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Perioperative pain and addiction interdisciplinary network (PAIN): protocol for the perioperative management of cannabis and cannabinoid-based medicines using a modified Delphi process

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ABSTRACT

Introduction At the conception of this study (January 2019), a literature search by the authors found no evidence-based or consensus perioperative guidelines for patients consuming cannabis products, or for those patients in whom a cannabinoid medication could be considered for perioperative treatment. Currently, there is a large global population that consumes cannabis. The availability of cannabis has also increased this decade with greater legal access to cannabis products in some countries such as USA, Canada, Uruguay, Israel, Australia and Germany. There are recognised possible therapeutic benefits for the use of cannabis in patients with chronic pain, chronic neuropathic pain and chemotherapy-induced nausea and vomiting. There are also potential side effects from cannabis use such as psychosis, cannabis hyperemesis syndrome, misuse disorder and cannabis withdrawal syndrome. There is evidence that cannabis may also affect factors in the perioperative period such as monitoring, quality of analgesia, sleep and opioid consumption. Given the large population of persons using cannabis, the heterogeneity of cannabis products and the paucity (and heterogeneity) of perioperative literature surrounding it, perioperative guidelines for cannabis consuming patients are both lacking and necessary. In this paper, we present the design for a modified Delphi technique that has been started with the intent of deriving cannabis perioperative guidelines from the available medical literature and the consensus of multidisciplinary experts.

Materials, methods and analysis This study will use a scoping narrative literature review and modified Delphi process to generate cannabis perioperative guidelines. A scoping narrative review of cannabis in the perioperative period by the authors of this proposal was completed and provided to a panel of 17 experts. These experts were recruited for their knowledge and expertise regarding cannabis and/or perioperative medicine. They were asked to rate a series of indications and clinical scenarios in two rounds. During the first round, the expert panel was blinded to each other's participation. During the second

Strengths and limitations of this study

- ► Cannabis use is increasing among patients presenting for surgery; however, there is currently no consensus on how to manage these patients and the drug during the perioperative period.
- ► A modified Delphi protocol with a diverse group of panellists spanning disciplines and geographical areas will be used to generate consensus-based perioperative guidelines for the management of cannabis users.
- ► Given that cannabis-related legislation, social practices and medical literature are heterogeneous and rapidly evolving recommendations should be reviewed and updated regularly after this project's completion.

round of this process, the expert panel met after being provided with an analysis of the first round's submissions so they could be discussed further and, if possible, reach a further consensus regarding them. Using the results obtained from the Delphi review process, a draft of proposed cannabis perioperative guidelines will be generated. These proposed guidelines will be returned to the expert panel for critiquing prior to their finalisation.

Ethics and dissemination Study and panellist data will be deidentified and stored as per institutional (Toronto General Hospital) guidelines. Institutional research ethics board provided a waiver for this modified Delphi protocol. Findings will be presented and published in peer-reviewed publications and conferences.

INTRODUCTION

While conceptualising this study in January 2019, a literature review of perioperative management strategies for patients engaged in the recreational or therapeutic use of cannabis found no formal consensus or evidence-driven perioperative cannabis

guidelines. Given the clinical uncertainty regarding the impact of cannabis on perioperative care, the creation of evidence and expert-reviewed guidelines is appropriate.

This project is aimed at developing a set of consensus guidelines for the optimal perioperative management of patients who are using cannabis, or who are considered for cannabis treatment, in the perioperative period.

In this paper, we present the design for a modified Delphi technique that will be used to derive cannabis perioperative guidelines from the available medical literature and the consensus of multidisciplinary experts. The design of this Delphi technique well be based on the RAND/UCLA (Research and Development/ University of California, Los Angeles) Appropriateness Method (RAM) developed by the RAND Corporation and also on the modified Delphi method used by Goel *et al* to create consensus guidelines for the perioperative management of buprenorphine.[1 2]

Cannabis is one of the most commonly used recreational drugs in the world. It has garnered increasing public favour (especially among young adults) in countries like Canada and USA—with cannabis use becoming legal in Canada, Uruguay and parts of USA.[3–6] In addition to legalised recreational use, cannabis has also been legalised for medical use in many other countries such as Israel, Australia, Germany and Thailand.[7] From a global perspective, the United Nations estimated that in 2016 3.9% of the world's population (192.2 million people) used cannabis—an increase of 16% compared with estimates of the previous decade.[6]

The main active components found in the cannabis plant are cannabinoids. These are a diverse group of chemical compounds that bind to peripheral and central inhibitory cannabinoid CB_1 receptors decreasing neurotransmitter release, and to CB_2 receptors which are mainly found on immune cells where they modulate cytokine release. Cannabinoids are naturally found in the humans (endocannabinoids), but may be produced synthetically or harvested from the cannabis plant (phytocannabinoids).[8]

Cannabis has been used to treat many conditions showing moderate therapeutic benefit for the treatment of chronic pain, spasticity and chemotherapy-induced nausea and vomiting.[9 10] In 2017, an expert review by the American National Academies of Sciences, Engineering and Medicine described substantial evidence for cannabinoid treatment of chronic pain in adults, as well as chemotherapy-induced nausea and vomiting, and multiple sclerosis-related spasticity symptoms.[11] This and other reviews also reported potential analgesic benefit of treating cancer-related pain with cannabis.[11 12]

There are several potential adverse effects related to recreational and therapeutic cannabis use. A review of the treatment of chronic pain using cannabis-based medicines published in 2018 concluded that the potential benefits of cannabis-based medicines for the treatment of chronic neuropathic pain might be outweighed by their potential harms.[13] Harms commonly associated with cannabis use include psychiatric disturbances such as psychosis, dysphoria or 'feeling high', as well as others such as withdrawal, hyperemesis, sedation, blurred vision, tinnitus and ataxia.[10–12]

The extent to which patient use of cannabis affects anaesthesia and is not fully known as reflected by the medical literature surrounding cannabis using patients and the perioperative period. A 2018 double-blinded randomised controlled trial examined the effect of preoperative cannabis extract (nabiximols) administration on anaesthetic depth. The authors reported significantly higher BIS (bispectral index) scores in those patients premedicated with nabiximols, which they thought to be due to a change in EEG (electroenchephalogram) patterns rather than a shallower anaesthetic state.[14]

A 2015 cohort analysis of patients with obesity undergoing bariatric surgery found that the patients who reported consuming cannabis had significantly higher postoperative opioid consumption, but overall lower pain scores. The study's secondary outcomes, such as perioperative complications, and 90-day weight loss were not significantly different in cannabis consuming patients.[15] A study of Jamaican postsurgical patients also described cannabis users requiring significantly more rescue analgesia than non-cannabis users.[16] A similar finding was reported in a recent 2019 Canadian retrospective cohort study of patients who had undergone major orthopaedic surgery.[17] This study also noted higher rates of postoperative myocardial infarction and sleep disruption in cannabis using patients. A 2019 retrospective cohort review of 4 186 122 elective surgical patients found that those patients with an ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) code for cannabis dependence or cannabis abuse had an adjusted odds of postoperative myocardial infarction of 1.88 times higher (p<0.001) compared with those without an active cannabis use disorder.[18]

In 2019, a narrative scoping review identified 27 articles related to the impact of perioperative cannabis use after screening 6683 articles relating to the author's initial search. The review acknowledged that medical cannabis may have adverse effects in the perioperative period (especially for cannabis-naïve patients), and that habitual recreational cannabis users likely would not benefit from abrupt discontinuation of their cannabis.[19] Furthermore, the authors of this study noted that pain control, postoperative sleep, induction of anaesthesia and maintenance of anaesthesia may be poorer or more difficult in cannabis using patients.[19]

AIMS

This project is using an international expert consensus Delphi-based method to propose and evaluate a set of recommendations for the perioperative period that addresses patient recreational and therapeutic cannabis use. Not all of these aims will be applicable to all patients

as cannabis product availability and legality vary globally. These recommendations have focused on:

1. The appropriateness of continued cannabis therapy, as well as preoperative cannabis dose reduction or cessation.
2. The appropriateness of cannabis substitution with nabiximols and nabilone in the perioperative period.
3. The appropriateness of in-hospital cannabis use in the postoperative period.
4. The appropriateness of increased anaesthetic induction agent in cannabis use.
5. The appropriateness of screening for cannabis misuse and other co-occurring substance misuse behaviour.
6. Addressing cannabis-related perioperative complications, such as nausea and vomiting and withdrawal.
7. Expected postoperative pain.
8. The appropriateness of using analgesics in cannabis consuming patients.

This project is following the 22-step checklist recommended by the Reporting Items for practice Guidelines in HealThcare (RIGHT) group for the EQUATOR (Enhancing the Quality and Transparancy of Health Research) network. (online supplementary appendix A).[20]

METHODS AND DESIGN

This study made use of a modified Delphi technique, the RAM, developed by the RAND Corporation.[2] This technique acknowledges that randomised controlled trials are often not available or cannot provide enough detail to provide appropriate care (benefits exceeding harms) to the wide range of patients seen in everyday practice.

In practice, the RAM process starts with a detailed literature review and the creation of specific clinical scenarios, or treatment indications, to categorise patients relevant to the clinical questions. A panel of experts are then identified and recruited. The expert panel will be supplied with the results of the literature review, a list of relevant definitions and questionnaires containing clinical indications and scenarios for appropriateness rating. For each questionnaire item, the panel members will rate the benefit-to-harm ratio on a scale of 1–9. A rating of 1 indicates expected harms greatly outweigh the benefits, while a rating of 9 indicates expected benefits greatly outweigh the harms. A middle rating, 5, indicates an either equal harm and benefit or that the panel member cannot make a judgement for the patient described in the indication/clinical scenario.[2]

Each indication/clinical scenario is rated twice in two separate rounds. The panel members' first-round ratings are to be made individually without any other interaction with, or knowledge of, the other panellists. During the second round, the panel members will meet under the leadership of a moderator experienced using the RAM method. During the second round, panel members are given the distribution of the other experts' first round ratings as well as a copy of their own ratings. The panel members will then be given a chance to modify the original scenarios/indications or definitions. After discussion, the panel will rerate each indication/scenario. There are no attempt to force panel consensus.[2]

Each questionnaire item then receives a finalised rating classified by its median rated score. 1–3 is inappropriate, 4–6 is uncertain and 7–9 is appropriate. If there is 'disagreement' lack of consensus due to panel polarisation or ratings spread over the 1–9 scale, then an indication/scenario will be classified as uncertain.[2]

Steering committee and literature review

A steering committee of four persons was recruited to lead this project. The committee is composed of Canadian anaesthesiologists with expertise in treating patients consuming prescribed or recreational cannabis products. These persons also had an interest, or prior experience, with guideline development using a modified Delphi technique.

A literature review on patient perioperative cannabis use was completed as part of the modified Delphi process by members of the steering committee. The literature review used was completed and published in December 2019.[19] The expert panel was provided with this review and the first round of questionnaires when their participation in this project was confirmed.

The literature review was directed at understanding the scope of cannabis perioperative management strategies that currently exist, as well as reviewing other existing evidence relating to patient perioperative cannabis use. Other RAM/modified Delphi studies, such as those published by Goel *et al*, Slade *et al* and Okoli and Pawlowski,[1 21 22] were also reviewed in preparation for this project when creating the initial institutional proposal for it.

Generation of therapeutic cannabis indications and clinical perioperative scenarios

Indications and clinical scenarios derived from the review of literature were combined with indications and scenarios proposed by perioperative clinicians with case experience treating patients who consume cannabis (the steering committee). These scenarios and indications were used to complete panel rater forms based on the format suggested by the 2001 RAM User's Manual.[2]

Indications and clinical scenarios were itemised and organised into three chapters of questionnaires under their relevant perioperative periods—preoperative, intraoperative and postoperative. Panellists (the recruited expert panel) rated these items on the proposed 1–9 scale in the first round of data collection. Clinical scenarios and indications included in the questionnaires encompassed preoperative assessment, cannabis weaning, nabilone and nabiximols substitution for inhaled cannabis and cannabis oil, cannabis withdrawal syndrome/symptoms, depth of anaesthesia monitoring, contact with cannabis prescribers and postoperative nausea and vomiting as

well as the appropriateness of anticipating increased analgesic and anaesthetic requirements.

A sample of the questionnaires used for this project is presented in online supplementary appendix B.

Panel selection: recruitment and participants
Panel size is recommended to be composed of 9–15 experts as per the RAM User's Manual.[2] For this study, the upper limit of 17 panellists was used as some panellist attrition was anticipated. Experts were recruited from different geographical locations and disciplines. Expertise was defined as experience with cannabis and with perioperative teaching, research, management and clinical experience. For the purpose of identifying experts, authorship of cannabis and perioperative-related guidelines was reviewed, as well as other relevant research and case reports. Prospective panellists were contacted with solicitation letters. Those interested in participating were asked to complete a form detailing conflicts of interest and their consent to participate. Conflicts of interest were reviewed by the steering committee prior to panellist finalisation.

The final panel consisted of clinicians from Canada (seven total), USA (four total), India (one total), Barbados (one total), Norway (one total), Australia (one total), New Zealand (one total) and UK (one total). Clinicians with backgrounds of practice across one or more specialities such as practise in anaesthesia (14 total), pain medicine (8 total), psychiatry (2 total), pharmacology (2 total), addiction medicine (2 total), intensive care (1 total) and emergency medicine (1 total).

Data collection
Blank questionnaires were emailed to participants along with an instruction form for completing the questionnaires. A systematic review and list of definitions compiled by the steering committee were provided in this correspondence. Authorship on the final guideline document will only be offered to panellists who complete the entire RAM/Delphi process to reduce panellist attrition.

Survey round 1
The study consisted of two primary survey rounds which are to be followed by a review of the proposed recommendations by the expert panel, a nurse practitioner and two patients.

In survey round 1, panellists were blinded to each other's participation and responses during the first survey round. This first survey round would last 6 weeks and the steering committee was available to address any concerns or questions raised by the panellists during that period. Panellists were asked to identify items for correction, deletion or clarification as part of their questionnaires.

Survey round 2
Once survey round 1 had been completed and data entry and analysis of the deidentified questionnaire data were finished, the results obtained were combined with a narrative report of the expert panel's areas of consensus and comments in preparation for survey round 2. This summary of findings and data analysis were provided to the panellists 4 weeks before the start of survey round 2.

Survey round 2 was completed with the expert panel meeting in person and by teleconference on 17 March 2020. Panellists unable to attend this meeting in person joined it by teleconference. Panellists were able to discuss items on the questionnaire and focused discussion on areas of consensus and near consensus.

Definition of consensus
Consensus (agreement) for this study will be defined as per the recommendation in chapter 8 of the 2001 RAM User's Manual.[2] Agreement will be defined as the lack of disagreement in the panellists' responses. Disagreement will be tested for using the interpercentile range (IPR) and IPR adjusted for symmetry (IPRAS). If the IPR of an item is larger than its IPRAS, the item will be rated with disagreement.[2]

Guidelines and recommendations development
Following the panellists' survey round 2 meeting, a revised summary of the panel recommendations will be created by the steering committee as per the EQUATOR network's RIGHT.[20] The expert panel will be asked to review ranking, rationale and ordering of the consensus recommendations based on the results of the questionnaires and meeting.

This summary will also be submitted to two patients and a nurse practitioner for further review and comment. These persons will have experience with cannabis consumption in the perioperative period. The patients will be identified and invited from the Toronto General Hospital, Transitional Pain Clinic.

Using the input received from the expert panel and patient advocates the summary recommendations, a draft of guidelines will be created. This draft will be circulated to the expert panel prior to guideline finalisation and submission for publication.

Quality assurance
The two-step RAND modified Delphi process will be used to create and define a perioperative guideline for patients consuming prescribed or recreational cannabis. A draft of the guideline will be created by the steering committee and reviewed by the expert panel, a nurse practitioner and two selected patients. Any reviewer comments will be explicitly addressed prior to the final guideline document.

After survey rounds 1 and 2, the expert panel, patients and nurse practitioner will be invited to submit feedback that might assist with the creation of future iterations of cannabis perioperative guidelines.

The guideline will attempt to address as many patient and perioperative issues related to perioperative cannabis as is reasonable using the UCLA/RAND Delphi technique. Final consensus guidelines will be submitted for publication and presentation.

Ethics and dissemination

Study and panellist data have been deidentified and stored as per institutional (Toronto General Hospital) guidelines. Institutional research ethics board provided a waiver for this modified Delphi protocol. Findings will be presented and published in peer-reviewed publications and conferences.

Technical considerations and data set

Data has been collected by Alexander McLaren-Blades and entered into Microsoft Excel files for electronic storage and analysis. All electronic data (questionnaires and data sets) have been stored at the Toronto General Hospital Department of Anesthesia and Pain Management (Toronto, Ontario, Canada) in accordance with the Toronto General Hospital's (and the University Health Network's) institutional guidelines. Any data recorded on paper will be stored at the Toronto General Hospital under lock and key.

All study data recorded on paper will be stored under lock and key. Only persons listed on the steering committee have access to the data. Collected data will be destroyed after 5 years of secure storage in accordance with institutional/local guidelines.

Panellists will be notified of policies regarding data storage, and that by completing study questionnaires, they are consenting to participate in this study. Responses will anonymised when subjected to data analysis and for the presentation of results and conclusions.

Patient and public involvement

Two cannabis using patients have been solicited from the patient population attending the Toronto General Hospital Transitional Pain Clinic. These patients also have prior perioperative experience. These patients have been invited to comment on recommendations developed from this study prior to guideline finalisation. Their comments will be explicitly addressed by the steering committee and expert panel. The patients will also be asked to assist in the development of our dissemination strategy of any published results.

Management of interests

This work was funded by a grant received from the Health System Research Fund by the Canadian Ministry of Health and Long-Term Care. Individuals considered for the expert panel will have to complete a conflict of interest form which will be reviewed by the steering committee before they are accepted as a panellist. All declarations will be included in the final guideline document. Original declaration forms outlining conflict of interest and the 1800 item (total) questionnaires will be available on request from the first author of this study.

Strengths and limitations

This modified Delphi process will enable an in-depth discussion of the perioperative management of cannabis consuming patients and facilitate the formulation of perioperative guidelines regarding their care. This process will enable a panel of international experts to express the appropriateness (weigh the benefits and harms) on this population's perioperative care using their collected expertise, as well as any other resources available to them. New hypotheses and research questions may be generated for future projects during this process.

This project's recommendations will be limited by and made more difficult to arrive at by the heterogeneity of cannabis products, cannabis legality and patient populations. Cannabis and the products derived from it are extremely diverse. Further complicating this are the different methods of cannabis administration. Geographically cannabis product availability, legality and culture are grossly varied. Patients consuming cannabis may have a trained prescriber, be self-treated or engaged in recreational use.

Ultimately as new and existing cannabis preparations are used and the evidence regarding them grows, these guidelines will require review and regular updating.

Timeline

The initial proposal for this study was completed in March 2019. The steering committee was also finalised at this time (March 2019). The literature review associated with this project was accepted for published in December 2019.[19] Expert panel recruitment was completed in August 2019. First round data collection was completed in October 2019. Data entry and analysis were completed by 30 November 2019. The second round meeting was held on 17 March 2020.

Currently, the guidelines are being drafted, after which they will be circulated to the panel, as well as two patients and a nurse practitioner with interests and experience relevant to the proposed guidelines. Following this, all comments from the panel, patients and nurse practitioner will be addressed and the guidelines will be submitted for publication in 2020.

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