Effective Health Care

Cannabinoids for Alcohol Withdrawal

Results of Topic Selection Process & Next Steps

The nominator is interested in research on the use of cannabinoids for alcohol use disorder.

Because no original research addresses the nomination, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Number and Name: Cannabinoids for Alcohol Withdrawal

Nomination Date: 3/29/2019

Topic Brief Date: 4/17/2019

Authors
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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

- Alcohol misuse is alcohol consumption that puts someone at higher risk for adverse health and social consequences. NIAA defines this as more than 4 drinks per day for men or more than 3 drinks per day for women; or more than 14 drinks per week for men or more than 7 drinks per week for women.[1]
- There are about 88,000 deaths attributable to excess alcohol use every year in the US[2]
- For people with alcohol dependence they may experience alcohol withdrawal when stopping drinking. Symptoms could milder such as headache, anxiety, nausea, tremulousness, and insomnia; or more severe such as mental confusion, hallucinations, disorientation and seizures.[3]
- When severe, alcohol withdrawal requires medical management. Types of medications used include benzodiazepines, clonidine, and gabapentin.[3]
- Recent evidence suggests that human endocannabinoid metabolism can affect alcohol dependence and targeting this system may be useful.[4]
- Cannabinoids are the active ingredients found in the cannabis plant. This includes
    - Tetrahydrocannabinol (THC), the main active chemical in cannabis.
    - Dronabinol is a synthetic form of THC. It is used to treat nausea and vomiting caused by cancer chemotherapy; and anorexia and weight loss in people with AIDS.
    - Cannabidiol is the second most prevalent of the active ingredients of cannabis. It is derived directly from the hemp plant, a cousin of the marijuana plant. It does not cause euphoria.
- The nominator shares about personal experience with use of THC to mitigate symptoms of alcohol withdrawal, and believes that this is an area for further study.
- The use of THC or cannabinoids for alcohol withdrawal is not well-accepted but has been described in multiple internet sources.

Key Questions and PICOs

The key questions for this nomination are:

1. What is the effectiveness and harms of cannabinoids to treat alcohol withdrawal symptoms?

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	
Population	Adults 18 years and older treated for alcohol misuse
Interventions	Cannabinoids
Comparators	Usual care
Outcomes	Symptoms of alcohol withdrawal Alcohol use Quality of life
Timing	All
Setting	Outpatient

Abbreviations:

Methods

We assessed nomination for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from April 2014 to May 2019. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

We reviewed all identified titles and abstracts for inclusion and classified identified studies by key question and study design to assess the size and scope of a potential evidence review.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This is an appropriate and important topic.

Desirability of New Review/Duplication

A new evidence review would not be duplicative of an existing evidence review. We identified two related reviews that were not duplicative. These reviews did not focus on the range of substances of interest, and did not specifically address alcohol withdrawal symptoms. Given the limited literature, these are included as resources that may be of interest.

- Tuma et al. Cannabidiol as a novel candidate alcohol use disorder pharmacotherapy: a systematic review. This 2019 review focused solely on cannabidiol, and did not include THC.[5]

- Sloan et al. The endocannabinoid system as a target for addiction treatment: trials and tribulations. This is a 2017 literature review that includes opioid, alcohol and cannabis addiction.[4]
- Subbaraman et al. Substitution and Complement arity of Alcohol and Cannabis: A review of the literature. This 2016 literature review did not directly address cannabis for alcohol withdrawal.[6]
- Lucas et al. Cannabis as a complement or substitute of opioids and alcohol: a systematic review of longitudinal studies. This is an in-process review.[7]
    - While this review protocol did include THC, it focuses on the use of cannabis as a substitute for alcohol and does not focus on the use of THC for alcohol withdrawal.

Impact of a New Evidence Review

A new systematic review may have uncertain impact.

Feasibility of a New Evidence Review

A new evidence review is not feasible. We identified no relevant studies. Our search identified preclinical and animal studies, but none that studied humans.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product. We found no systematic reviews related to this topic.
- Impact: A new systematic review has unclear impact potential.
- Feasibility: A new review is not feasible. We identified no studies.

References

1. Drinking Levels Defined. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking. Accessed on 6 may 2019.
2. Alcohol Related Disease Impact (ARDI) application. Atlanta, GA: Centerse for Disease Control and Prevention; 2013. www.cdc.gov/ARDI.
3. Treatment for Alcohol Problems: Finding and Getting Help. Rockville, MD: national Institute on Alcohol Abuse and Alcoholism; 2014. https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/treatment-alcohol-problems-finding-and-getting-help. Accessed on 6 May 2019.
4. Sloan ME, Gowin JL, Ramchandani VA, et al. The endocannabinoid system as a target for addiction treatment: Trials and tribulations. Neuropharmacology. 2017 Sep 15;124:73-83. doi: 10.1016/j.neuropharm.2017.05.031. PMID: 28564576. https://www.ncbi.nlm.nih.gov/pubmed/28564576
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6. Subbaraman MS. Substitution and Complementarity of Alcohol and Cannabis: A Review of the Literature. Subst Use Misuse. 2016 Sep 18;51(11):1399-414. doi: 10.3109/10826084.2016.1170145. PMID: 27249324. https://www.ncbi.nlm.nih.gov/pubmed/27249324
7. Lucas P, Walsh Z, Crosby K, et al. Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors. Drug Alcohol Rev. 2016 May;35(3):326-33. doi: 10.1111/dar.12323. PMID: 26364922. https://www.ncbi.nlm.nih.gov/pubmed/26364922

8. Wiese B, Wilson-Poe AR. Emerging Evidence for Cannabis' Role in Opioid Use Disorder. Cannabis Cannabinoid Res. 2018;3(1):179-89. doi: 10.1089/can.2018.0022. PMID: 30221197. https://www.ncbi.nlm.nih.gov/pubmed/30221197

Appendix A. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	No
1c. Is the focus on effectiveness or comparative effectiveness?	No
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes
2c. Represents important uncertainty for decision makers	No
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	We identified no relevant reviews. We identified three completed reviews and one in-process reviews that have related information but do not directly address the nominator's question. These reviews were either not systematic reviews, did not address alcohol withdrawal, or did not include research on humans.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	The standard of care is clear. Typically benzodiazepines and supportive care are the mainstay for managing symptoms of alcohol withdrawal. This is used in conjunction with anticonvulsants if needed. THC is not mentioned as an acceptable option for treatment. It has however been mentioned as a potential option for those with opioid use disorder.[8] However on multiple industry-related websites, THC or cannabinoids are discussed as a potential option for outpatient detoxification from alcohol, and it appears that individuals are trying it on their own.

4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	While it THC and cannabinoids are not cited in guidelines and may not be recommended by the clinician community, individuals may be using these substances to manage alcohol withdrawal without medical supervision.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	We identified no relevant studies. We identified no relevant studies in ClinicalTrials.gov.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed below are the sources searched, hierarchically

Primary Search
AHRQ: Evidence reports and technology assessments https://effectivehealthcare.ahrq.gov/; https://www.ahrq.gov/research/findings/ta/index.html; https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program https://www.hsrd.research.va.gov/publications/esp/
Cochrane Systematic Reviews http://www.cochranelibrary.com/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
Secondary Search
AHRQ Products in development https://effectivehealthcare.ahrq.gov/
VA Products in development https://www.hsrd.research.va.gov/publications/esp/
Cochrane Protocols http://www.cochranelibrary.com/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
Tertiary Search
PubMed https://www.ncbi.nlm.nih.gov/pubmed/

Appendix C. Search Strategy & Results (Feasibility)

("dronabinol"[MeSH Terms] OR "dronabinol"[All Fields] OR "tetrahydrocannabinol"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND withdrawal[All Fields]

(("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND withdrawal[All Fields]) AND ("dronabinol"[MeSH Terms] OR "dronabinol"[All Fields] OR "thc"[All Fields]) AND ("2014/05/04"[PDat] : "2019/05/02"[PDat] AND "humans"[MeSH Terms])

(("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND withdrawal[All Fields]) AND ("cannabinoids"[MeSH Terms] OR "cannabinoids"[All Fields] OR "cannabinoid"[All Fields]) AND ("2014/05/04"[PDat] : "2019/05/02"[PDat] AND "humans"[MeSH Terms])

https://clinicaltrials.gov/ct2/results?cond=Alcohol+Withdrawal