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# **PROTOCOL FOR A SCOPING REVIEW OF SYSTEMATIC REVIEWS: BENEFITS AND HARMS OF MEDICAL MARIJUANA**

**SUBMITTED TO THE COCHRANE COMPLEMENTARY MEDICINE FIELD**  
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**DATE SUBMITTED:**  
JANUARY 16, 2018

**SUBMITTED BY:**  
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## 1. BACKGROUND

In 1999, a report by the Institute of Medicine (now known as the National Academies of Sciences, Engineering and Medicine) supported the use of marijuana (*cannabis sativa*) in medicine, and regulatory medical colleges in a variety of countries published recommendations/considerations for its prescription to patients<sup>1</sup>. An updated report in 2017 called for a national research agenda, improvement of research quality, improvement in data collection and surveillance efforts, and strategies for addressing barriers in advancing the cannabis agenda.<sup>2</sup>

Interest in medical applications of marijuana has increased dramatically during the past twenty years. Claims of its benefits for a highly varied range of medical conditions have long been described. A simple search of Medline identifies a broad range of conditions wherein the use of medical marijuana has been reported. This includes (but is not limited to): pain control<sup>3,4</sup> of many forms, including cancer pain, pain from headaches, pain from rheumatic conditions and various other disorders; nausea and vomiting prevention/control;<sup>5</sup> anxiety;<sup>6</sup> sleep disorders;<sup>7</sup> spasticity in multiple sclerosis;<sup>8</sup> appetite stimulation<sup>9</sup> (in patients with cancer or chronic diseases such as HIV, AIDS and nerve pain); abdominal pain in inflammatory bowel disease<sup>10</sup>; disorders such as epilepsy<sup>10</sup> which are associated with seizures; glaucoma<sup>11</sup>; autoimmune diseases<sup>12</sup>; and for its anti-tumor effects in certain cancers<sup>13</sup>.

The number of Canadian residents with prescriptions to purchase medical marijuana from Health Canada approved growers tripled from 30,537 in 2015 to near 100,000 in 2016<sup>14</sup>. It is estimated that over 2 million people in the US are legally using medical marijuana (<https://medicalmarijuana.procon.org/view.resource.php?resourceID=005889>). Estimates suggest a total of \$6.7 billion US was spent in North America on legal marijuana in 2016.

Marijuana can be consumed by patients in a variety of ways including smoking, vaporizing, ingesting or administering sublingually or rectally. It consists of more than 100 known cannabinoids, the main ones of relevance to medical applications being *tetrahydrocannabinol* (THC) and *Cannabidiol* (CBD)<sup>15</sup>. Its psychotropic (e.g. feelings of euphoria, relaxation, increased creativity, well-being, and so forth<sup>6,16</sup>) and physical effects (e.g. muscle relaxation, appetite increase, and so forth<sup>17</sup>) underpin interest in its medical applications, with these effects often setting in for patients within minutes and lasting up to six hours depending on the route of exposure. In the body two cannabinoid receptors have been identified (CB1 and CB2). CB1 receptors are most commonly found in the central nervous system while CB2 receptors are typically found in peripheral nerve cells and on cells with immune function. While other receptors that have not been as well described exist, the effect of THC and CBD are a result of binding in the same manner as endogenous cannabinoids.

In Canada, cannabis products are available for purchase and use with a valid prescription but as of July 1, 2018 it is anticipated that these products will also be made available to adults for recreational purposes. In the United States, a majority of states have comprehensive medical marijuana programs as of 2017 (<http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>) and seven states so far have legalized marijuana for recreational use (<http://www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html>).

Medicinal use of marijuana is not monitored as more traditional medicines are, and thus there exists a variety of unknowns regarding its potential health risks to patients. As different cannabis plants and products will contain varied concentrations of THC and CBD, the effects of exposure may be unpredictable. While short-lasting side effects including drowsiness, loss of short term memory and dizziness are relatively well known and may be considered minor, other possible effects (e.g. psychosis, paranoia, anxiety, infection, withdrawal and so forth) may be more harmful to patients.

## 2. OBJECTIVES

There remains a considerable degree of clinical equipoise as to the benefits and harms of marijuana use for medical purposes<sup>18-21</sup>. To establish a robust understanding of the state of the evidence underlying this issue, we will conduct a scoping review *of existing systematic reviews*<sup>22-24</sup> which have previously evaluated the benefits and/or harms of medical marijuana for any indication. In locating and mapping SRs, we will summarize the state of research and thematically describe research findings for the purpose of answering practice and/or policy questions in relation to medical marijuana<sup>23</sup>. If possible, we will note any identified gaps in the synthesized literature. However, it will be important to clarify that gaps in SR literature does not necessarily equate to gaps in primary literature.

The completed work will provide an overview of the literature and answer the following question:

**PRIMARY QUESTION:** What evidence from systematic reviews (SRs) exists on the harms and benefits of medical marijuana?

## 3. METHODS

### 3.1 PICOTS FRAMEWORK

Systematic review eligibility will be determined according to the following criteria:

#### INCLUSION CRITERIA:

1. Systematic reviews will be included if they report to investigate harms and/or benefits of medical or therapeutic use of marijuana for adults and children for any indication (see Table 1 for definitions related to medical marijuana.)
2. Any systematic review, meta-analysis, guideline, health technology assessment or similar will be included if:
  - At least one database was searched, and search dates are reported
  - At least one eligibility criterion is reported
  - References having assessed quality of studies

- There is a narrative or quantitative synthesis of evidence
3. Systematic reviews assessing numerous interventions (including cannabis) will be included as long as data for marijuana is provided separately.
  4. For practical reasons we will only include systematic reviews written in English

### EXCLUSION CRITERIA:

1. Overviews of reviews will be excluded but their reference lists will be hand searched for systematic reviews not included otherwise.
2. Abstracts and protocols of systematic reviews will be excluded, and time permitting, full texts of these documents will be searched.
3. Systematic reviews that look at recreational, acute or general cannabis use/abuse (not for therapeutic use for illness or condition) will be excluded, as well as reviews assessing athletic or cognitive performance.
4. Synthetic cannabinoids (SCs) not approved for therapeutic use (e.g. “K2” or “Spice”)
5. Systematic reviews on cannabis use disorders (treatment options and health outcomes for substance users)
6. Systematic reviews that assess only accidental cannabis use will be excluded.

**Table 1**

TERM	DEFINITION
Medical Marijuana (or marijuana for medical use)	<p>The term medical marijuana refers to using the whole, unprocessed marijuana plant or its basic extracts to treat symptoms of illness and other conditions (<a href="https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine">https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine</a>)</p> <p>Whether marijuana is recognized as medicine varies from country to country. The U.S. Food and Drug Administration (FDA) has not recognized or approved the marijuana plant as medicine, but a growing number of states have legalized marijuana for medical use. In Canada it is legal to possess cannabis for medical purposes, and legalization for non-medical use is set to take place in 2018.</p>
Cannabis for Therapeutic Purposes (CTP)	A similar term to “medical marijuana,” CTP refers to legal access to cannabis for therapeutic purposes; this includes symptoms associated with health or mental disorders <sup>25</sup>

## 3.2 SEARCH METHODS

An experienced medical information specialist developed and tested the search strategy using an iterative process in consultation with the review team. Another senior information specialist peer

reviewed the strategy prior to execution using the PRESS Checklist<sup>26</sup>. We searched seven Ovid databases: Ovid MEDLINE®, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase, Allied and Complementary Medicine Database, PsycINFO, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. The search strategy was developed for MEDLINE and will be translated to the other databases (see Appendix 1.) We performed the searches on November 3, 2017.

We incorporated controlled vocabulary (e.g., “Cannabis”, “Cannabinoids”, “Medical Marijuana”) and keywords (e.g., “marijuana”, “hashish “, “tetrahydrocannabinol”) into the searches and applied a broad systematic review filter where appropriate. We adjusted vocabulary and syntax across the databases and removed animal-only and opinion pieces, where possible, from the results.

Grey literature searching will be limited to relevant drug and mental health databases, as well as HTA (Health Technology Assessment) and SR databases. Searches will be conducted on TRIP, CAMH, Campbell Systematic Reviews, American Society of Neurology, National Institute of Mental Health, Substance Abuse and Mental Health Services Administration. We will also consider major integrative oncology, complementary medicine, gastrointestinal, and neurological societies or associations.

If feasible, reference lists of included systematic reviews will be scanned for additional relevant reviews.

Specific details regarding the final strategies appear in Appendix 1.

### 3.3 STUDY SCREENING

Management of all screening will be performed using Distiller SR Software (Evidence Partners Inc., Ottawa, Canada). Citations from the literature search will be collated and de-duplicated in Reference Manager, and then uploaded to Distiller. The review team will use Distiller for Levels 1 and 2 screening, and pilot testing of screening questions for both levels will be completed prior to implementation. At level 1 screening, titles and abstracts will be assessed by one reviewer for potential relevance; a second reviewer will verify those records deemed not relevant. At level 2 screening full-text reports will be assessed for eligibility by two independent reviewers. Disagreements during full-text screening will be resolved through consensus, or by a third team member. As recommended by the PRISMA statement<sup>27,28</sup>, a flow diagram will be presented to describe the process of study selection.

### 3.4 DATA EXTRACTION AND ANALYSIS

**Data charting.** Data collection will be performed by one reviewer with verification by a second reviewer, and involvement of a third reviewer, as needed, to establish consensus for data extraction disagreements. All data collection will be performed electronically using Microsoft Excel software (Microsoft Corporation, Seattle, USA). A draft data extraction form with the list of proposed variables is provided in Appendix B, and includes quality assessment of included reviews using AMSTAR-2<sup>29</sup>. The data collection form will be piloted on select systematic reviews (up to 10) to refine the form. We intend to harness additional, relevant information not captured by the data extraction framework, if possible. The extent of breadth and depth of the extraction will be determined according to the volume of retrieved reviews, for feasibility.

**Collating and summarizing results.** As reflected above, we will use a directed content analytic approach with an initial deductive framework that has flexibility for inductive analysis if refinement or development of new categorization is needed. The final presentation of results will include tabulation of data and diagrammatic figures. Where appropriate, the narrative description of the data will be presented as frequencies and percentages, medians and interquartile ranges, or means and standard deviations. We will also discuss the implications of the scope of the literature located, including that of perceived gaps in the body of synthesized research.

See Appendix 2 for draft data extraction variables.

### 3.5 COLLABORATION AND KNOWLEDGE TRANSLATION

We will work in collaboration with the Cochrane Complementary Medicine Field (Cochrane CAM Field) to carry out the proposed work. Susan Wieland will assist in determining the scope of the review, and will provide guidance by reviewing the list of included SRs and providing input on the final evidence map. Dr. Marc Clemons and Dr. Salmaan Kanji are clinical experts in the field, and will provide input on issues that arise during each step of the project.

A dissemination strategy is forthcoming, and will be developed in collaboration with the Cochran CAM Field

## 4. TIMELINES

- Protocol and search strategy – December 15<sup>th</sup>, 2017
- Study Screening – February 28<sup>th</sup>, 2018
- Data extraction and analysis – March 31<sup>st</sup>, 2018
- Draft report – May 31<sup>st</sup>, 2018
- Final report (incorporating any revisions) – June 30<sup>th</sup>, 2018

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## Appendix 1: Search Strategy

2017 Oct 5

Database: AMED (Allied and Complementary Medicine) <1985 to September 2017>, Embase Classic+Embase <1947 to 2017 October 03>, PsycINFO <1806 to September Week 4 2017>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

- 
- 1 Cannabis/ (43137)
  - 2 exp Cannabinoids/ (75395)
  - 3 Medical Marijuana/ (1090)
  - 4 Marijuana Smoking/ (6712)
  - 5 (cannabi\* or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana).tw,kw. (110153)
  - 6 or/1-5 [MARIJUANA] (137105)
  - 7 limit 6 to systematic reviews [Limit not valid in AMED,Embase; records were retained] (72882)
  - 8 meta analysis.pt. (91879)
  - 9 exp meta-analysis as topic/ (54578)
  - 10 (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*).tw,kw. (326270)
  - 11 (systematic review\* or systematic overview\* or evidence-based review\* or evidence-based overview\* or (evidence adj3 (review\* or overview\*)) or meta-review\* or meta-overview\* or meta-synthes\* or "review of reviews" or technology assessment\* or HTA or HTAs).tw,kw. (383728)
  - 12 exp Technology assessment, biomedical/ (23001)
  - 13 (cochrane or health technology assessment or evidence report).jw. (34958)
  - 14 (network adj (MA or MAs)).tw,kw. (15)
  - 15 (NMA or NMAs).tw,kw. (3850)
  - 16 indirect comparison?.tw,kw. (3961)
  - 17 (indirect treatment\* adj1 comparison?).tw,kw. (521)
  - 18 (mixed treatment\* adj1 comparison?).tw,kw. (1268)
  - 19 (multiple treatment\* adj1 comparison?).tw,kw. (229)
  - 20 (multi-treatment\* adj1 comparison?).tw,kw. (3)
  - 21 simultaneous comparison?.tw,kw. (1019)
  - 22 mixed comparison?.tw,kw. (47)
  - 23 or/8-22 (682615)

24 6 and 23 (2431)  
25 7 or 24 [MARIJUANA - REVIEWS] (73418)  
26 exp Animals/ not (exp Animals/ and Humans/) (15992866)  
27 25 not 26 [ANIMAL-ONLY REMOVED] (40363)  
28 (comment or editorial or interview or letter or news or newspaper article).tw,kw. (865409)  
29 27 not 28 [OPINION PIECES REMOVED] (38981)  
30 29 use ppez [MEDLINE RECORDS] (1028)  
31 cannabis/ (43137)  
32 exp cannabinoid/ (62692)  
33 medical cannabis/ (1482)  
34 exp "cannabis use"/ (6933)  
35 (cannabis or bhang or cannador or charas or ganja or ganjah or hashish or hemp or  
marihuana or marijuana).tw,kw. (74801)  
36 or/31-35 [MARIJUANA] (115456)  
37 meta-analysis/ (230418)  
38 "systematic review"/ (151380)  
39 "meta analysis (topic)"/ (37237)  
40 (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or  
integrative review\* or integrative overview\* or research integration or research overview\* or  
collaborative review\*).tw,kw. (326270)  
41 (systematic review\* or systematic overview\* or evidence-based review\* or evidence-based  
overview\* or (evidence adj3 (review\* or overview\*)) or meta-review\* or meta-overview\* or  
meta-synthes\* or "review of reviews" or technology assessment\* or HTA or HTAs).tw,kw.  
(383728)  
42 biomedical technology assessment/ (21865)  
43 (cochrane or health technology assessment or evidence report).jw. (34958)  
44 (network adj (MA or MAs)).tw,kw. (15)  
45 (NMA or NMAs).tw,kw. (3850)  
46 indirect comparison?.tw,kw. (3961)  
47 (indirect treatment\* adj1 comparison?).tw,kw. (521)  
48 (mixed treatment\* adj1 comparison?).tw,kw. (1268)  
49 (multiple treatment\* adj1 comparison?).tw,kw. (229)  
50 (multi-treatment\* adj1 comparison?).tw,kw. (3)  
51 simultaneous comparison?.tw,kw. (1019)  
52 mixed comparison?.tw,kw. (47)  
53 or/37-52 (729315)  
54 36 and 53 [MARIJUANA - REVIEWS] (2484)  
55 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or  
nonhuman/ or exp vertebrate/ (47677665)  
56 exp human/ or exp human experimentation/ or exp human experiment/ (36991239)  
57 55 not 56 (10688142)  
58 54 not 57 [ANIMAL-ONLY REMOVED] (2435)  
59 (editorial or letter).pt. (3037776)  
60 58 not 59 [OPINION PIECES REMOVED] (2410)  
61 60 use emczd [EMBASE RECORDS] (1439)  
62 exp cannabis/ (45629)

63 cannabinoids/ (20435)  
64 (cannabi\* or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana).tw. (108847)  
65 or/62-64 [MARIJUANA] (123486)  
66 meta analysis/ (230418)  
67 (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*).tw. (322718)  
68 (systematic review\* or systematic overview\* or evidence-based review\* or evidence-based overview\* or (evidence adj3 (review\* or overview\*)) or meta-review\* or meta-overview\* or meta-synthes\* or "review of reviews" or technology assessment\* or HTA or HTAs).tw. (379629)  
69 (network adj (MA or MAs)).tw. (15)  
70 (NMA or NMAs).tw. (3821)  
71 indirect comparison?.tw. (3900)  
72 (indirect treatment\* adj1 comparison?).tw. (507)  
73 (mixed treatment\* adj1 comparison?).tw. (1203)  
74 (multiple treatment\* adj1 comparison?).tw. (220)  
75 (multi-treatment\* adj1 comparison?).tw. (3)  
76 simultaneous comparison?.tw. (1019)  
77 mixed comparison?.tw. (46)  
78 or/66-77 (645760)  
79 65 and 78 [MARIJANA - REVIEWS] (2188)  
80 79 use amed [AMED RECORDS] (9)  
81 exp cannabis/ (45629)  
82 exp cannabinoids/ (75395)  
83 marijuana usage/ (2489)  
84 (cannabis or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana).tw. (74085)  
85 or/81-84 [MARIJUANA] (121470)  
86 meta analysis/ (230418)  
87 (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*).tw. (322718)  
88 (systematic review\* or systematic overview\* or evidence-based review\* or evidence-based overview\* or (evidence adj3 (review\* or overview\*)) or meta-review\* or meta-overview\* or meta-synthes\* or "review of reviews" or technology assessment\* or HTA or HTAs).tw. (379629)  
89 (network adj (MA or MAs)).tw. (15)  
90 (NMA or NMAs).tw. (3821)  
91 indirect comparison?.tw. (3900)  
92 (indirect treatment\* adj1 comparison?).tw. (507)  
93 (mixed treatment\* adj1 comparison?).tw. (1203)  
94 (multiple treatment\* adj1 comparison?).tw. (220)  
95 (multi-treatment\* adj1 comparison?).tw. (3)  
96 simultaneous comparison?.tw. (1019)  
97 mixed comparison?.tw. (46)  
98 or/86-97 (645760)

- 99 85 and 98 [MARIJUANA - REVIEWS] (2172)
- 100 99 use ppez (617)
- 101 99 use emczd (1143)
- 102 99 use amed (9)
- 103 99 not (100 or 101 or 102) [PSYCINFO RECORDS] (403)
- 104 30 or 61 or 80 or 103 [ALL DATABASES] (2879)
- 105 remove duplicates from 104 (1943) [TOTAL UNIQUE RECORDS]
- 106 105 use ppez [MEDLINE UNIQUE RECORDS] (932)
- 107 105 use emczd [EMBASE UNIQUE RECORDS] (869)
- 108 105 use amed [AMED UNIQUE RECORDS] (2)
- 109 105 not (106 or 107 or 108) [PSYCINFO UNIQUE RECORDS] (140)

## Appendix 2: Draft Data Extracted Variables

- General characteristics: publication status, publication date, country of corresponding author, funding sources
- objective of the SR
- Searching attributes: sources of evidence (databases; whether grey literature searched), date range searched
- (Eligibility vs inclusion)
- total number of included studies
- total number of participants
- cannabis related properties (cannabis or type of cannabinoid – e.g. THC and CBD)
- method of administration:
  - smoked
  - inhaled (vaporized)
  - intramuscular
  - ingested (food or tea)
  - herbal form (capsules)
  - oil
  - spray
- Dose evaluated
- Comparator: other treatment, usual care, placebo, or no treatment
- Indication for prescription (e.g., pain control)
- Condition being treated (e.g. multiple sclerosis, cancer pain)
- Included populations
  - Adults (men only)
  - Adults (female only)
  - Adults (mixed)
  - Adults (not defined)
  - Children
  - Adolescents
  - Other
  - Not defined
- Special populations reported:
  - Pregnant women
  - Infants
- Type of Analyses
  - Quantitative synthesis (meta-analysis)
  - Narrative synthesis only
  - Mixed (quantitative and qualitative)
- Outcomes (including consideration of primary and secondary outcomes)

