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Canadian Clinical Practice Guidelines for the Use of Cannabis and Cannabinoid-Based Products in the Management of Chronic Pain and Co-occurring Conditions: Protocol for a Systematic Literature Review

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Abstract

Introduction: Chronic pain and co-occurring disorders, such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders, are among the most common conditions for which cannabis and cannabinoid-based products (CBP) are used for therapeutic purposes. However, healthcare providers report that they lack sufficient information on the risks, benefits and appropriate use of cannabis and CBP for therapeutic purposes.

Methods and Analysis: We will conduct a systematic review of studies investigating the use of cannabis and CBP for the treatment of chronic pain and co-occurring conditions. Randomized controlled trials, meta-analyses and observational studies will be prioritized. We will exclude reviews of cannabinoid mechanisms of actions, commentary articles and narrative reviews. The primary outcome of interest will be efficacy in relieving chronic pain. Secondary outcomes will be efficacy in ameliorating conditions such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders. We will search electronic bibliographic databases including Academic Search Complete, Cochrane Database of Systematic Reviews, Evidence based Medicine Reviewes, OVID Medline, PsychINFO, PubMed, CINAHL and Web of Science. Two reviewers will conduct screening and data collection independently. Study level of bias will be assessed using the Cochrane Risk of Bias Assessment Tool for randomized controlled trials and non-randomized studies. Narrative analysis will be utilized to interpret the data.

Ethics and Dissemination: The results of this systematic review will inform guideline development for the use of cannabis and CBP in the management of chronic pain and co-occurring conditions. Areas requiring further study will also be highlighted.

Systematic review registration: PROSPERO #135886

Strengths and limitations

- Extensive review of literature with rigorous study selection and methods for data extraction, quality assessment and data synthesis
- Breadth and consideration of diverse methodologies distinguishes this review for other recent reviews of cannabis and pain
- Wide variety of panel members comprised of clinicians, academics and community members with unique perspectives and synergistic skills
- A timely systematic review given liberalization of cannabis regulations across Europe and the Americas
- Conclusions may be limited by inclusion of relatively few controlled trials

Background

Approximately 19% to 29% of Canadian adults aged 18 and older live with chronic pain, most commonly attributed to lower back pain and arthritis, with an average duration of more than 10 years[1 2]. Arthritis alone, which includes more than 100 rheumatic diseases and conditions that affect joints, affects over 4.2 million Canadians (16% of those aged 15 years and older), and this prevalence is estimated to reach approximately 7 million, or 1 in 5 Canadians aged 15 and older, by 2031[3].

Chronic pain often co-occurs with sleep disorders, anxiety, depression, post traumatic stress disorder, and substance use disorders such as opioid use disorder and alcohol use disorder[4-10]. Chronic pain and these co-occurring conditions are also among the most common conditions for which cannabinoid-based products (CBP) are used for therapeutic purposes[11-14].

The cannabis plant contains over 100 phytocannabinoids, although Δ^9-tetrahydrocannabinol and cannabindiol are the most well-characterized. Other cannabinoids contained in the plant include cannabigerol, cannabichromene, cannabinodiol, cannabielsoin, cannabicyclol, cannabinol, cannabitriol and others[15 16]. The cannabis plant also contains terpenoids which provide characteristic aromas[17]. Different cannabinoids and terpeneoids in combination behave in synergy, through what has been coined "the entourage effect," explaining why plants are often more efficacious than their components in isolation[18]. Extracts include nabiximols (Sativex®). In contrast, synthethic pharmaceutical-grade cannabinoids include nabilone (Cesamet®) and

dronabinol (Marinol®). In contrast to the role of synthetic pharmaceutical-grade cannabinoids, a major knowledge gap relates to the use of cannabis and plant-derived cannabinoids in the management of chronic pain and co-occurring conditions.

In Canada, surveys indicate that patients frequently treat multiple symptoms with CBP[14]. Since 2001, Canada has had a federal program that authorizes the use of CBP and as of October 2018, has legalized and regulated the sale of cannabis for adult recreational use. Thus, for Canadians, the role of CBP in the context of chronic pain management and its associated co-occurring conditions is likely to increase. Managing chronic pain and co-occurring morbidities is a complex public health and medical challenge, which is compounded by the introduction of CBP into the panacea of therapeutic options.

Healthcare providers have expressed concerns about the use of CBP, stating that they did not have the quality of evidence they require to feel comfortable discussing CBP as a therapeutic option with their patients[19]. They reported that they lack sufficient information on risks, benefits, and appropriate use of CBP for therapeutic purposes and were reluctant to support their patients' request for access to CBP[20 21].

The frequent co-occurrence of chronic pain and substance use disorders is often explained as patients' self-medicating to manage living with chronic pain[6]. CBP substitution for opioids is increasingly reported in the literature[22-25]. The potential for CBP use as a drug-related harm reduction strategy is being recognized[24 26 27], however it is not without risks[28]. Regardless of the hypothesis that links chronic pain and substance

use disorders, understanding the role of CBP in this context is crucial for the development of clinical practice guidelines.

Recent years have seen a proliferation of systematic literature reviews on CBP and their effects on chronic pain and co-occurring conditions. Systematic reviews have been conducted on CBP and chronic pain[29-33]; sleep disorders[32 34] and mood disorders[32 35]. While a few publications offer recommendations regarding administration and dosing strategies[36 37] and one recent publication offers clinical practice guidelines for prescribing CBP in primary care[38], clinicians and patients have no specific guidance on the use of CBP for the management of chronic pain and co-occurring conditions. Given the new legal regimes globally and in Canada regarding recreational cannabis and CBP, healthcare providers need to be aware of the efficacy of CBP in regards to chronic pain and confident in knowing when such therapies may be beneficial for their patients.

There is a need for detailed, up-to-date tools and information for healthcare providers and patients to assist them with decisions about CBP as a treatment option. We propose to develop the Canadian Clinical Practice Guidelines for the Use of Cannabis and Cannabinoid-Based Products in the Management of Chronic Pain and Co-Occurring Conditions. Of note, to fill an important knowledge gap, these guidelines will examine literature focused on cannabis and CBP rather than synthetic, pharmaceutical-grade cannabinoids.

Methods and Analysis

Outcome(s)

Primary outcome: Chronic Pain

Chronic pain includes any painful condition that persists for more than three months, including nociceptive, neuropathic, and centralized pain[13 39]. Chronic pain outcomes are measured with scales, including but not limited to: the numeric rating scale, a visual analog scale, Euro-Quality of life-5 Dimensions-5 Levels (EQ-5D5L), Profile of Mood States (POMS) Questionnaire, 36-item short-form survey (FS36), the Neuropathic Pain Scale, the McGill Pain Questionnaire[30]. Some of these examples importantly include measurements that focus on patient reported outcomes, patient functionality, and quality of life.

Secondary outcomes

Sleep Disorders

Although many sleep disorders exist, insomnia is the most common. Insomnia refers to a condition whereby sleep is disturbed despite the presence of an adequate opportunity and circumstance for sleep, which has a negative effect on daily function[40]. Sleep measures include sleep behaviour inventory, sleep evaluation questionnaire, electro-encephalogram (EEG) measures, and visual observation of sleep activity[34].

Anxiety, Depression, and Post Traumatic Stress Disorder

The co-occurrence of chronic pain and mood disorders such as anxiety, depression, and post-traumatic stress disorder is well documented[4 5 7 10]. Mood disorder outcomes are measured by Structured Clinical Interview for DSM and self-reported questionnaire (e.g. self report, with the Beck Depression Inventory, Hamilton Depression Inventory, Centre for Epidemiological Studies Depression Scale (CES-D).

Substance Use Disorders

Changes in the use of non-cannabinoid products and other substances, in conjunction with cannabis use, will be reviewed. CBP substitution is assessed through questionnaires. Diagnostic and Statistical Manual of Mental Disorders (DSM)-V diagnoses for drug abuse and dependence can be obtained using instruments such as the World Health Organization Composite International Diagnostic Interview (CIDI), Drug User Disorder Identification Test (DUDIT), Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), and others[6 41]. Alcohol use disorder and opioid use disorder are also often measured using specific instruments including The Alcohol Use Disorders Identification Test (AUDIT)[42], the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV)[43] and the Current Opioid Misuse Measure (COMM)[44], as well as others.

Previous studies have focused on risks and harms associated with cannabis and few have addressed the health promoting or beneficial effects of CBP[45 46]. However, as the development of a cannabis use disorder is a possible consequence of cannabis consumption in susceptible individuals, the presence of cannabis use disorders will be

noted. Specific screening and diagnostic instruments to assess cannabis use disorders include the Cannabis Problems Questionnaire (CPQ), Cannabis Abuse Screening Test (CAST), Cannabis Use Disorder Identification Test (CUDIT) and its revised version (CUDIT-R), and others[41 47].

Search strategy

An electronic search will be conducted for peer-reviewed articles (2001-2019), restricted to the English language, in the following electronic bibliographic databases: Academic Search Complete, Cochrane Database of Systematic Reviews (CDSR), Evidence Based Medicine Reviews (EBMR), OVID Medline, PsychINFO, PubMed, CINAHL, and Web of Science. The search strategy will include the following controlled vocabulary and relevant key terms:

(cannabi* OR marijuana OR endocannabi* OR THC OR Tetrahydrocannabinol OR weed OR CBD OR Indica OR Sativa OR nabiximols OR dronabinol OR pot) AND (pain OR headache OR neuralgia OR migraine)

This search strategy was developed with the assistance of a medical librarian experienced is systematic reviews. As the journal "Cannabis and Cannabinoid Research" is currently one of the few journals specifically devoted to cannabis research, this journal be hand searched for studies that meet the inclusion criteria. Based on the recommendations of the medical librarian, the terms "nabiximols" and "dronabinol" were included in the search strategy to ensure that we capture all relevant studies. However, studies focused exclusively on the efficacy of synthetic cannabinoids of pharmaceutical grade (such as nabilone or dronabinol) approved for human use will be excluded.

Study screening and inclusion

Following the implementation of our search, we will obtain the titles and abstracts from all references. First we will examine the tiles and abstracts, and then full-texts of studies which appear relevant will be screened by two reviewers independently. We will conduct pilot exercises to identify and address any inconsistencies in applying the screening criteria. The inclusion and exclusion criteria for each stage of screening are indicated below. When no abstract is available, and the article can not be confidently excluded by solely the title, the full-text will be obtained. In general, if there is uncertainty as to whether a study should be excluded, the study will proceed to the full-text screen. Two reviewers will resolve disagreements on inclusion, and a third person will reconcile any remaining disagreements. The process of study selection will be summarized using a PRISMA flow diagram[48].

Study eligibility criteria

Study selection will be based on the criteria listed in Table 1. Study inclusion and exclusion criteria are listed in Table 2.

Table 1 PICOS breakdown of study eligibility criteria

Category	**Description of criteria**
Population	Human of any age living with chronic, or non-acute, pain (pain of greater than 3 month duration) Humans of any age living with chronic pain and co-occurring conditions:

	sleep disorders, mood disorders (anxiety, depression, post-traumatic stress disorder), alcohol use disorder and opioid use disorder
Intervention	Cannabis or cannabinoid-based products (CBP) in the form of herbal cannabis and derivatives
Comparison(s)	Placebo or other medications or intervention Studies without comparators will also be included*
Outcome(s)	Primary outcome: 1) Efficacy, tolerability and safety of cannabis and CBP in the management of chronic pain 2) Improvement in chronic pain, symptom management 3) Improvement in quality of life, patient-reported outcomes and patient functionality Secondary outcomes: Improvement in sleep disorders, anxiety, depression, alcohol use disorder, and opioid use disorder
Study design	Randomized controlled trials, controlled trials, meta-analyses and observational studies will be included Studies that focus on cannabinoid mechanisms, commentary articles or clinical reviews will be excluded.

*An example of a study without a comparator would be a study examining the efficacy of a single dosing regimen comparing baseline to end study scores

Table 2: Inclusion and Exclusion Criteria

Inclusion criteria	• Cannabis and the management of chronic pain • Cannabis and the management of chronic pain and co-occurring conditions: sleep disorders, mood disorders (anxiety, depression, post-traumatic stress disorder), alcohol use disorder and opioid use disorder • Efficacy, tolerability and safety studies on the use of cannabis in the management of chronic pain • Indications and dosing strategies of cannabis for the treatment of chronic pain • Drug interactions, adverse events, negative effects and contraindications for the use of cannabis in the treatment of chronic pain • Considerations regarding the use of cannabis for the management of chronic pain for individuals with a history of sleep disorders, anxiety, depression, post-traumatic stress disorder, opioid use disorder and alcohol use disorder • The substitution effect of cannabis for medications or other drugs in the context of the management of chronic pain
Exclusion criteria	• Studies published before 2001 • Studies in a language other than English

	• Studies focused on the use of cannabis for recreational purposes or which do not differentiate between recreational vs. medicinal use • Studies focused exclusively on synthetic cannabinoids of pharmaceutical grade approved for human use* • Studies focused on the prevention or cessation of cannabis use • Studies focused exclusively on cancer-related pain** • Studies focused on cannabis use disorder • Studies where cannabis is only one aspect of an intervention, and not the main focus • Studies on non-humans/animals

*These compounds should be distinguished from those used in basic science research, not approved for human use, and which are known on the streets by terms such as "Spice" and "K2"

**Due to the large number of studies focused exclusively on cancer-related pain, we have excluded these studies from the current systematic review in order to narrow the focus. However, we acknowleddge the importance of cancer-related pain and suggest that this be the focus of a separate systematic review.

Data extraction

Selection of studies

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) conventions[49], an Evidence Synthesis Working Group, working with the

Guidelines Panel, will determine eligibility of studies by reading the abstracts identified by the search. Grey literature will also be included when appropriate. Studies will be selected based on inclusion and exclusion criteria. The Evidence Synthesis Working Group will independently read the selected studies and reach agreement about inclusion and exclusion by discussion. A PRISMA flow chart will be created. The CBP Task Force will come to the final conclusion when there is debate.

Data extraction and management

The Evidence Synthesis Working Group will extract data from the selected studies independently using a standardized Data Extraction Form (Supplementary File) to create evidence tables. For each study, relevant data will be extracted related to study identification (author, year published, number and location of centres, funding, journal name), the number of participants, form of CBP, dose and route, study design and setting, inclusion and exclusion criteria of the study sample, aggregate demographic (age, sex, type of pain, co-occurring conditions) and clinical characteristics (co-morbidities), and outcome measures (e.g., scores on the Visual Analog Scales or McGill Pain Questionnaire) and results. We will also record the number of GRADE 1-4 adverse events, using the World Health Organization (WHO) Toxicity grading scale for determining the severity of adverse events.

Strategy for data synthesis

Data will be extracted from reviews, including existing meta-analyses, using a standardized data extraction tool. Due to the high variability in previous cannabis

research, a meta-analysis is likely inappropriate. This variability is due to heterogeneity of sample populations, study types and lengths, and CBP interventions (e.g. CBP type, dosing, administration route, etc.). Similar challenges have prevented the execution of meta-analyses in previous, related reviews[50]. Patterns related to efficacy, safety, tolerability will be explored through narrative synthesis[50 51]. Data from relevant categories (Ex. sub-populations, age groups, alternative therapies, etc.) will be compiled based on the availability of quality evidence. Consistent findings and discrepancies will be discussed. Findings will be aggregated or synthesised to generate a set of statements rated according to their quality.

Assessment of Evidence and Recommendations

The Task Force will use the GRADE system to rate the quality of the evidence and strength of its recommendations[52-58].

Analysis of subgroups or subsets

Evidence for the use of CBP in the management of chronic pain and co-occurring conditions will be presented for clinical considerations related to efficacy, tolerability, safety, indications, dosing, drug interactions, adverse events, negative effects, contraindications. Evidence regarding considerations related to the use of CBP for patients with a history of substance use disorder. The phenomenon of CBP substitution for other drugs will be included.

Risk of bias assessment

Two reviewers (MSP and PW) will assess the potential bias and discrepancies will be discussed and adjudicated by the Data Synthesis committee (CC, ZW, SM). The National Institutes of Health risk of bias assessment tools[59] will be used to assess the quality of included studies. These tools have been developed specifically for different study design types, and therefore the heterogeneity of included study designs will not affect the ability to assess quality appropriately. Each included study will be dually and independently reviewed and disagreements will be solved through discussion. These tools utilized for quality assessment are "not intended to create a list that is simply tallied up to arrive at a summary judgment of quality", meaning reviewers will evaluate studies utilizing the tools but will not solely rely on the cumulative score, and will make decisions through discussion when necessary. Studies will be graded as either "good quality" (score of 3), implying low risk of bias, "fair quality" (score of 2) implying some risk of bias or "poor quality" (score of 1), implying high risk of bias. Assessment of bias will be performed at the overall study level. Specific Questions to assess for study limitations and the risk of bias are included on our Data Extraction Form (Supplementary File).

Data analysis/synthesis

Findings from the review will be synthesized to highlight where multiple reviews find consistent effects and where reviews have come to different conclusions about the strength of the evidence. In the narrative synthesis, we will discuss the findings both within and between studies, based on guidance from the Centre for Reviews and

Dissemination (For example, a study examining the efficacy of a single dosing regimen comparing baseline to end study scores). Findings will be aggregated or synthesized to generate a set of statements rates according to their quality.

Reporting of the review

The Cannabis Guidelines Task Force plans on publishing both the protocol for the development of the clinical practice guidelines, as well as the systematic review protocol. Once the guidelines and decision aid are developed, they will also be published and disseminated. Members of the Task Force will be encouraged to present the guidelines at relevant conferences and meetings.

Patient and Public involvement

Among the authors of this systematic review protocol are patient community advisors (SM and EM). They have been involved in all stages of this project, beginning from conception and design of this systematic review. They will continue to be involved at all stages, including study appraisal, guideline drafting and publication.

Discussion

In this systematic review, we will prepare a detailed, up-to-date tool for healthcare providers and patients to assist them with decisions about CBP as a treatment option for chronic pain and co-occurring conditions including sleep disorders, mood disorders alcohol use disorder and opioid use disorder. Although some publications provide guidance with respect to administration and dosing of CBP[36 37] and one recent publication

offers clinical practice guidelines for prescribing CBP in primary care[38], our systematic review geared for both healthcare providers and patients will add to the current literature by providing a balanced view of both the benefits and potential risks, and will also highlight specific areas requiring additional research.

We anticipate some challenges with our systematic review. Firstly, there is likely to be very high heterogeneity with regards to patient populations, CBP dosage form and dosages, study design and reported outcomes. When CBP is administered in different dosage forms, such as by capsule *vs.* by inhaled form, the kinetics vary widely which may make direct, head-to-head comparisons between studies inappropriate. In addition, individual differnces in patient characteristics between studies may preclude us from generalizing results across studies. Nonetheless, despite these anticipated challenges, our systematic review aims to provide a broad, balanced view of both the potential benefits and harms associated with the use of CBP for pain and co-occurring conditions. These results are likely to serve as an reference tool for both healthcare providers and patients suffering from such conditions, and will also underscore the specific areas of CBP research requiring further study.

Authors' contributions:

PW and LBI drafted the protocol. All authors critically reviewed and revised the protocol. TS and SA devised the search strategy, performed data extraction and data interpretation. PW and CC prepared the manuscript. The Data Synthesis Team (CC, ZW, SM, GL) was consulted for interpretation of the results. All authors conceived and

designed the review, and read and approved the final manuscript. PW and CC are the guarantors of the review.

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Neither the funders nor authors'affiliated institutions played any role in the development of the protocol.

Conflicts of interest

TS, SA, LBI, MS, JXY and JO do not have any conflicts of interest.

PW's employer, the Canadian AIDS Society, has received a grant from canopy Growth Corporation for the development of the clinical practice guidelines.

ZW is an advisory board member of Multidisciplinary Association for Psychedelic Studies – Canada, and for the Canadian Association of Medical Cannabis Dispensaries.

He is in the planning phases of becoming an investigator on a survey study sponsored by Doja, from which he does not receive any direct financial compensation, however, graduate students in his lab receive paid Research Assistantships. He is the Coordinating Principal Investigator on a clinical trial of cannabis for PTSD that is sponsored by Tilray, from which he does not receive any direct financial compensation. Graduate students in his lab receive paid Research Assistantships from Tilray.

SM is the co-owner of a start-up company ("Cannabiscotti Inc") that will be applying for a cannabis processing license. She holds shares in Canopy Growth Corporation, Emblem Corp and Aphria Inc. She has received honorarium for research projects funded by Canopy Growth Corporation and Tilray.

AB is a member of the medical advisory board of Canopy Growth Corporation. He has received payment from Canopy Growth Corporation for consulting and speaking engagements. He has received unrestricted grants to attend academic presentations on the topic of the medical use of cannabis from Canopy Growth Corporation, and holds shares in the company.

PJD is a member of the Medical Advisory Board for Shopper's Drug Mart, Tetra Bio-Pharma, a consultant for ReFormulary Group and Tallc Corporation, a member of the Speaker's Bureau for Medical Cannabis Education for Shopper's Drug Mart and Spectrum Therapeuics, and participates in clinical trials for CancerCare Manitoba in contract positions.

MG is the president and co-founder of the Harm Reduction Nurses Association. She was a board member of The Canadian HIV/AIDS Legal Network. She has received an honorarium payment from Merck for a presentation on HIV medication side-effects.

CM is the Medical Director of Greenleaf Medical Clinic and the Translational Life Sciences. She is on the Board of Directors for the Green Organic Dutchman and is on the Medical Advisor Board for Emerald Health Therapeutics. She has provided medical consultation and/or receive support for industry sponsored continuing medical education from: Canopy/Spectrum, Stainprint, Scientus Pharma, Aurora, MedReleaf, Shoppers Drug Mart, MD Briefcase. Previously she has worked with Vitality Biopharma, True Leaf, Resolve Digital Health, Doja and Compass Cannabis Clinics.

EM is the co-owner of a start-up company ("Cannabiscotti Inc") that will be applying for a cannabis processing license, and is employed by MJardin Canada.

CTC has received cannabinoids from Tilray Inc. for use in a clinical trial but has not received any grant support nor honoraria from the company. She has received research funding from Merck and Gilead, speaker honorarium from Gilead and consultant fees from Viiv Healthcare. She has received funding to attend conferences from Gilead and Viiv Healthcare.

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Data Extraction Form and Quality Assessment Tool

Canadian Clinical Practice Guidelines for the Use of Cannabinoid-Based Medicine in the Management of Chronic Pain and Co-Occurring Conditions

Reference

Reviewer Extracting Data

Date form completed

Eligibility form

Factors	Assessment	Comments
Type of Study		
1) Is the study a systematic review or meta-analysis?	Yes No	
2) Is the study a controlled intervention study (randomized, non-randomized or quasi-experimental)?	Yes No	
3) Is the study an observational cohort or cross-sectional study?	Yes No	
4) Is the study a case-control study?	Yes No	
5) Is the article a review of system mechanisms, a commentary article or a clinical overview? - identify the type of article in comments section	Yes (exclude) No	

Participants		
6) Do participants explicitly present with chronic pain? 7) Was the pain cancer-related?	Yes No (exclude) Unclear Yes (exclude) No Unclear	
Exclusion Criteria		
8) Did the study measure the effects of non-synthetic CBM use on chronic pain? 9) Was cannabis use one aspect of an intervention, but not the main focus?	Yes No (exclude) Unclear Yes (exclude) No Unclear	

Do not proceed if study excluded from review

Systematic Review and Meta-Analysis Data Extraction (Complete only if the answer to question 1 is "yes")

Review Characteristics	
Type(s) of studies included	
# of studies included	
Population studied (HIV+, PTSD, prescribed opioids, etc.)	
Type(s) of CBM included in review (whole plant, extract, synthetic)	
Main outcome(s)	
Meta-analyses conducted?	Yes No
Key findings	

Conclusions	

Systematic Review and Meta-Analysis Quality Assessment (Complete only if the answer to question 1 is "yes")

Criteria	
1. Is the review based on a focused question that is adequately formulated and described?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Were eligibility criteria for included and excluded studies predefined and specified?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Did the literature search strategy use a comprehensive systematic approach?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the included studies listed along with important characteristics and results of each study?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. Was the publication bias assessed?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was heterogeneity assessed? (This question applies only to meta-analyses)	
Yes	

No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Controlled Intervention Studies Data Extraction (Complete only if the answer to question 2 is "yes")

Study Characteristics	
Study year	
Location	
Study design type (i.e., RCT, Quasi-experimental)	
Study aim (i.e., efficacy, safety, tolerability)	
Population characteristics (from which study participants are drawn. i.e., HIV+, PTSD, adolescence)	
Sample size: Intervention population sample (#) Control population sample (#)	
Sample demographics (and differences between samples) Age Sex Race/Ethnicity	
Method of recruitment	
Length of the intervention	
CBM characteristics: - Type - Administration route - Dosing	
Type of control (Placebo, alternative, no treatment)	

Main outcome measures	
Main findings	
Comorbidities measured	
Conclusions	

Controlled Intervention Studies Quality Assessment (Complete only if the answer to question 2 is "yes")

Criteria	
1. Is the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the method of randomization adequate (ie. Use of a randomly generated assignment)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were the study participants and providers blinded to treatment group assignment?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Were the people assessing the outcomes blinded to the participants' group assignments?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
9. Was there high adherence to the intervention protocols for each treatment group?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
13. Were the outcomes reported or subgroups analyzed pre-specified (i.e., identified before analyses were conducted)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Observational Cohort or Cross-sectional Study Data Extraction (Complete only if the answer to question 3 is "yes")

Study Characteristics	
Study year	
Study location	
Study design type (i.e., prospective, retrospective, cross-sectional)	
Population Characteristics (HIV+, prescribed opioids, etc)	
Sample Size	
Sample characteristics Age Sex Race/Ethnicity	
Method of recruitment	
Length of study	
CBM Characteristics	
Main outcome measures (and any other important outcomes measured)	
Main Findings/conclusions	

Observational Cohort or Cross-sectional Study Quality Assessment (Complete only if the answer to question 3 is "yes")

Criteria	
1. Was the research question or objective in this paper clearly stated?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the study population clearly specified and defined?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Was the participation rate of eligible persons at least 50%?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Was a sample size justification, power description, or variance and effect estimates provided?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. For the analysis of this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if It existed?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	
Yes	
No	
Other (Cannot determine, Not applicable, not	

reported)	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Was the exposure(s) assessed more than once over time?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Were the outcome assessors blinded to the exposure status of the participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
13. Was loss to follow-up after baseline 20% or less?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Case-Control Studies Data Extraction (Complete only if the answer to question 4 is "yes")

Study Characteristics	
Study year	

Study location	
Study design type (i.e., prospective, retrospective, cross-sectional)	
Population Characteristics (HIV+, prescribed opioids, etc)	
Sample Size	
Sample characteristics Age Sex Race/Ethnicity	
Control Group	
Method of recruitment	
Length of study	
CBM Characteristics	
Main outcome measures (and any other important outcomes measured)	
Main Findings/conclusions	

Case-Control Studies Quality Assessment (Complete only if the answer to question 4 is "yes")

Criteria	
1. Was the research question or objective in this paper clearly stated and appropriate?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the study population clearly specified and defined?	
Yes	
No	
Other (Cannot determine, Not applicable, not	

reported)	
3. Did the authors include a sample size justification?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the cases clearly defined and differentiated from controls?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was there use of concurrent controls?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	

Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	20-21
Sponsor	5b	Provide name for the review funder and/or sponsor	20-21
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	21
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	12-14; Table 1
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-14
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	16
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	15-16
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	18
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	18
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	17-18
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	18-19
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	18-19
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16-17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16-18
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Canadian Clinical Practice Guidelines for the Use of Plant-Based Cannabis and Cannabinoid-Based Products in the Management of Chronic Non-Cancer Pain and Co-occurring Conditions: Protocol for a Systematic Literature Review

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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Medical management
Keywords:	Anxiety disorders < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, SLEEP MEDICINE, THERAPEUTICS, Substance misuse < PSYCHIATRY, PAIN MANAGEMENT

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cCanadian Clinical Practice Guidelines for the Use of Plant-Based Cannabis and Cannabinoid-Based Products in the Management of Chronic Non-Cancer Pain and Co-occurring Conditions:

Protocol for a Systematic Literature Review

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Abstract

Introduction: Chronic pain and co-occurring disorders, such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders, are among the most common conditions for which cannabis and cannabinoid-based products derived from the cannabis plant (CBP) are used for therapeutic purposes. However, healthcare providers report that they lack sufficient information on the risks, benefits and appropriate use of cannabis and CBP derived from the cannabis plant for therapeutic purposes.

Methods and Analysis: We will conduct a systematic review of studies investigating the use of cannabis and CBP derived from the cannabis plant for the treatment of chronic pain and co-occurring conditions. Randomized controlled trials, meta-analyses and observational studies will be prioritized. We will exclude reviews of cannabinoid mechanisms of actions, commentary articles and narrative reviews. The primary outcome of interest will be efficacy in relieving chronic pain. Secondary outcomes will be efficacy in ameliorating conditions such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders. We will search electronic bibliographic databases including Academic Search Complete, Cochrane Database of Systematic Reviews, Evidence based Medicine Reviewes, OVID Medline, PsychINFO, PubMed, CINAHL and Web of Science. Two reviewers will conduct screening and data collection independently. Study level of bias will be assessed using the Cochrane Risk of Bias

Assessment Tool for randomized controlled trials and non-randomized studies. Narrative analysis will be utilized to interpret the data.

Ethics and Dissemination: The results of this systematic review will inform guideline development for the use of cannabis and CBP derived from the cannabis plant in the management of chronic pain and co-occurring conditions. Areas requiring further study will also be highlighted.

Systematic review registration: PROSPERO #CRD42020135886

Strengths and limitations

- Extensive review of literature with rigorous study selection and methods for data extraction, quality assessment and data synthesis
- Breadth and consideration of diverse methodologies distinguishes this review for other recent reviews of cannabis and pain
- Wide variety of panel members comprised of clinicians, academics and community members with unique perspectives and synergistic skills
- A timely systematic review given liberalization of cannabis regulations across Europe and the Americas
- Conclusions may be limited by inclusion of relatively few controlled trials

Background

Approximately 19% to 29% of Canadian adults aged 18 and older live with chronic pain, most commonly attributed to lower back pain and arthritis, with an average duration of more than 10 years[1 2]. Arthritis alone, which includes more than 100 rheumatic diseases and conditions that affect joints, affects over 4.2 million Canadians (16% of those aged 15 years and older), and this prevalence is estimated to reach approximately 7 million, or 1 in 5 Canadians aged 15 and older, by 2031[3].

Chronic pain often co-occurs with sleep disorders, anxiety, depression, post traumatic stress disorder, and substance use disorders such as opioid use disorder and alcohol use disorder[4-10]. Chronic pain and these co-occurring conditions are also among the most common conditions for which cannabinoid-based products derived from the cannabis plant (CBP) are used for therapeutic purposes[11-14].

The cannabis plant contains over 100 phytocannabinoids, although Δ^9-tetrahydrocannabinol and cannabindiol are the most well-characterized. Other cannabinoids contained in the plant include cannabigerol, cannabichromene, cannabinodiol, cannabielsoin, cannabicyclol, cannabinol, cannabitriol and others[15 16]. The

cannabis plant also contains terpenoids which provide characteristic aromas[17]. Different cannabinoids and terpeneoids in combination behave in synergy, through what has been coined "the entourage effect," explaining why plants are often more efficacious than their components in isolation[18]. Extracts include nabiximols (Sativex®), a 1:1 tetrahydrocannabinol (THC):cannabidiol (CBD) sublingual spray. Synthethic pharmaceutical-grade cannabinoids include nabilone (Cesamet®) and dronabinol (Marinol®), synthetic products administered orally by capsule. A major knowledge gap relates to the use of cannabis and plant-derived cannabinoids derived from the cannabis plant in the management of chronic pain and co-occurring conditions.

In Canada, surveys indicate that patients frequently treat multiple symptoms with CBP derived from the cannabis plant [14]. Since 2001, Canada has had a federal program that authorizes the use of CBP derived from the cannabis plant and as of October 2018, has legalized and regulated the sale of cannabis for adult recreational use. Thus, for Canadians, the role of CBP derived from the cannabis plant in the context of chronic pain management and its associated co-occurring conditions is likely to increase. Managing chronic pain and co-occurring morbidities is a complex public health and medical challenge, which is compounded by the introduction of CBP into the pharmacopoeia of therapeutic options.

Healthcare providers have expressed concerns about the use of CBP derived from the cannabis plant, stating that they did not have the quality of evidence they require to feel comfortable discussing CBP derived from the cannabis plant as a therapeutic option with their patients[19]. They reported that they lack sufficient information on risks, benefits, and

appropriate use of CBP derived from the cannabis plant for therapeutic purposes and were reluctant to support their patients' request for access to CBP[20 21].

The frequent co-occurrence of chronic pain and substance use disorders is often explained as patients' self-medicating to manage living with chronic pain[6]. Approximately 21-29% of individuals prescribed opioids for chronic pain misuse them, while 8-12% develop opioid use disorder [22-26]. CBP substitution for opioids is increasingly reported in the literature[27-30]. The potential for CBP use as a drug-related harm reduction strategy is being recognized[29 31 32], however it is not without risks, as its use may be associated with an increased risk of relapse, for example[33-35]. Regardless of the hypothesis that links chronic pain and substance use disorders, understanding the role of CBP derived from the cannabis plant in this context is crucial for the development of clinical practice guidelines.

Recent years have seen a proliferation of systematic literature reviews on CBP and their effects on chronic pain and co-occurring conditions. Systematic reviews have been conducted on CBP and chronic pain[36-39]; sleep disorders[39 40] and mood disorders[39 41]. While a few publications offer recommendations regarding administration and dosing strategies[42 43] and one recent publication offers clinical practice guidelines for prescribing CBP in primary care[44], clinicians and patients have no specific guidance on the use of CBP for the management of chronic pain and co-occurring conditions. Given the new legal regimes globally and in Canada regarding recreational cannabis and CBP derived from the cannabis plant, healthcare providers need to be aware of the efficacy of CBP derived from the

cannabis plant in regards to chronic pain and confident in knowing when such therapies may be beneficial for their patients.

There is a need for detailed, up-to-date tools and information for healthcare providers and patients to assist them with decisions about CBP derived from the cannabis plant as a treatment option. We propose to develop the Canadian Clinical Practice Guidelines for the Use of Cannabis and Cannabinoid-Based Products in the Management of Chronic Pain and Co-Occurring Conditions. Of note, to fill an important knowledge gap, these guidelines will examine literature focused on cannabis and CBP derived from the cannabis plant rather than synthetic, pharmaceutical-grade cannabinoids.

Methods and Analysis

Outcome(s)

Primary outcome: Chronic Pain

Chronic pain includes any painful condition that persists for more than three months, including nociceptive, neuropathic, and centralized pain[13 45]. Chronic pain outcomes are measured with scales, including but not limited to: the numeric rating scale, a visual analog scale, Euro-Quality of life-5 Dimensions-5 Levels (EQ-5D5L), Profile of Mood States (POMS) Questionnaire, 36-item short-form survey (FS36), the Neuropathic Pain Scale, the McGill Pain Questionnaire[37]. Some of these examples importantly include measurements that focus on patient reported outcomes, patient functionality, and quality of life.

Secondary outcomes

Sleep Disorders

Although many sleep disorders exist, insomnia is the most common. Insomnia refers to a condition whereby sleep is disturbed despite the presence of an adequate opportunity and circumstance for sleep, which has a negative effect on daily function[46]. Sleep measures include sleep behaviour inventory, sleep evaluation questionnaire, electro-encephalogram (EEG) measures, and visual observation of sleep activity[40].

Anxiety, Depression, and Post Traumatic Stress Disorder

The co-occurrence of chronic pain and mood disorders such as anxiety, depression, and post-traumatic stress disorder is well documented[4 5 7 10]. Mood disorder outcomes are measured by Structured Clinical Interview for DSM and self-reported questionnaire (e.g. self report, with the Beck Depression Inventory, Hamilton Depression Inventory, Centre for Epidemiological Studies Depression Scale (CES-D).

Substance Use Disorders

Changes in the use of non-cannabinoid products and other substances, in conjunction with cannabis use, will be reviewed. CBP derived from the cannabis plant substitution is assessed through questionnaires. Diagnostic and Statistical Manual of Mental Disorders (DSM)-V diagnoses for drug abuse and dependence can be obtained using instruments such as the World Health Organization Composite International Diagnostic Interview (CIDI), Drug User Disorder Identification Test (DUDIT), Alcohol, Smoking, and Substance

Involvement Screening Test (ASSIST), and others[6 47]. Alcohol use disorder and opioid use disorder are also often measured using specific instruments including The Alcohol Use Disorders Identification Test (AUDIT)[48], the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV)[49] and the Current Opioid Misuse Measure (COMM)[50], as well as others.

Previous studies have focused on risks and harms associated with cannabis and few have addressed the health promoting or beneficial effects of CBP derived from the cannabis plant[51 52]. However, as the development of a cannabis use disorder is a possible consequence of cannabis consumption in susceptible individuals, the presence of cannabis use disorders will be noted. Specific screening and diagnostic instruments to assess cannabis use disorders include the Cannabis Problems Questionnaire (CPQ), Cannabis Abuse Screening Test (CAST), Cannabis Use Disorder Identification Test (CUDIT) and its revised version (CUDIT-R), and others[47 53].

Search strategy

An electronic search will be conducted for peer-reviewed articles (2001-2019), restricted to the English language, in the following electronic bibliographic databases: Academic Search Complete, Cochrane Database of Systematic Reviews (CDSR), Evidence Based Medicine Reviews (EBMR), OVID Medline, PsychINFO, PubMed, CINAHL, and Web of Science. The search strategy will include the following controlled vocabulary and relevant key terms:

(cannabi* OR marijuana OR endocannabi* OR THC OR Tetrahydrocannabinol OR weed OR CBD OR Indica OR Sativa OR nabiximols OR dronabinol OR pot) AND (pain OR headache OR neuralgia OR migraine)

This search strategy was developed with the assistance of a medical librarian experienced is systematic reviews. As the journal "Cannabis and Cannabinoid Research" is currently one of the few journals specifically devoted to cannabis research, this journal will be hand searched for studies that meet the inclusion criteria. Based on the recommendations of the medical librarian, the terms "nabiximols" and "dronabinol" were included in the search strategy to ensure that we capture all relevant studies. However, studies focused exclusively on the efficacy of synthetic cannabinoids of pharmaceutical grade (such as nabilone or dronabinol) approved for human use will be excluded. Only studies published since 2001 will be included to focus the review on recent evidence. Since 2001 there have been technological advances and regulatory changes, , such as the legalization of medicinal cannabis in Canada, that may have improved the quality of research.

Study screening and inclusion

Following the implementation of our search, we will obtain the titles and abstracts from all references. First we will examine the tiles and abstracts, and then full-texts of studies which appear relevant will be screened by two reviewers independently. We will conduct pilot exercises to identify and address any inconsistencies in applying the screening criteria. The inclusion and exclusion criteria for each stage of screening are indicated below. When no abstract is available, and the article can not be confidently excluded by solely the title, the full-text will be obtained. In general, if there is uncertainty as to whether a study should

be excluded, the study will proceed to the full-text screen. Two reviewers will resolve disagreements on inclusion, and a third person will reconcile any remaining disagreements. We will not exlude studies based on poor research quality, but we will note the low quality. The process of study selection will be summarized using a PRISMA flow diagram[54].

Study eligibility criteria

Study selection will be based on the criteria listed in Table 1. Study inclusion and exclusion criteria are listed in Table 2.

Table 1 PICOS breakdown of study eligibility criteria

Category	**Description of criteria**
Population	Human of any age living with chronic, or non-acute, pain (pain of greater than 3 month duration) Humans of any age living with chronic pain and co-occurring conditions: sleep disorders, mood disorders (anxiety, depression, post-traumatic stress disorder), alcohol use disorder and opioid use disorder
Intervention	Cannabis or cannabinoid-based products (CBP) derived from the cannabis plant in the form of herbal cannabis and derivatives
Comparison(s)	Placebo or other medications or intervention Studies without comparators will also be included*
Outcome(s)	Primary outcome: 1) Efficacy, tolerability and safety of cannabis and CBP derived from the cannabis plant in the management of chronic pain

	2) Improvement in chronic pain, symptom management 3) Improvement in quality of life, patient-reported outcomes and patient functionality <u>Secondary outcomes:</u> Improvement in sleep disorders, anxiety, depression, alcohol use disorder, and opioid use disorder
Study design	Randomized controlled trials, controlled trials, studies listed in meta-analyses and observational studies will be included Studies that focus on cannabinoid mechanisms, commentary articles or non-systematic reviews will be excluded.

*An example of a study without a comparator would be a study examining the efficacy of a single dosing regimen comparing baseline to end study scores

Table 2: Inclusion and Exclusion Criteria

Inclusion criteria	• Cannabis and the management of chronic pain • Cannabis and the management of chronic pain and co-occurring conditions: sleep disorders, mood disorders (anxiety, depression, post-traumatic stress disorder), alcohol use disorder and opioid use disorder

	• Efficacy, tolerability and safety studies on the use of cannabis in the management of chronic pain • Indications and dosing strategies of cannabis for the treatment of chronic pain • Drug interactions, adverse events, negative effects and contraindications for the use of cannabis in the treatment of chronic pain • Considerations regarding the use of cannabis for the management of chronic pain for individuals with a history of sleep disorders, anxiety, depression, post-traumatic stress disorder, opioid use disorder and alcohol use disorder • The substitution effect of cannabis for medications or other drugs in the context of the management of chronic pain
Exclusion criteria	• Studies published before 2001 • Studies in a language other than English • Studies focused on the use of cannabis for recreational purposes or which do not differentiate between recreational vs. medicinal use • Studies focused exclusively on synthetic cannabinoids of pharmaceutical grade approved for human use* • Studies focused on the prevention or cessation of cannabis use • Studies focused exclusively on cancer-related pain** • Studies focused on cannabis use disorder

	• Studies where cannabis is only one aspect of an intervention, and not the main focus • Studies on non-humans/animals

*These compounds should be distinguished from those used in basic science research, not approved for human use, and which are known on the streets by terms such as "Spice" and "K2"

**Due to the large number of studies focused exclusively on cancer-related pain, we have excluded these studies from the current systematic review in order to narrow the focus. However, we acknowleddge the importance of cancer-related pain and suggest that this be the focus of a separate systematic review.

Data extraction

Selection of studies

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) conventions[55], an Evidence Synthesis Working Group, working with the Guidelines Panel, will determine eligibility of studies by reading the abstracts identified by the search. Grey literature will also be included when appropriate. Studies will be selected based on inclusion and exclusion criteria. The Evidence Synthesis Working Group will independently read the selected studies and reach agreement about inclusion and exclusion by discussion. A PRISMA flow chart will be created. The CBP Task Force will come to the final conclusion when there is debate.

Data extraction and management

The Evidence Synthesis Working Group will extract data from the selected studies independently using a standardized Data Extraction Form (Supplementary File) to create evidence tables. For each study, relevant data will be extracted related to study identification (author, year published, number and location of centres, funding, journal name), the number of participants, form of CBP derived from the cannabis plant, dose and route, study design and setting, inclusion and exclusion criteria of the study sample, aggregate demographic (age, sex, type of pain, co-occurring conditions) and clinical characteristics (co-morbidities), and outcome measures (e.g., scores on the Visual Analog Scales or McGill Pain Questionnaire) and results. We will also record adverse events as reported in individual studies, including the frequency and severity of cases when applicable. Adverse events will collectively be analyzed utilizing the World Health Organization (WHO) Toxicity grading scale for determining the safety of adverse events.

In addition, we plan to examine secondary outcomes within standalone studies on the use of cannabis (e.g., effects of cannabinoids on anxiety) as well as within studies of cannabinoids being used to manage chronic pain (e.g., looking at anxiety as a secondary outcome in a pain clinical trial). Records of all searches will be kept on secure databases only accessible to the investigators. Records of all data extraction forms and consensus discussions will also be kept on the same databases.

Strategy for data synthesis

Data will be extracted from reviews, including existing meta-analyses, using a standardized data extraction tool. Due to the high variability in previous cannabis research, a meta-analysis is likely inappropriate. This variability is due to heterogeneity of sample

populations, study types and lengths, and CBP derived from the cannabis plant interventions (e.g. CBP type, dosing, administration route, etc.). Similar challenges have prevented the execution of meta-analyses in previous, related reviews[56]. Patterns related to efficacy, safety, tolerability will be explored through narrative synthesis[56 57]. Data from relevant categories (Ex. sub-populations, age groups, alternative therapies, etc.) will be compiled based on the availability of quality evidence. Consistent findings and discrepancies will be discussed. Findings will be aggregated or synthesised to generate a set of statements rated according to their quality. We do not plan to conduct a meta-analysis.

Assessment of Evidence and Recommendations

The Task Force will use the GRADE system to rate the quality of the evidence and strength of its recommendations[58-64].

Analysis of subgroups or subsets

Evidence for the use of CBP derived from the cannabis plant in the management of chronic pain and co-occurring conditions will be presented for clinical considerations related to efficacy, tolerability, safety, indications, dosing, drug interactions, adverse events, negative effects, contraindications. Evidence regarding considerations related to the use of CBP derived from the cannabis plant for patients with a history of substance use disorder. The phenomenon of CBP substitution for other drugs will be included.

Risk of bias assessment

Two reviewers (MSP and PW) will assess the potential bias and discrepancies will be discussed and adjudicated by the Data Synthesis committee (CC, ZW, SM). The National Institutes of Health risk of bias assessment tools[65] will be used to assess the quality of included studies. These tools have been developed specifically for different study design types, and therefore the heterogeneity of included study designs will not affect the ability to assess quality appropriately. Each included study will be dually and independently reviewed and disagreements will be solved through discussion. These tools utilized for quality assessment are "not intended to create a list that is simply tallied up to arrive at a summary judgment of quality", meaning reviewers will evaluate studies utilizing the tools but will not solely rely on the cumulative score, and will make decisions through discussion when necessary. Studies will be graded as either "good quality" (score of 3), implying low risk of bias, "fair quality" (score of 2) implying some risk of bias or "poor quality" (score of 1), implying high risk of bias. Assessment of bias will be performed at the overall study level. Specific Questions to assess for study limitations and the risk of bias are included on our Data Extraction Form (Supplementary File).

Data analysis/synthesis

Findings from the review will be synthesized to highlight where multiple reviews find consistent effects and where reviews have come to different conclusions about the strength of the evidence. In the narrative synthesis, we will discuss the findings both within and between studies, based on guidance from the Centre for Reviews and Dissemination (For example, a study examining the efficacy of a single dosing regimen comparing baseline to

end study scores). Findings will be aggregated or synthesized to generate a set of statements rates according to their quality.

Reporting of the review

The Cannabis Guidelines Task Force plans on publishing both the protocol for the development of the clinical practice guidelines, as well as the systematic review protocol. Once the guidelines and decision aid are developed, they will also be published and disseminated. Members of the Task Force will be encouraged to present the guidelines at relevant conferences and meetings.

Patient and Public involvement

Among the authors of this systematic review protocol are patient community advisors (SM and EM). They have been involved in all stages of this project, beginning from conception and design of this systematic review. They will continue to be involved at all stages, including study appraisal, guideline drafting and publication.

Discussion

In this systematic review, we will prepare a detailed, up-to-date tool for healthcare providers and patients to assist them with decisions about CBP derived from the cannabis plant as a treatment option for chronic pain and co-occurring conditions including sleep disorders, mood disorders alcohol use disorder and opioid use disorder. Although some publications provide guidance with respect to administration and dosing of CBP derived from the cannabis plant[42 43] and one recent publication offers clinical practice guidelines

for prescribing CBP in primary care[44], our systematic review geared for both healthcare providers and patients will add to the current literature by providing a balanced view of both the benefits and potential risks, and will also highlight specific areas requiring additional research.

We anticipate some challenges with our systematic review. Firstly, there is likely to be very high heterogeneity with regards to patient populations, CBP derived from the cannabis plant dosage form and dosages, study design and reported outcomes. When CBP is administered in different dosage forms, such as by capsule *vs.* by inhaled form, the kinetics vary widely which may make direct, head-to-head comparisons between studies inappropriate. In addition, individual differnces in patient characteristics between studies may preclude us from generalizing results across studies. Furthermore, our search terms may not enable us to pick up common chronic pain conditions such as arthritis, fibromyalgia, spinal cord injury, diabetic neuropathy. Nonetheless, within the context of chronic pain, our systematic review aims to provide a broad, balanced view of both the potential benefits and harms associated with the use of CBP for pain and co-occurring conditions. These results are likely to serve as an reference tool for both healthcare providers and patients suffering from such conditions, and will also underscore the specific areas of CBP research requiring further study.

Study Status:

At the time of protocol publication, discussions within the evidence synthesis working group have resulted in the plan to summarize data from systematic reviews separately from the data from original research. This data will be presented to the guidelines writing committee, who will draft the guidelines.

Authors' contributions:

PW and LBI drafted the protocol. All authors, including MSP, ADB, PJD, MG, MC, EM, JXY and JOH, had input into the protocol design and critically reviewed and revised the manuscript. TS and SA devised the search strategy, performed data extraction and data interpretation. PW and CC prepared the manuscript. The Data Synthesis Team (CC, ZW, SM, GL) was consulted for interpretation of the results. All authors conceived and designed the review, and read and approved the final manuscript. PW and CC are the guarantors of the review.

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Neither the funders nor authors'affiliated institutions played any role in the development of the protocol.

Conflicts of interest

TS, SA, LBI, MS, JXY and JO do not have any conflicts of interest.

PW's employer, the Canadian AIDS Society, has received a grant from Canopy Growth Corporation (a cannabis company) for the development of the clinical practice guidelines.

ZW is an advisory board member of Multidisciplinary Association for Psychedelic Studies – Canada, and for the Canadian Association of Medical Cannabis Dispensaries. He is in the planning phases of becoming an investigator on a survey study sponsored by Doja, from which he does not receive any direct financial compensation, however, graduate students in his lab receive paid Research Assistantships. He is the Coordinating Principal Investigator on a clinical trial of cannabis for PTSD that is sponsored by Tilray, from which he does not receive any direct financial compensation. Graduate students in his lab receive paid Research Assistantships from Tilray (a pharmaceuticals and cannabis company).

SM is the co-owner of a start-up company ("Cannabiscotti Inc") that will be applying for a cannabis processing license. She holds shares in Canopy Growth Corporation, Emblem Corp (a medical cannabis producer) and Aphria Inc (a cannabis company). She has received honorarium for research projects funded by Canopy Growth Corporation and Tilray.

AB is a member of the medical advisory board of Canopy Growth Corporation. He has received payment from Canopy Growth Corporation for consulting and speaking engagements. He has received unrestricted grants to attend academic presentations on the

topic of the medical use of cannabis from Canopy Growth Corporation, and holds shares in the company.

PJD is a member of the Medical Advisory Board for Shopper's Drug Mart, Tetra Bio-Pharma (a pharmaceutical company), a consultant for ReFormulary Group and Tallc Corporation, a member of the Speaker's Bureau for Medical Cannabis Education for Shopper's Drug Mart and Spectrum Therapeuics, and participates in clinical trials for CancerCare Manitoba in contract positions.

MG is the president and co-founder of the Harm Reduction Nurses Association. She was a board member of The Canadian HIV/AIDS Legal Network. She has received an honorarium payment from Merck (a pharmaceutical company) for a presentation on HIV medication side-effects.

CM is the Medical Director of Greenleaf Medical Clinic and the Translational Life Sciences. She is on the Board of Directors for the Green Organic Dutchman (a cannabis company) and is on the Medical Advisor Board for Emerald Health Therapeutics. She has provided medical consultation and/or receive support for industry sponsored continuing medical education from: Canopy/Spectrum, Stainprint, Scientus Pharma, Aurora, MedReleaf, Shoppers Drug Mart, MD Briefcase. Previously she has worked with Vitality Biopharma, True Leaf, Resolve Digital Health, Doja and Compass Cannabis Clinics.

EM is the co-owner of a start-up company ("Cannabiscotti Inc") that will be applying for a cannabis processing license, and is employed by MJardin Canada.

CTC has received cannabinoids from Tilray Inc. for use in a clinical trial but has not received any grant support nor honoraria from the company. She has received research funding from Merck and Gilead (pharmaceutical companies), speaker honorarium from Gilead and consultant fees from Viiv Healthcare (a pharmaceutical company). She has received funding to attend conferences from Gilead and Viiv Healthcare.

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Data Extraction Form and Quality Assessment Tool

Canadian Clinical Practice Guidelines for the Use of Cannabinoid-Based Medicine in the Management of Chronic Pain and Co-Occurring Conditions

Reference

Reviewer Extracting Data

Date form completed

Eligibility form

Factors	Assessment	Comments
Type of Study		
1) Is the study a systematic review or meta-analysis?	Yes No	
2) Is the study a controlled intervention study (randomized, non-randomized or quasi-experimental)?	Yes No	
3) Is the study an observational cohort or cross-sectional study?	Yes No	
4) Is the study a case-control study?	Yes No	
5) Is the article a review of system mechanisms, a commentary article or a clinical overview? - identify the type of article in comments section	Yes (exclude) No	

Participants		
6) Do participants explicitly present with chronic pain? 7) Was the pain cancer-related?	Yes No (exclude) Unclear Yes (exclude) No Unclear	
Exclusion Criteria		
8) Did the study measure the effects of non-synthetic CBM use on chronic pain? 9) Was cannabis use one aspect of an intervention, but not the main focus?	Yes No (exclude) Unclear Yes (exclude) No Unclear	

Do not proceed if study excluded from review

Systematic Review and Meta-Analysis Data Extraction (Complete only if the answer to question 1 is "yes")

Review Characteristics	
Type(s) of studies included	
# of studies included	
Population studied (HIV+, PTSD, prescribed opioids, etc.)	
Type(s) of CBM included in review (whole plant, extract, synthetic)	
Main outcome(s)	
Meta-analyses conducted?	Yes No
Key findings	

Conclusions	

Systematic Review and Meta-Analysis Quality Assessment (Complete only if the answer to question 1 is "yes")

Criteria	
1. Is the review based on a focused question that is adequately formulated and described?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Were eligibility criteria for included and excluded studies predefined and specified?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Did the literature search strategy use a comprehensive systematic approach?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the included studies listed along with important characteristics and results of each study?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. Was the publication bias assessed?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was heterogeneity assessed? (This question applies only to meta-analyses)	
Yes	

No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Controlled Intervention Studies Data Extraction (Complete only if the answer to question 2 is "yes")

Study Characteristics	
Study year	
Location	
Study design type (i.e., RCT, Quasi-experimental)	
Study aim (i.e., efficacy, safety, tolerability)	
Population characteristics (from which study participants are drawn. i.e., HIV+, PTSD, adolescence)	
Sample size: Intervention population sample (#) Control population sample (#)	
Sample demographics (and differences between samples) Age Sex Race/Ethnicity	
Method of recruitment	
Length of the intervention	
CBM characteristics: - Type - Administration route - Dosing	
Type of control (Placebo, alternative, no treatment)	

Main outcome measures	
Main findings	
Comorbidities measured	
Conclusions	

Controlled Intervention Studies Quality Assessment (Complete only if the answer to question 2 is "yes")

Criteria	
1. Is the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the method of randomization adequate (ie. Use of a randomly generated assignment)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were the study participants and providers blinded to treatment group assignment?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Were the people assessing the outcomes blinded to the participants' group assignments?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
9. Was there high adherence to the intervention protocols for each treatment group?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
13. Were the outcomes reported or subgroups analyzed pre-specified (i.e., identified before analyses were conducted)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Observational Cohort or Cross-sectional Study Data Extraction (Complete only if the answer to question 3 is "yes")

Study Characteristics	
Study year	
Study location	
Study design type (i.e., prospective, retrospective, cross-sectional)	
Population Characteristics (HIV+, prescribed opioids, etc)	
Sample Size	
Sample characteristics Age Sex Race/Ethnicity	
Method of recruitment	
Length of study	
CBM Characteristics	
Main outcome measures (and any other important outcomes measured)	
Main Findings/conclusions	

Observational Cohort or Cross-sectional Study Quality Assessment (Complete only if the answer to question 3 is "yes")

Criteria	
1. Was the research question or objective in this paper clearly stated?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the study population clearly specified and defined?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Was the participation rate of eligible persons at least 50%?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Was a sample size justification, power description, or variance and effect estimates provided?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. For the analysis of this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if It existed?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	
Yes	
No	
Other (Cannot determine, Not applicable, not	

reported)	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Was the exposure(s) assessed more than once over time?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Were the outcome assessors blinded to the exposure status of the participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
13. Was loss to follow-up after baseline 20% or less?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Case-Control Studies Data Extraction (Complete only if the answer to question 4 is "yes")

Study Characteristics	
Study year	

Study location	
Study design type (i.e., prospective, retrospective, cross-sectional)	
Population Characteristics (HIV+, prescribed opioids, etc)	
Sample Size	
Sample characteristics Age Sex Race/Ethnicity	
Control Group	
Method of recruitment	
Length of study	
CBM Characteristics	
Main outcome measures (and any other important outcomes measured)	
Main Findings/conclusions	

Case-Control Studies Quality Assessment (Complete only if the answer to question 4 is "yes")

Criteria	
1. Was the research question or objective in this paper clearly stated and appropriate?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the study population clearly specified and defined?	
Yes	
No	
Other (Cannot determine, Not applicable, not	

reported)	
3. Did the authors include a sample size justification?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the cases clearly defined and differentiated from controls?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was there use of concurrent controls?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	

Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	22
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	22-23
Sponsor	5b	Provide name for the review funder and/or sponsor	22-23
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	22
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-9
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	12-14; Table 1
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-14
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11-12

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	17
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	16-17
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	16-17
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	17
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	17-19
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	18-20
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	18-20
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16-18
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16-19
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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BMJ Open

Canadian Clinical Practice Guidelines for the Use of Plant-Based Cannabis and Cannabinoid-Based Products in the Management of Chronic Non-Cancer Pain and Co-occurring Conditions: Protocol for a Systematic Literature Review

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Secondary Subject Heading:	Medical management
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Canadian Clinical Practice Guidelines for the Use of Plant-Based Cannabis and Cannabinoid-Based Products in the Management of Chronic Non-Cancer Pain and Co-occurring Conditions:

Protocol for a Systematic Literature Review

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Abstract

Introduction: Chronic pain and co-occurring disorders, such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders, are among the most common conditions for which cannabis and cannabinoid-based products derived from the cannabis plant (CBP) are used for therapeutic purposes. However, healthcare providers report that they lack sufficient information on the risks, benefits and appropriate use of cannabis and CBP derived from the cannabis plant for therapeutic purposes.

Methods and Analysis: We will conduct a systematic review of studies investigating the use of cannabis and CBP derived from the cannabis plant for the treatment of chronic pain and co-occurring conditions. Randomized controlled trials, meta-analyses and observational studies will be prioritized. We will exclude reviews of cannabinoid mechanisms of actions, commentary articles and narrative reviews. The primary outcome of interest will be efficacy in relieving chronic pain. Secondary outcomes will be efficacy in ameliorating conditions such as sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders. We will search electronic bibliographic databases including Academic Search Complete, Cochrane Database of Systematic Reviews, Evidence based Medicine Reviewes, OVID Medline, PsychINFO, PubMed, CINAHL and Web of Science. Two reviewers will conduct screening and data collection

independently. Study level of bias will be assessed using the Cochrane Risk of Bias Assessment Tool for randomized controlled trials and non-randomized studies. Narrative analysis will be utilized to interpret the data.

Ethics and Dissemination: The results of this systematic review will inform guideline development for the use of cannabis and CBP derived from the cannabis plant in the management of chronic pain and co-occurring conditions. Areas requiring further study will also be highlighted.

Systematic review registration: PROSPERO #CRD42020135886

Strengths and limitations

- Extensive review of literature with rigorous study selection and methods for data extraction, quality assessment and data synthesis
- Breadth and consideration of diverse methodologies distinguishes this review for other recent reviews of cannabis and pain
- Wide variety of panel members comprised of clinicians, academics and community members with unique perspectives and synergistic skills
- A timely systematic review given liberalization of cannabis regulations across Europe and the Americas
- Conclusions may be limited by inclusion of relatively few controlled trials

Background

Approximately 19% to 29% of Canadian adults aged 18 and older live with chronic pain, most commonly attributed to lower back pain and arthritis, with an average duration of more than 10 years[1, 2]. Arthritis alone, which includes more than 100 rheumatic diseases and conditions that affect joints, affects over 4.2 million Canadians (16% of those aged 15 years and older), and this prevalence is estimated to reach approximately 7 million, or 1 in 5 Canadians aged 15 and older, by 2031[3].

Chronic pain often co-occurs with sleep disorders, anxiety, depression, post traumatic stress disorder, and substance use disorders such as opioid use disorder and alcohol use disorder[4-10]. Chronic pain and these co-occurring conditions are also among the most common conditions for which cannabinoid-based products derived from the cannabis plant (CBP) are used for therapeutic purposes[11-14].

The cannabis plant contains over 100 phytocannabinoids, although Δ^9-tetrahydrocannabinol and cannabidiol are the most well-characterized. Other cannabinoids contained in the plant include cannabigerol, cannabichromene,

cannabinodiol, cannabielsoin, cannabicyclol, cannabinol, cannabitriol and others[15 16]. The cannabis plant also contains terpenoids which provide characteristic aromas[17]. Different cannabinoids and terpeneoids in combination behave in synergy, through what has been coined "the entourage effect," explaining why plants are often more efficacious than their components in isolation[18]. Extracts include nabiximols (Sativex®), a 1:1 tetrahydrocannabinol (THC):cannabidiol (CBD) sublingual spray. Synthetic pharmaceutical-grade cannabinoids include nabilone (Cesamet®) and dronabinol (Marinol®), synthetic products administered orally by capsule. A major knowledge gap relates to the use of cannabis and plant-derived cannabinoids derived from the cannabis plant in the management of chronic pain and co-occurring conditions.

In Canada, surveys indicate that patients frequently treat multiple symptoms with CBP derived from the cannabis plant [14]. Since 2001, Canada has had a federal program that authorizes the use of CBP derived from the cannabis plant and as of October 2018, has legalized and regulated the sale of cannabis for adult recreational use. Thus, for Canadians, the role of CBP derived from the cannabis plant in the context of chronic pain management and its associated co-occurring conditions is likely to increase. Managing chronic pain and co-occurring morbidities is a complex public health and medical challenge, which is compounded by the introduction of CBP into the pharmacopoeia of therapeutic options.

Healthcare providers have expressed concerns about the use of CBP derived from the cannabis plant, stating that they did not have the quality of evidence they require to

feel comfortable discussing CBP derived from the cannabis plant as a therapeutic option with their patients[19]. They reported that they lack sufficient information on risks, benefits, and appropriate use of CBP derived from the cannabis plant for therapeutic purposes and were reluctant to support their patients' request for access to CBP[20 21].

The frequent co-occurrence of chronic pain and substance use disorders is often explained as patients' self-medicating to manage living with chronic pain[6]. Approximately 21-29% of individuals prescribed opioids for chronic pain misuse them, while 8-12% develop opioid use disorder [22-26.] CBP substitution for opioids is increasingly reported in the literature[27-30]. The potential for CBP use as a drug-related harm reduction strategy is being recognized[29 31 32], however it is not without risks, as its use may be associated with an increased risk of relapse, for example[33-35]. Regardless of the hypothesis that links chronic pain and substance use disorders, understanding the role of CBP derived from the cannabis plant in this context is crucial for the development of clinical practice guidelines.

Recent years have seen a proliferation of systematic literature reviews on CBP and their effects on chronic pain and co-occurring conditions. Systematic reviews have been conducted on CBP and chronic pain[36-39]; sleep disorders[39 40] and mood disorders[39 41]. While a few publications offer recommendations regarding administration and dosing strategies[42 43] and one recent publication offers clinical practice guidelines for prescribing CBP in primary care[44], clinicians and patients have no specific guidance on the use of CBP for the management of chronic pain and co-occurring conditions. Given the new

legal regimes globally and in Canada regarding recreational cannabis and CBP derived from the cannabis plant, healthcare providers need to be aware of the efficacy of CBP derived from the cannabis plant in regards to chronic pain and confident in knowing when such therapies may be beneficial for their patients.

There is a need for detailed, up-to-date tools and information for healthcare providers and patients to assist them with decisions about CBP derived from the cannabis plant as a treatment option. We propose to develop the Canadian Clinical Practice Guidelines for the Use of Cannabis and Cannabinoid-Based Products in the Management of Chronic Pain and Co-Occurring Conditions. Of note, to fill an important knowledge gap, these guidelines will examine literature focused on cannabis and CBP derived from the cannabis plant rather than synthetic, pharmaceutical-grade cannabinoids.

Methods and Analysis

Outcome(s)

Primary outcome: Chronic Pain

Chronic pain includes any painful condition that persists for more than three months, including nociceptive, neuropathic, and centralized pain[13 45]. Chronic pain outcomes are measured with scales, including but not limited to: the numeric rating scale, a visual analog scale, Euro-Quality of life-5 Dimensions-5 Levels (EQ-5D5L), Profile of Mood States (POMS) Questionnaire, 36-item short-form survey (FS36), the Neuropathic Pain Scale, the McGill Pain Questionnaire[37]. Some of these examples importantly include

measurements that focus on patient reported outcomes, patient functionality, and quality of life.

Secondary outcomes

Sleep Disorders

Although many sleep disorders exist, insomnia is the most common. Insomnia refers to a condition whereby sleep is disturbed despite the presence of an adequate opportunity and circumstance for sleep, which has a negative effect on daily function[46]. Sleep measures include sleep behaviour inventory, sleep evaluation questionnaire, electro-encephalogram (EEG) measures, and visual observation of sleep activity[40].

Anxiety, Depression, and Post Traumatic Stress Disorder

The co-occurrence of chronic pain and mood disorders such as anxiety, depression, and post-traumatic stress disorder is well documented[4 5 7 10]. Mood disorder outcomes are measured by Structured Clinical Interview for DSM and self-reported questionnaire (e.g. self report, with the Beck Depression Inventory, Hamilton Depression Inventory, Centre for Epidemiological Studies Depression Scale (CES-D).

Substance Use Disorders

Changes in the use of non-cannabinoid products and other substances, in conjunction with cannabis use, will be reviewed. CBP derived from the cannabis plant substitution is

assessed through questionnaires. Diagnostic and Statistical Manual of Mental Disorders (DSM)-V diagnoses for drug abuse and dependence can be obtained using instruments such as the World Health Organization Composite International Diagnostic Interview (CIDI), Drug User Disorder Identification Test (DUDIT), Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), and others[6 47]. Alcohol use disorder and opioid use disorder are also often measured using specific instruments including The Alcohol Use Disorders Identification Test (AUDIT)[48], the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV)[49] and the Current Opioid Misuse Measure (COMM)[50], as well as others.

Previous studies have focused on risks and harms associated with cannabis and few have addressed the health promoting or beneficial effects of CBP derived from the cannabis plant[51 52]. However, as the development of a cannabis use disorder is a possible consequence of cannabis consumption in susceptible individuals, the presence of cannabis use disorders will be noted. Specific screening and diagnostic instruments to assess cannabis use disorders include the Cannabis Problems Questionnaire (CPQ), Cannabis Abuse Screening Test (CAST), Cannabis Use Disorder Identification Test (CUDIT) and its revised version (CUDIT-R), and others[47 53].

Search strategy

An electronic search will be conducted for peer-reviewed articles (2001-2019), restricted to the English language, in the following electronic bibliographic databases: Academic Search Complete, Cochrane Database of Systematic Reviews (CDSR), Evidence Based

Medicine Reviews (EBMR), OVID Medline, PsychINFO, PubMed, CINAHL, and Web of Science. The search strategy will include the following controlled vocabulary and relevant key terms:

(cannabi* OR marijuana OR endocannabi* OR THC OR Tetrahydrocannabinol OR weed OR CBD OR Indica OR Sativa OR nabiximols OR dronabinol OR pot) AND (pain OR headache OR neuralgia OR migraine)

This search strategy was developed with the assistance of a medical librarian experienced is systematic reviews. As the journal "Cannabis and Cannabinoid Research" is currently one of the few journals specifically devoted to cannabis research, this journal will be hand searched for studies that meet the inclusion criteria. Based on the recommendations of the medical librarian, the terms "nabiximols" and "dronabinol" were included in the search strategy to ensure that we capture all relevant studies to screen. However, studies focused *exclusively* on the efficacy of synthetic cannabinoids of pharmaceutical grade (such as nabilone or dronabinol) approved for human use will be excluded. As nabiximols contain plant derived cannabinoids, they will be included. Only studies published since 2001 will be included to focus the review on recent evidence. Since 2001 there have been technological advances and regulatory changes, , such as the legalization of medicinal cannabis in Canada, that may have improved the quality of research. All database searches will be completed by May 2019.

Study screening and inclusion

Following the implementation of our search, we will obtain the titles and abstracts from all references. First we will examine the tiles and abstracts, and then full-texts of studies

which appear relevant will be screened by two reviewers independently. We will conduct pilot exercises to identify and address any inconsistencies in applying the screening criteria. The inclusion and exclusion criteria for each stage of screening are indicated below. When no abstract is available, and the article can not be confidently excluded by solely the title, the full-text will be obtained. In general, if there is uncertainty as to whether a study should be excluded, the study will proceed to the full-text screen. Two reviewers will resolve disagreements on inclusion, and a third person will reconcile any remaining disagreements. We will not exlude studies based on poor research quality, but we will note the low quality. The process of study selection will be summarized using a PRISMA flow diagram[54].

Study eligibility criteria

Study selection will be based on the criteria listed in Table 1. Study inclusion and exclusion criteria are listed in Table 2.

Table 1 PICOS breakdown of study eligibility criteria

Category	**Description of criteria**
Population	Human of any age living with chronic, or non-acute, pain (pain of greater than 3 month duration) Humans of any age living with chronic pain and co-occurring conditions: sleep disorders, mood disorders (anxiety, depression, post-traumatic stress disorder), alcohol use disorder and opioid use disorder
Intervention	Cannabis or cannabinoid-based products (CBP) derived from the cannabis

	plant in the form of herbal cannabis and derivatives
Comparison(s)	Placebo or other medications or intervention Studies without comparators will also be included*
Outcome(s)	Primary outcome: 1) Efficacy, tolerability and safety of cannabis and CBP derived from the cannabis plant in the management of chronic pain 2) Improvement in chronic pain, symptom management 3) Improvement in quality of life, patient-reported outcomes and patient functionality Secondary outcomes: Improvement in sleep disorders, anxiety, depression, alcohol use disorder, and opioid use disorder
Study design	Randomized controlled trials, controlled trials, studies listed in meta-analyses and observational studies will be included Studies that focus on cannabinoid mechanisms, commentary articles or non-systematic reviews will be excluded.

*An example of a study without a comparator would be a study examining the efficacy of a single dosing regimen comparing baseline to end study scores

Table 2: Inclusion and Exclusion Criteria

Inclusion criteria	• Cannabis and the management of chronic pain • Cannabis and the management of chronic pain and co-occurring conditions: sleep disorders, mood disorders (anxiety, depression, post-traumatic stress disorder), alcohol use disorder and opioid use disorder • Efficacy, tolerability and safety studies on the use of cannabis in the management of chronic pain • Indications and dosing strategies of cannabis for the treatment of chronic pain • Drug interactions, adverse events, negative effects and contraindications for the use of cannabis in the treatment of chronic pain • Considerations regarding the use of cannabis for the management of chronic pain for individuals with a history of sleep disorders, anxiety, depression, post-traumatic stress disorder, opioid use disorder and alcohol use disorder • The substitution effect of cannabis for medications or other drugs in the context of the management of chronic pain
Exclusion criteria	• Studies published before 2001 • Studies in a language other than English • Studies focused on the use of cannabis for recreational purposes or which do not differentiate between recreational vs. medicinal use

	• Studies focused exclusively on synthetic cannabinoids of pharmaceutical grade approved for human use* • Studies focused on the prevention or cessation of cannabis use • Studies focused exclusively on cancer-related pain** • Studies focused on cannabis use disorder • Studies where cannabis is only one aspect of an intervention, and not the main focus • Studies on non-humans/animals

*These compounds should be distinguished from those used in basic science research, not approved for human use, and which are known on the streets by terms such as "Spice" and "K2"

**Due to the large number of studies focused exclusively on cancer-related pain, we have excluded these studies from the current systematic review in order to narrow the focus. However, we acknowleddge the importance of cancer-related pain and suggest that this be the focus of a separate systematic review.

Data extraction

Selection of studies

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) conventions[55], an Evidence Synthesis Working Group, working with the Guidelines Panel, will determine eligibility of studies by reading the abstracts identified by the search. Grey literature will also be included when appropriate. Studies will be selected based on inclusion and exclusion criteria. The Evidence Synthesis Working

Group will independently read the selected studies and reach agreement about inclusion and exclusion by discussion. A PRISMA flow chart will be created. The CBP Task Force will come to the final conclusion when there is debate.

Data extraction and management

The Evidence Synthesis Working Group will extract data from the selected studies independently using a standardized Data Extraction Form (Supplementary File) to create evidence tables. For each study, relevant data will be extracted related to study identification (author, year published, number and location of centres, funding, journal name), the number of participants, form of CBP derived from the cannabis plant, dose and route, study design and setting, inclusion and exclusion criteria of the study sample, aggregate demographic (age, sex, type of pain, co-occurring conditions) and clinical characteristics (co-morbidities), and outcome measures (e.g., scores on the Visual Analog Scales or McGill Pain Questionnaire) and results. We will also record adverse events as reported in individual studies, including the frequency and severity of cases when applicable. Adverse events will collectively be analyzed utilizing the World Health Organization (WHO) Toxicity grading scale for determining the safety of adverse events. In addition, we plan to examine secondary outcomes within standalone studies on the use of cannabis (e.g., effects of cannabinoids on anxiety) as well as within studies of cannabinoids being used to manage chronic pain (e.g., looking at anxiety as a secondary outcome in a pain clinical trial). Records of all searches will be kept on secure databases only accessible to the investigators. Records of all data extraction forms and consensus discussions will also be kept on the same databases.

Strategy for data synthesis

Data will be extracted from reviews, including existing meta-analyses, using a standardized data extraction tool. Due to the high variability in previous cannabis research, a meta-analysis is likely inappropriate. This variability is due to heterogeneity of sample populations, study types and lengths, and CBP derived from the cannabis plant interventions (e.g. CBP type, dosing, administration route, etc.). Similar challenges have prevented the execution of meta-analyses in previous, related reviews[56]. Patterns related to efficacy, safety, tolerability will be explored through narrative synthesis[56 57]. Data from relevant categories (Ex. sub-populations, age groups, alternative therapies, etc.) will be compiled based on the availability of quality evidence. Consistent findings and discrepancies will be discussed. Findings will be aggregated or synthesised to generate a set of statements rated according to their quality. We do not plan to conduct a meta-analysis.

Assessment of Evidence and Recommendations

The Task Force will use the GRADE system to rate the quality of the evidence and strength of its recommendations[58-64].

Analysis of subgroups or subsets

Evidence for the use of CBP derived from the cannabis plant in the management of chronic pain and co-occurring conditions will be presented for clinical considerations related to efficacy, tolerability, safety, indications, dosing, drug interactions, adverse

events, negative effects, contraindications. Evidence regarding considerations related to the use of CBP derived from the cannabis plant for patients with a history of substance use disorder. The phenomenon of CBP substitution for other drugs will be included.

Risk of bias assessment

Two reviewers (MSP and PW) will assess the potential bias and discrepancies will be discussed and adjudicated by the Data Synthesis committee (CC, ZW, SM). The National Institutes of Health risk of bias assessment tools[65] will be used to assess the quality of included studies. These tools have been developed specifically for different study design types, and therefore the heterogeneity of included study designs will not affect the ability to assess quality appropriately. Each included study will be dually and independently reviewed and disagreements will be solved through discussion. These tools utilized for quality assessment are "not intended to create a list that is simply tallied up to arrive at a summary judgment of quality", meaning reviewers will evaluate studies utilizing the tools but will not solely rely on the cumulative score, and will make decisions through discussion when necessary. Studies will be graded as either "good quality" (score of 3), implying low risk of bias, "fair quality" (score of 2) implying some risk of bias or "poor quality" (score of 1), implying high risk of bias. Assessment of bias will be performed at the overall study level. Specific Questions to assess for study limitations and the risk of bias are included on our Data Extraction Form (Supplementary File).

Data analysis/synthesis

Findings from the review will be synthesized to highlight where multiple reviews find consistent effects and where reviews have come to different conclusions about the strength of the evidence. In the narrative synthesis, we will discuss the findings both within and between studies, based on guidance from the Centre for Reviews and Dissemination (For example, a study examining the efficacy of a single dosing regimen comparing baseline to end study scores). Findings will be aggregated or synthesized to generate a set of statements rates according to their quality.

Reporting of the review

The Cannabis Guidelines Task Force plans on publishing both the protocol for the development of the clinical practice guidelines, as well as the systematic review protocol. Once the guidelines and decision aid are developed, they will also be published and disseminated. Members of the Task Force will be encouraged to present the guidelines at relevant conferences and meetings.

Patient and Public involvement

Among the authors of this systematic review protocol are patient community advisors (SM and EM). They have been involved in all stages of this project, beginning from conception and design of this systematic review. They will continue to be involved at all stages, including study appraisal, guideline drafting and publication.

Discussion

In this systematic review, we will prepare a detailed, up-to-date tool for healthcare providers and patients to assist them with decisions about CBP derived from the cannabis plant as a treatment option for chronic pain and co-occurring conditions including sleep disorders, mood disorders alcohol use disorder and opioid use disorder. Although some publications provide guidance with respect to administration and dosing of CBP derived from the cannabis plant[42 43] and one recent publication offers clinical practice guidelines for prescribing CBP in primary care[44], our systematic review geared for both healthcare providers and patients will add to the current literature by providing a balanced view of both the benefits and potential risks, and will also highlight specific areas requiring additional research.

We anticipate some challenges with our systematic review. Firstly, there is likely to be very high heterogeneity with regards to patient populations, CBP derived from the cannabis plant dosage form and dosages, study design and reported outcomes. When CBP is administered in different dosage forms, such as by capsule *vs.* by inhaled form, the kinetics vary widely which may make direct, head-to-head comparisons between studies inappropriate. In addition, individual differnces in patient characteristics between studies may preclude us from generalizing results across studies. Furthermore, our search terms may not enable us to pick up common chronic pain conditions such as arthritis, fibromyalgia, spinal cord injury, diabetic neuropathy. Nonetheless, within the context of chronic pain, our systematic review aims to provide a broad, balanced view of both the potential benefits and harms associated with the use of CBP for pain and co-occurring conditions. These results are likely to serve as an reference tool for both

healthcare providers and patients suffering from such conditions, and will also underscore the specific areas of CBP research requiring further study.

Study Status:

At the time of protocol publication, discussions within the evidence synthesis working group have resulted in the plan to summarize data from systematic reviews separately from the data from original research. This data will be presented to the guidelines writing committee, who will draft the guidelines.

Authors' contributions:

PW and LBI drafted the protocol. All authors, including MSP, ADB, PJD, MG, MC, EM, JY and JOH, had input into the protocol design and critically reviewed and revised the manuscript. TS and SA devised the search strategy, performed data extraction and data interpretation. PW and CC prepared the manuscript. The Data Synthesis Team (CC, ZW, SM, GL) was consulted for interpretation of the results. All authors conceived and designed the review, and read and approved the final manuscript. PW and CC are the guarantors of the review.

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Neither the funders nor authors'affiliated institutions played any role in the development of the protocol.

Conflicts of interest

TS, SA, LBI, MS, JXY and JO do not have any conflicts of interest.

PW's employer, the Canadian AIDS Society, has received a grant from Canopy Growth Corporation (a cannabis company) for the development of the clinical practice guidelines.

ZW is an advisory board member of Multidisciplinary Association for Psychedelic Studies – Canada, and for the Canadian Association of Medical Cannabis Dispensaries. He is in the planning phases of becoming an investigator on a survey study sponsored by Doja, from which he does not receive any direct financial compensation, however, graduate students in his lab receive paid Research Assistantships. He is the Coordinating Principal Investigator on a clinical trial of cannabis for PTSD that is sponsored by Tilray, from which he does not receive any direct financial compensation. Graduate students in his lab receive paid Research Assistantships from Tilray (a pharmaceuticals and cannabis company).

SM is the co-owner of a start-up company ("Cannabiscotti Inc") that will be applying for a cannabis processing license. She holds shares in Canopy Growth Corporation, Emblem Corp (a medical cannabis producer) and Aphria Inc (a cannabis company). She has received honorarium for research projects funded by Canopy Growth Corporation and Tilray.

AB is a member of the medical advisory board of Canopy Growth Corporation. He has received payment from Canopy Growth Corporation for consulting and speaking engagements. He has received unrestricted grants to attend academic presentations on the topic of the medical use of cannabis from Canopy Growth Corporation, and holds shares in the company.

PJD is a member of the Medical Advisory Board for Shopper's Drug Mart, Tetra Bio-Pharma (a pharmaceutical company), a consultant for ReFormulary Group and Tallc Corporation, a member of the Speaker's Bureau for Medical Cannabis Education for Shopper's Drug Mart and Spectrum Therapeuics, and participates in clinical trials for CancerCare Manitoba in contract positions.

MG is the president and co-founder of the Harm Reduction Nurses Association. She was a board member of The Canadian HIV/AIDS Legal Network. She has received an honorarium payment from Merck (a pharmaceutical company) for a presentation on HIV medication side-effects.

CM is the Medical Director of Greenleaf Medical Clinic and the Translational Life Sciences. She is on the Board of Directors for the Green Organic Dutchman (a cannabis company) and is on the Medical Advisor Board for Emerald Health Therapeutics. She has provided medical consultation and/or receive support for industry sponsored continuing medical education from: Canopy/Spectrum, Stainprint, Scientus Pharma, Aurora, MedReleaf, Shoppers Drug Mart, MD Briefcase. Previously she has worked with Vitality Biopharma, True Leaf, Resolve Digital Health, Doja and Compass Cannabis Clinics.

EM is the co-owner of a start-up company ("Cannabiscotti Inc") that will be applying for a cannabis processing license, and is employed by MJardin Canada.

CTC has received cannabinoids from Tilray Inc. for use in a clinical trial but has not received any grant support nor honoraria from the company. She has received research funding from Merck and Gilead (pharmaceutical companies), speaker honorarium from Gilead and consultant fees from Viiv Healthcare (a pharmaceutical company). She has received funding to attend conferences from Gilead and Viiv Healthcare.

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Data Extraction Form and Quality Assessment Tool

Canadian Clinical Practice Guidelines for the Use of Cannabinoid-Based Medicine in the Management of Chronic Pain and Co-Occurring Conditions

Reference

Reviewer Extracting Data

Date form completed

Eligibility form

Factors	Assessment	Comments
Type of Study		
1) Is the study a systematic review or meta-analysis?	Yes No	
2) Is the study a controlled intervention study (randomized, non-randomized or quasi-experimental)?	Yes No	
3) Is the study an observational cohort or cross-sectional study?	Yes No	
4) Is the study a case-control study?	Yes No	
5) Is the article a review of system mechanisms, a commentary article or a clinical overview? - identify the type of article in comments section	Yes (exclude) No	

Participants		
6) Do participants explicitly present with chronic pain? 7) Was the pain cancer-related?	Yes No (exclude) Unclear Yes (exclude) No Unclear	
Exclusion Criteria		
8) Did the study measure the effects of non-synthetic CBM use on chronic pain? 9) Was cannabis use one aspect of an intervention, but not the main focus?	Yes No (exclude) Unclear Yes (exclude) No Unclear	

Do not proceed if study excluded from review

Systematic Review and Meta-Analysis Data Extraction (Complete only if the answer to question 1 is "yes")

Review Characteristics	
Type(s) of studies included	
# of studies included	
Population studied (HIV+, PTSD, prescribed opioids, etc.)	
Type(s) of CBM included in review (whole plant, extract, synthetic)	
Main outcome(s)	
Meta-analyses conducted?	Yes No
Key findings	

Conclusions	

Systematic Review and Meta-Analysis Quality Assessment (Complete only if the answer to question 1 is "yes")

Criteria	
1. Is the review based on a focused question that is adequately formulated and described?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Were eligibility criteria for included and excluded studies predefined and specified?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Did the literature search strategy use a comprehensive systematic approach?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the included studies listed along with important characteristics and results of each study?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. Was the publication bias assessed?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was heterogeneity assessed? (This question applies only to meta-analyses)	
Yes	

No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Controlled Intervention Studies Data Extraction (Complete only if the answer to question 2 is "yes")

Study Characteristics	
Study year	
Location	
Study design type (i.e., RCT, Quasi-experimental)	
Study aim (i.e., efficacy, safety, tolerability)	
Population characteristics (from which study participants are drawn. i.e., HIV+, PTSD, adolescence)	
Sample size: Intervention population sample (#) Control population sample (#)	
Sample demographics (and differences between samples) Age Sex Race/Ethnicity	
Method of recruitment	
Length of the intervention	
CBM characteristics: - Type - Administration route - Dosing	
Type of control (Placebo, alternative, no treatment)	

Main outcome measures	
Main findings	
Comorbidities measured	
Conclusions	

Controlled Intervention Studies Quality Assessment (Complete only if the answer to question 2 is "yes")

Criteria	
1. Is the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the method of randomization adequate (ie. Use of a randomly generated assignment)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were the study participants and providers blinded to treatment group assignment?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Were the people assessing the outcomes blinded to the participants' group assignments?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
9. Was there high adherence to the intervention protocols for each treatment group?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
13. Were the outcomes reported or subgroups analyzed pre-specified (i.e., identified before analyses were conducted)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Observational Cohort or Cross-sectional Study Data Extraction (Complete only if the answer to question 3 is "yes")

Study Characteristics	
Study year	
Study location	
Study design type (i.e., prospective, retrospective, cross-sectional)	
Population Characteristics (HIV+, prescribed opioids, etc)	
Sample Size	
Sample characteristics Age Sex Race/Ethnicity	
Method of recruitment	
Length of study	
CBM Characteristics	
Main outcome measures (and any other important outcomes measured)	
Main Findings/conclusions	

Observational Cohort or Cross-sectional Study Quality Assessment (Complete only if the answer to question 3 is "yes")

Criteria	
1. Was the research question or objective in this paper clearly stated?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the study population clearly specified and defined?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
3. Was the participation rate of eligible persons at least 50%?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Was a sample size justification, power description, or variance and effect estimates provided?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. For the analysis of this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if It existed?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	
Yes	
No	
Other (Cannot determine, Not applicable, not	

reported)	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Was the exposure(s) assessed more than once over time?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Were the outcome assessors blinded to the exposure status of the participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
13. Was loss to follow-up after baseline 20% or less?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

Case-Control Studies Data Extraction (Complete only if the answer to question 4 is "yes")

Study Characteristics	
Study year	

Study location	
Study design type (i.e., prospective, retrospective, cross-sectional)	
Population Characteristics (HIV+, prescribed opioids, etc)	
Sample Size	
Sample characteristics Age Sex Race/Ethnicity	
Control Group	
Method of recruitment	
Length of study	
CBM Characteristics	
Main outcome measures (and any other important outcomes measured)	
Main Findings/conclusions	

Case-Control Studies Quality Assessment (Complete only if the answer to question 4 is "yes")

Criteria	
1. Was the research question or objective in this paper clearly stated and appropriate?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
2. Was the study population clearly specified and defined?	
Yes	
No	
Other (Cannot determine, Not applicable, not	

reported)	
3. Did the authors include a sample size justification?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
6. Were the cases clearly defined and differentiated from controls?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
8. Was there use of concurrent controls?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	

Yes	
No	
Other (Cannot determine, Not applicable, not reported)	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	
Yes	
No	
Other (Cannot determine, Not applicable, not reported)	

Quality Rating (Good, Fair or Poor)
Rater 1 initials:
Rater 2 initials:
Additional comments (if poor, please state why):

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	22
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	22-23
Sponsor	5b	Provide name for the review funder and/or sponsor	22-23
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	22
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-9
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	12-14; Table 1
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-14
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11-12

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	17
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	16-17
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	16-17
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	17
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	17-19
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	18-20
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	18-20
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16-18
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16-19
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.