Pharmacology
Research Protocol

OPEN

PAIN REPORTS®

# 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

Ian Gilron[a,b,c,*], Fiona M. Blyth[d], Louisa Degenhardt[e], Marta Di Forti[f,g,h], Christopher Eccleston[i], Simon Haroutounian[j], Andrew Moore[k], Andrew S.C. Rice[l], Mark Wallace[m]

**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,

*Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.*

*[a] Department of Anesthesiology and Perioperative Medicine, Kingston General Hospital, Queen's University, Kingston, ON, Canada, [b] Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada, [c] School of Policy Studies, Queen's University, Kingston, ON, Canada, [d] University of Sydney Centre for Education and Research on Ageing, Concord Repatriation General Hospital, Concord, New South Wales, Australia, [e] National Drug and Alcohol Research Centre, UNSW Sydney, Sydney, New South Wales, Australia, [f] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [g] National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London, Maudsley NHS Foundation Trust, King's College London, London, United Kingdom, [h] South London and Maudsley NHS Mental Health Foundation Trust, London, United Kingdom, [i] Centre for Pain Research, The University of Bath, Bath, United Kingdom, [j] Division of Clinical and Translational Research, Department of Anesthesiology, Washington University Pain Center, Washington University School of Medicine, St Louis, MO, USA, [k] Nuffield Department of Clinical Neurosciences, University of Oxford, Pain Research, The Churchill, Oxford, United Kingdom, [l] Pain Research Group, Department Surgery and Cancer, Faculty of Medicine, Imperial College London, London, United Kingdom, [m] Department of Anesthesiology, University of California San Diego, San Diego, CA, USA*

**Corresponding author. Address: Department of Anesthesiology & Perioperative Medicine, Victory 2 Pavillion, 76 Stuart Street, Kingston, Ontario, Canada, K7L2V7. Tel.: 1-613-548-7827. E-mail address: gilroni@queensu.ca (I. Gilron).*

*Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).*



*PR9 4 (2019) e742*

*http://dx.doi.org/10.1097/PR9.0000000000000742*

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

I. Gilron is a co-principal investigator of the CIHR SPOR Canadian Pain Network (CPN). I. Gilron has received industry support from Adynxx, Biogen, Eupraxia, Novaremed, and Teva. I. Gilron is co-chair of the Clinical Research Network of the CPN, which receives research support from Canopy Health, Toronto Poly Clinic, and CannTrust. L. Degenhardt has received untied educational grants from Reckitt Benckiser, Indivior, Munipharma, and Seqirus for the conduct of postmarketing surveillance studies of opioid medications. M. Di Forti reports grants from MRC and personal fees from Janssen, outside the submitted work. S. Haroutounian has received research support from Pfizer Inc (ASPIRE neuropathic pain grant program) and industry support from Medoc Ltd. A. Moore reports personal fees from Novartis and personal fees from RB, outside the submitted work. A.S.C. Rice reports other from International Association for Study of Pain, during the conduct of the study; personal fees from Imperial College Consultants; and other from Spinifex/Novartis, outside the

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.

This work was supported, in part, by the Queen's University Department of Anesthesiology & Perioperative Medicine, and the Chronic Pain Network of the Canadian Institutes of Health Research Strategy on Patient-Oriented Research.

## Appendix A. Supplemental digital content

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

**Article history:**
Received 7 February 2019
Received in revised form 6 March 2019
Accepted 9 March 2019

## References

[1] Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. PAIN 2001;89:127–34.
[2] Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 2001;323:13–6.
[3] Deshpande MA, Holden RR, Gilron I. The impact of therapy on quality of life and mood in neuropathic pain: what is the effect of pain reduction? Anesth Analg 2006;102:1473–9.
[4] Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152:85–92.
[5] Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet 1999;354:1248–52.
[6] Flor H, Fydrich T, Turk DC. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. PAIN 1992;49:221–30.
[7] Gilron I, Dickenson AH. Emerging drugs for neuropathic pain. Expert Opin Emerg Drugs 2014;19:329–41.
[8] Golder S, Loke Y. Search strategies to identify information on adverse effects: a systematic review. J Med Libr Assoc 2009;97:84–92.
[9] Guzmán J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary bio- psycho-social rehabilitation for chronic low back pain. Cochrane Database Syst Rev 2002;1:CD000963.
[10] Hernández-Díaz S, Rodríguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000;160:2093–9.
[11] Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. JAMA 2015;313:2474–83.
[12] Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an internet-based survey. J Pain 2010;11:1230–9.
[13] Kaiser U, Treede RD, Sabatowski R. Multimodal pain therapy in chronic noncancer pain-gold standard or need for further clarification? PAIN 2017;158:1853–9.
[14] Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77:1048–56.
[15] Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, Alexander GC. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. Annu Rev Public Health 2015;36:559–74.
[16] Kroenke K, Price RK. Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. Arch Intern Med 1993;153:2474–80.
[17] Max MB. Is mechanism-based pain treatment attainable? Clinical trial issues. J Pain 2000;1(3 suppl):2–9.
[18] McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633–44.
[19] Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. Nature 1998;395:381–3.
[20] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group PP. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[21] Mohiuddin MM, Mizubuti G, Haroutounian S, Smith S, Campbell F, Park R, Gilron I. Adherence to consolidated standards of reporting trials (CONSORT) guidelines for reporting safety outcomes in trials of cannabinoids for chronic pain: protocol for a systematic review. JMIR Res Protoc 2019;8:e11637.
[22] Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology (Oxford) 2008;47:670–8.
[23] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.
[24] St Sauver JL, Warner DO, Yawn BP, Jacobson DJ, McGree ME, Pankratz JJ, Melton LJ III, Roger VL, Ebbert JO, Rocca WA. Why patients visit their doctors: assessing the most prevalent conditions in a defined American population. Mayo Clin Proc 2013;88:56.
[25] Themistocleous AC, Crombez G, Baskozos G, Bennett DL. Using stratified medicine to understand, diagnose, and treat neuropathic pain. PAIN 2018;159(suppl 1):S31–42.
[26] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the International Classification of Diseases (ICD-11). PAIN 2019;160:19–27.
[27] Wilkinson ST, Yarnell S, Radhakrishnan R, Ball SA, D'Souza DC. Marijuana legalization: impact on physicians and public health. Annu Rev Med 2016;67:453–66.
[28] Woodcock J, Witter J, Dionne RA. Stimulating the development of mechanism-based, individualized pain therapies. Nat Rev Drug Discov 2007;6:703–10.
[29] Woodcock J. A difficult balance—pain management, drug safety, and the FDA. N Engl J Med 2009;361:2105–7.
[30] Woolf CJ; American College of Physicians, American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441–51.
[31] Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S; PRISMA Harms Group. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016;352:i157.