described the new evidence in the context of prior findings. They were designed to be stand-alone documents providing a brief background of the topic, important aspects of the methodology used, and the findings from the quarterly literature search. A summary table was created to describe new findings in the context of previous conclusions, with italics and bolding of text to distinguish them from prior surveillance results. Quarterly reports were posted on the AHRQ webpage, which also hosts the full systematic reviews and the data visualization dashboard.

We obtained input from the TEP to help understand user perspectives on the presentation format and frequency of update reports. Overall, it was noted that the quarterly updates and annual reports were useful, and may not result in reader fatigue or burnout. However, the TEP felt that the frequency and format of updates could be informed by the quantity and quality of new evidence. Given the low rate of new eligible studies for this living review, it was considered appropriate to potentially reduce the frequency of quarterly updates to every four or six months. Also, for updates with no studies, a brief note or summary describing the update search results was thought to potentially be sufficient. When new eligible studies were available but there was no change to findings (i.e., strength of evidence assessment or effect size), it was considered appropriate to briefly describe the new studies and note no changes to the findings. When new eligible studies were available that changed findings, a more detailed update describing the new evidence, how results changed, and updated summary of evidence tables, with changes highlighted, was thought to be useful. The strategy of matching the report format to the new evidence and its impact on findings is similar to the approach implemented by Annals of Internal Medicine.[22] For the annual updates, the TEP felt that a more detailed, comprehensive/cumulative report format was reasonable, though a shorter format might also be considered if new evidence is sparse and does not impact conclusions.

To further inform the frequency of update reports, we performed a search on clinicaltrials.gov for ongoing trials of cannabis for chronic and subacute pain. We identified 11 trials of cannabis for chronic pain, with estimated completion from March 2023 to February 2027 (**Table 3**), representing a substantial expansion of the evidence base when they are published.

Table 3. Studies on cannabis for subacute or chronic pain in adults and adolescents in clinicaltrials.gov

Title	Comparison	Enrollment	Anticipated Completion Date
Treatment of Chronic Pain With Cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC)	Delta-9-tetrahydrocannabinol; Cannabidiol; Placebo	75	March 2023
Cannabis Versus Oxycodone for Pain Relief	Cannabis; Oxycodone; Placebo	100	June 2023
Efficacy and Safety of VER-01 in the Treatment of Patients with Chronic Non-specific Low Back Pain	VER-01; Placebo	808	December 2023
Opioid-Sparing Effect of Oral Cannabinoids	CBD oil (MPL-001); CBD+THC oil (MPL-005); Placebo oil	51	December 2023
Safety and Efficacy of Oral Cannabis in Chronic Spine Pain	THC/CBD; CBD; Placebo	157	June 2024
Cannabinoids vs. Placebo on Persistent Post-surgical Pain Following TKA: A Pilot RCT	MPL-001 (CBD: THC 25:1); Placebo	40	August 2024
Sublingual Cannabidiol for Chronic Pain	Cannabidiol; Placebo	55	September 2024
Cannabis Vs. Opioids Pain Management Objective Testing Comparisons	Monochromatic Infrared Photo Energy (MIRE); Transcutaneous Electrical Nerve Stimulation (TENS); Opioids; Cannabis	1000	January 2025
Comparison of VER-01 to Opioids in Patients With Chronic Non-specific Low Back Pain	VER-01; Opioid Therapy	350	March 2025
Evaluation of Medical Cannabis and Prescription Opioid Taper Support for Reduction of Pain and Opioid Dose in Patients with Chronic Non-Cancer Pain	Medical Marijuana; Prescription Opioid Taper Support (POTS)	250	June 2025
Reducing Pain and Opioid Use With CBD	Cannabidiol; Placebo	150	February 2027

Abbreviations: CBD = cannabidiol; MIRE = Monochromatic Infrared Photo Energy; NR = not reported; POTS = Prescription Opioid Taper Support; RCT = randomized controlled trial; TENS = Transcutaneous Electrical Nerve Stimulation; THC = tetrahydrocannabinol; TKA = total knee arthroplasty.

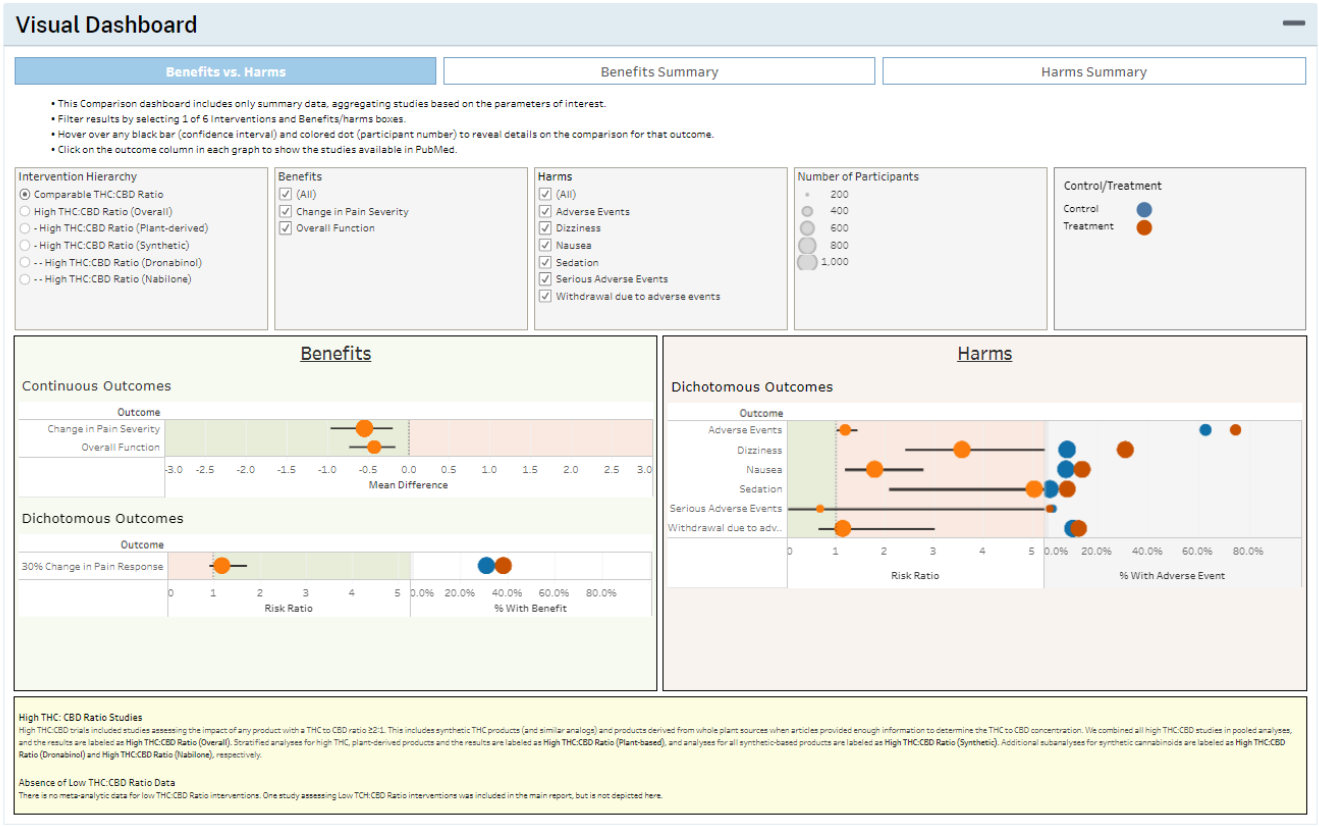
At this time, we plan to continue conducting quarterly updates and an annual review reflecting the protocol expansions. If changes in the frequency of updates occur in the future, these will be documented as protocol changes, as described in the prior section.

5. Use of Data Visualization To Present Findings of the Living Systematic Review

To enhance the usability and readability of our living systematic review, especially by busy clinician executives and policymakers, an interactive visual data dashboard was created to complement the update reports and annual reviews (Figure 1). These included development of a visual dashboard with interactive presentation of data and results and development of a "report snapshot." This visual dashboard, developed using the software program Tableau, shows pooled results for benefits and harms for different cannabis product categories (e.g., products with comparable tetrahydrocannabinol (THC) to cannabidiol (CBD) ratios, and those with high THC:CBD ratios). Results were shown for relative estimates of effects as well as absolute estimates in order to provide complementary information that could aid in interpretation of results. The interactive features allow users to focus on specific outcomes or comparisons and sub-analyses of interest (e.g., high THC:CBD ratio product results could be restricted to synthetic products, plant-derived products, dronabinol, or nabilone). In addition, hovering over the pooled results provides additional details (e.g., number of studies, number of persons with

outcome, sample size, statistical heterogeneity, and others). The report snapshot is intended to provide a brief summary of the review methods and findings, with separate tabs showing a summary of findings (organized by cannabis product and outcome), Key Questions addressed, definitions used, clinical and policy implications, and information on applicability and limitations. The data dashboard will also be updated synchronously with the quarterly report and annual review, reflecting the most current information.

Figure 1. Screenshot of Tableau visual dashboard hosted on AHRQ webpage



Abbreviations: AHRQ = Agency for Healthcare Research and Quality; CBD = cannabidiol; THC = tetrahydrocannabinol.

To better understand the impact and usefulness of these efforts, we sought feedback from the TEP on the usefulness of the data visualization and areas for improvement. The TEP agreed that both the visual dashboard and report snapshot were indeed useful to convey the findings from the living review updates and annual reviews and could potentially also be used as a resource for medical education. The TEP members did not describe specific areas for improvement, though they noted that there may be a learning curve associated with navigating the visual dashboard.

While we don't have a direct measure of readership and usage of the living review and the visual dashboard, webpage traffic data captured by the Google Analytics feature was available. From November 2021, soon after the original systematic review was published, to October 2022, there were a total of 10,523 views of the main web page that hosts the report snapshot and the visual dashboard. There were 1,773 views of the pooled estimates in the visual dashboard on the main webpage.

We sought input from the TEP on the summary of evidence (SOE) tables provided in the report (**Appendix A**). The SOE tables display results for different cannabis product categories

for pain response, pain severity, function, and various harms, including the effect size, number of studies, and strength of evidence ratings. The TEP members felt that the SOE tables were useful, though they suggested that additional shading or colors might be useful for distinguishing different strengths of evidence. The TEP also emphasized the importance of highlighting changes in effect size or strength of evidence assessments (e.g., with bolded/italicized text, colored text, or some other method), which we planned to do (there have not been any changes in strength of evidence assessments to date).

A visual abstract based on our living review[23] has been developed by the Systematically Testing the Evidence on Marijuana (STEM) project, which is funded by the U.S. Department of Veterans Affairs and the Center for Evidence-based Policy at Oregon Health & Science University (OHSU) (**Appendix B**). Over the past year, the webpage that the visual abstract is hosted on received 1,105 page views, of which 926 were views by unique users.

In addition to the visual dashboards and visual abstract, we also sought to disseminate the results of the systematic review by publishing a manuscript based on the findings.[24] The article, published in August 2022, has been cited 14 times, and was mentioned by 104 news outlets. The Altmetrics Attention Score is 868, which puts the manuscript in the top 5 percent of all research outputs scored by Altmetric.[25] Annals of Internal Medicine has also highlighted the manuscript in its "Best of Annals 2022."[26]

In order to obtain insight into alternative styles of visualization, we also obtained feedback from the TEP on the visual abstract developed by the STEM project,[23] based on the findings of the living review. The visual abstract summarizes the methods and findings in a single page, including a table showing strength of evidence and size of effects for specific cannabis products, with the aid of colors and symbols.

Overall, the feedback from the TEP and the available usage data suggest that readers found the visual dashboard and the report snapshot to be useful. Considering the large amount of information being presented, the TEP indicated that the use of colors and symbols was useful and noted that adding clear definitions of the outcomes and other terms used would improve usability and readability. Our experience suggests that data visualization techniques utilizing colors and symbols, are a useful complement to living reviews and warrant the time and resources required to develop and maintain them. We plan to continue these data visualization efforts and work to improve them, while ensuring that any changes comply with federal section 508 requirements. We will explore opportunities to obtain input from users of the report who are not members of the TEP, to better understand use in persons who are not experts or highly familiar with the report. We will also explore opportunities to obtain more detailed or specific usage data.

6. Conclusions

This white paper, drawing on the experience from the second year of conducting a living review on plant-based products for chronic pain, addressed four key issues relevant for conducting systematic reviews: (1) adapting or expanding the review scope; (2) utilizing ongoing input from experts; (3) optimizing living review report frequency and format; and (4) using data visualization and other visual methods to complement the living review reports. Our experience illustrates the value of maintaining a TEP on an ongoing basis when conducting living reviews. It also highlights the importance of periodically reassessing the composition of the TEP and inviting new members to provide the necessary expertise in key areas that may evolve over time. We recommend that living systematic review authors periodically reassess the scope of living systematic reviews and revise if necessary to ensure that the review remains useful, maintain

engagement with a TEP with the appropriate mix of expertise to inform methodological and technical issues, tailor the frequency and format of update reports based on the impact of new evidence on review findings, and utilize data visualization methods to enhance the usability of report findings.

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Appendix A. Summary of Evidence Tables

Table A-1. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

Product, THC to CBD Ratio	Pain Response Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD Oromucosal Spray	Potential effect (4)[a] [+]	Small effect (7) [++]	Small effect (6) [++]
High THC – Synthetic, Oral	Large effect (1) [+]	Moderate effect (6) [+]	No effect (3) [+]
High THC – Extracted From Whole Plant, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Topical CBD	No evidence	Insufficient (1)	No evidence
Low THC – Oral CBD	No evidence	Insufficient (1)	Insufficient (1)
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[b]	No evidence	Insufficient (1)	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[b] Comparison was "usual care."
Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased benefit; SOE: [+] = low, [++] = moderate, [+++] = high.

Table A-2. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

Product/THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Comparable THC/CBD Oromucosal Spray	No effect (5) [+]	No effect (3) [+]	Large effect (6) [+]	Moderate effect (6) [+]	Large effect (6) [+]
High THC – Synthetic, Oral	Potential effect[a] (4) [+]	Insufficient (1)	Large effect (2) [++]	Potential effect[a] (2) [+]	Moderate effect (3) [+]
High THC – Extracted From Whole Plant, Oral	Large effect (1) [+]	Insufficient (1)	Large effect (1) [+]	No evidence	No evidence
Low THC – Topical CBD	No evidence	No evidence	No evidence	No evidence	No evidence
Low THC – Oral CBD	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC)[b]	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.
[a] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[b] Comparison was "usual care."
Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: [+] = low, [++] = moderate, [+++] = high.

Appendix B. Visual Abstract

Figure B-1. Systematically Testing the Evidence on Marijuana (STEM) visual abstract