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Risks of harm with cannabinoids, cannabis, and cannabis-based medicine for pain management relevant to patients receiving pain treatment: protocol for an overview of systematic reviews

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Abstract

Introduction: With the increasing availability of cannabis and cannabinoids and their potential utility for pain treatment, there is a growing need to evaluate the risk-benefit considerations of cannabinoids for the management of pain. As part of the IASP Cannabis and Cannabinoids Task Force, this protocol describes a planned overview of systematic reviews summarizing the risks of harm with cannabinoids that are relevant to patients receiving pain treatment.

Methods: This overview will involve literature searches of several databases and a defined search strategy that will target systematic reviews or meta-analyses of cannabinoids where harms are the primary focus. Data extraction will include various features of the cannabinoid(s) and the harm(s) being studied as well as other methodological features of each included systematic review. Methodological quality of each included review will be assessed using AMSTAR-2 as well as compliance with the PRISMA harms checklist. Prospero registration pending.

Discussion: The broad overview of reviews defined by this protocol is expected to synthesize available good quality evidence of harms that will help inform risk-benefit considerations about the use of cannabinoids for pain management.

Keywords: Cannabis, Cannabinoids, Harms, Adverse events, Adverse effects, Pain management, Clinical trials

1. Introduction

Pain, a common symptom of many acute and chronic health problems, as well as a disease in its own right in the case of chronic pain,[26] is one of the most costly and disabling health care problems today.[1,5,12,16,24] Due to its complex biopsychosocial contributing and modulating factors, it has been long recognized that effective pain management very often requires a multidisciplinary and multimodal treatment approach.[3,6,9,13,14,22] Very few single pain treatments are highly effective for a majority of pain sufferers,[7,17,30] and commonly used treatments such as acetaminophen (paracetamol), nonsteroidal anti-inflammatory drugs, opioids,

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anticonvulsants, and antidepressants are associated with risks of serious harms.[4,10,15,18] Thus, there is a continued search for more widely effective, and, perhaps more importantly, safer pain therapies.[25,28,29]

With the recognition of analgesic effects of cannabis and cannabinoids and their potential utility for pain management,[2,19] the legalization of cannabis in a growing number of jurisdictions in the world,[27] and an increasing level of prescribing of cannabinoids for medicinal purposes in some countries,[11] there is a growing need to carefully evaluate the risk–benefit considerations of cannabinoids for the management of pain. Thus, the Cannabis and Cannabinoids Task Force was established by the International Association for the Study of Pain for this purpose (https://www.iasp-pain.org/About/Content.aspx?ItemNumber=7917). The efforts of this task force involve 4 work packages (WP) to address 4 respective areas of focus: (WP1) chemical classification, basic pharmacology, and preclinical evidence of analgesic efficacy; (WP2) synthesis of evidence of clinical efficacy in pain management; (WP3) synthesis of evidence of harms relevant to patients receiving cannabinoids for pain management; and (WP4) consideration of societal harms. This review is intended to focus on WP3. Evidence on harms from pain management clinical trials is being synthesized by another ongoing review.[21] However, such trials are limited by short treatment duration and narrowly defined patient populations or clinical settings. Therefore, this protocol will define a broad overview of systematic reviews summarizing the risks of harm with cannabinoids that are relevant to patients receiving pain treatment.

2. Objectives

The objective of this overview is to synthesize evidence of harms of cannabinoids—other than the evidence reported in pain treatment clinical trials—that is relevant to patients receiving cannabinoids for the management of pain.

3. Methods

This protocol is developed in accordance with PRISMA-P guidelines[20] and will be registered in the PROSPERO register (protocol number pending).

3.1. Sources of evidence

As an overview of reviews on harms, this broad-spectrum search protocol targets reviews where harms are the primary focus. We will search for systematic reviews in PubMed, EMBASE, and the Cochrane Database of Systematic Reviews. The literature search strategy is shown in Appendix 1 (available at http://links.lww.com/PR9/A44). This search strategy was developed with careful consideration of other previous reviews of cannabinoid-related harms, as well as previous generic approaches to harms reviews.[8] In addition to the reviews identified by this search strategy, other reviews identified by hand searching of the reviewed articles will be considered for inclusion in this overview of reviews.

3.2. Report selection

To be included in this overview, reports were required to be a systematic review (with or without meta-analysis) focusing on one or more harms related to cannabinoids (as defined in Appendix 1, available at http://links.lww.com/PR9/A44) in any setting that could be considered relevant to patients receiving cannabinoids for pain management.

3.3. Data extraction

Data extracted from each report will include type(s) of cannabinoid(s) evaluated, type(s) of harm(s) evaluated, type(s) of studies (eg, randomized controlled trials of nonpain conditions, case series, prospective cohort studies, large database studies, epidemiological studies etc.), numbers of studies and subjects/participants included in each review, patient population and/or clinical setting, specific harm(s) being reported and methods for their assessment/quantification, cannabinoid being studied (eg, recreational, medicinal, pharmaceutical, smoked, and ingested), and reported dosage/duration.

3.4. Quality assessment

For each review included in the overview, methodological quality will be assessed using AMSTAR-2[23] as well as evaluating compliance with items included in the PRISMA harms checklist.[31] Other elements of evidence quality will be evaluated including use of control groups/comparators, study size, precision/accuracy of cannabinoid exposure, and methodology for the measurement of harm.

4. Discussion

In various national, state, or provincial jurisdictions where cannabis is legal for medical purposes, cannabis can be "authorized" for medical purposes, rather than "prescribed," because there may be no drug identification number or other such recognition by the relevant drug regulatory agencies. However, pharmaceutical cannabinoid agents that have been approved by drug regulatory agencies for clinical use are indeed "prescribed." Patients may receive a variety of cannabinoids to treat chronic or acute pain either prescribed/dispensed with direct clinician supervision or self-sought and obtained without clinician supervision. The most direct evidence of harms would come from studies in these 2 different settings. However, further evidence of harms that would be considered relevant to patients receiving cannabinoids for pain treatment could also come from settings where cannabinoids are prescribed/dispensed for a nonpain indication or self-sought for recreational use. Thus, the broad overview of reviews defined by this protocol is expected to synthesize the available good-quality evidence of harms that will help inform risk–benefit considerations about the use of cannabinoids for pain management.

Disclosures

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submitted work. In addition, A.S.C. Rice has a patent null pending and is an IASP Councillor and Chair of the Cannabis Presidential Task Force. M. Wallace—Consultant, Insys. The remaining authors have no conflicts of interest to disclose.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A44.

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