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The Perioperative management of Buprenorphine: Protocol for a modified Delphi process

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None of the authors declared a conflict of interest

Key Words

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Abstract

Introduction
The ongoing opioid epidemic has necessitated increasing prescriptions of buprenorphine, which is intended to reduce opioid cravings and harms associated with unsafe opioid administration. A systematic review of perioperative management strategies for patients taking buprenorphine concluded that there was little guidance for managing buprenorphine perioperatively. The aim of this project is to develop consensus guidelines on the optimal perioperative management strategies for this group of patients. In this paper we present the design for a modified Delphi technique that will be used to gain consensus among patients and multidisciplinary experts in addiction, pain, community and perioperative medicine.

Methods and Analysis

A national panel of experts was identified by perioperative, pain, and/or addiction systematic review authorship, established international profile in perioperative, pain and/or addiction research, community clinical excellence, and by peer referral. A steering group will develop a first round a list of indications to be rated by the panel of national experts, patients, and allied health care professionals. In round 1, the expert panel will rate the appropriateness of each individual item and provide additional suggestions for revisions, additions, or deletions. The definition for consensus will be set *a priori*. Consensus will be gauged for both appropriateness and inappropriateness of treatment strategies. Where agreement is not reached and items are suggested for addition/deletion/modification, round 2 will take place over teleconference in order to obtain consensus.

Ethics and Dissemination
Ethics approval was not required by institutional IRB. We plan on developing a national guideline for the management of patients taking buprenorphine in the perioperative period that will be generalizable across 3 sets of pre-operative diagnoses including Opioid Use Disorder and/or Co-occurring Pain Disorders. The findings will be published in peer-reviewed publications and conference presentations.

Article Summary (Strengths and Limitations)

1. Existing Perioperative Strategies to manage patients on buprenorphine are based on expert opinion and regional practices
2. We will employ a modified Delphi Protocol optimizing medical and geographical diversity of panellists to ensure the development of a trustworthy set of guidelines
3. We will aim to include patient and allied-health care experts on our panel to ensure that the Delphi process and guideline development is patient-centered
4. Agreement and Disagreement will be measured by apriori agreed upon consensus criteria
5. Given that new buprenorphine products are being released and diagnostic scales are being constantly re-evaluated, we will aim to re-visit our guidelines regularly

Introduction

Buprenorphine has been used for opioid detoxification, addiction therapy, acute pain and chronic pain management since 2002 (1). Its unique pharmacological properties and wide safety profile have made it increasingly prescribed in the chronic pain and addiction patient population. The number of patients on buprenorphine treatment is increasing (2,3). Since its approval in 2002, the number of buprenorphine/naloxone tablets sold increased from 8 million in 2005 to over 145 million in 2009. Emerging studies have shown that increasing Medicaid coverage for Buprenorphine-naloxone has resulted in an overall increase in people filing prescriptions for buprenorphine-naloxone (4).

Until now, inadequate pain management is the main impetus for the perioperative discontinuation of buprenorphine. Emerging opinions suggest that its perioperative discontinuation may hinder harm

reduction by destabilizing patients with opioid use disorder. For example, transitioning a patient off buprenorphine to a full agonist opioid will permit free access to opioid receptors for the purposes of analgesia, but will not address the substance use disorder that may worsen as a result (5). Emerging evidence suggests that certain subsets of patients are less likely to experience deterioration of their substance use disorder (5,6) no matter which strategy is pursued (continue or discontinue).

Currently, the quality of evidence regarding perioperative management of patients on buprenorphine is weak. A systematic review conducted by Goel et al (In press) revealed that the number of studies to address the perioperative dilemma is limited, and few directly evaluated the question of continuation versus discontinuation of buprenorphine (7-23). Few studies make considerations for the possibility of relapse in cases where there has been a history of Opioid Use Disorder (OUD). Many studies highlighted the importance of multimodal and regional anesthesia techniques. Furthermore, the only RCT combined patients taking buprenorphine and methadone into one group (24), limiting the study's applicability to the important question: Should buprenorphine be continued in the perioperative period or not?

There is a need to develop specific guidance on how to manage OUD perioperatively. Until now, 8 major guidelines (1, 25-31) were built on the backbone of anesthesiologists' opinions and existing case reports (7-23) (Table 1, Appendix 1). Many of the existing guidelines propose discontinuation of buprenorphine before surgery, especially where high-pain is expected. However, more recently, editorialized guidelines have proposed continuation of buprenorphine depending on the pre-operative dose and indication (31). Moreover, there is disagreement on the best discharge strategies for patients taking buprenorphine, irrespective of diagnosis. While most guidelines agree upon major principles such as multimodal analgesia, there is no consensus on which strategies are more likely to succeed. Overall, there is disagreement on optimal pre-, intra-, and post-operative strategies for managing buprenorphine in patients with OUD and/or chronic pain disorders.

Given the lack of RCTs, the strength of a Delphi process is to bring geographically and medically diverse experts together and determine where there is agreement in the perioperative management of buprenorphine. Furthermore, this process ensures the integration of multidisciplinary and patient opinions, resulting in more patient-centered and trustworthy guidelines.

Aim

We will aim to use a national expert consensus Delphi-based survey technique to develop and evaluate a set of recommendations that address perioperative buprenorphine management strategies. We will seek to focus on the following factors: 1) Indication for Buprenorphine therapy, 2) Risk of worsening of substance use disorder and/or co-occurring pain disorder, 3) Expected pain after surgery, 4) Feasibility of perioperative regional anesthesia technique, 5) Utility of adjunct analgesia and 6) Dose and formulation of buprenorphine therapy. We will follow the 22-step checklist recommended by the RIGHT group (36) for the EQUATOR network.

Methods and Design

This study will use a modified Delphi technique, which was developed by the RAND corporation (32) in order to address complex problems that cannot be solved without a group of experts. The Delphi technique involves anonymous voting and controlled feedback in order to generate discussion and eventual consensus on controversial topics. The Delphi method reduces the likelihood of situations in which group consensus is dominated by the perspectives of a strong minority (33).

An International Research Steering Committee has developed the list of indications, and we plan to conduct 2 Delphi rounds in which experts rate appropriateness of buprenorphine management. Panel responses will be de-identified, compiled, analyzed and summarized before being returned to panelists. The summary report will entail qualitative and quantitative details about individual panelists' responses compared to their counterparts. It is expected that the panelist can then review their responses in light of the replies of other panelists prior to a round 2 in-person discussion and re-rating.

Steering Committee

An International Steering Committee (Harvard University, University of Toronto, McMaster University, Queen's University) was formed to develop and conduct this project and consists of representation from various disciplines (Anaesthesiology, Family Practice, Epidemiology, Addictions Medicine, Pain Medicine), geographical areas (Canada, United States) and research expertise (Delphi, health services, and quantitative methods). A literature review including a systematic review was conducted by the steering committee to understand the scope of management strategies published to date. The protocol and associated methods were established and agreed upon through in-person, telephone, and email communication. Important functional domains of the research question were considered by the steering committee after completion of the literature review (i.e. Pre-Operative Management, Post-operative buprenorphine management, inpatient use of opioids and adjuncts for analgesia, involvement of outpatient providers, and discharge planning). These domains are represented as 'sections' in the final questionnaire. Reference was made to previous and published Delphi studies (33,34). There were 3 drafts reviewed by the Steering committee, and a final draft after a self-test by the steering committee provided a further set of comments and suggestions.

Generation of the Chapters with Indications (Items)

The indications and domains identified from the systematic review (35) were examined along with the available evidence from existing recommendations on this topic (1, 25-31). Furthermore, case experience from addiction and pain physicians was used to complete a panel rater-form based on the RAND questionnaires used in existing studies (32). The form was generated in order to reflect the essential processes involved in the perioperative experience of patients maintained on Buprenorphine. In total, 840 indications will be divided into 3 chapters of pre-operative diagnoses. – 1. Opioid Use Disorder Only, 2. Opioid Use Disorder with Co-occurring Pain Disorder, 3. Pain Disorder Only. Panellists will indicate their preference for various perioperative strategies (continue, reduce, stop) by systematically rating these indications from chapters 1 to 3.

Selection of National Panel of Experts (Participants and Recruitment)

'Experts' were defined as individuals involved in the management, development, research, teaching or analysis of clinical perioperative buprenorphine strategies. Because the Delphi group size depends more on optimizing group dynamics to obtain consensus than statistical analysis, we aimed for a panel size based on original Delphi methodology from the RAND study (32) (optimal panel size of 9 and no greater than 15). We set an a priori estimate of panellist attrition rate (20%) and aimed to select up to 15 panellists for Round 1 (the maximum recommended by the RAND authors).

To identify experts in the field of addiction and perioperative medicine, we reviewed authorship of published guidelines and case reports of buprenorphine management in the perioperative period; we identified established national and regional profiles in addiction, pain, or perioperative medicine; we solicited peer recommendations from individuals on boards of the National Canadian Pain, Addiction, and Anaesthesiology Societies (CSAM, CPS, CAS). In order to optimize the face validity of our panel, we sought to include allied healthcare professionals and patients as well. Inclusion of a nurse practitioner and patient allowed the panellists to consider the values and preferences of the target population. We sought to diversify our panel by selecting panellists with practice experience in all the Canadian provinces, membership on professional societies, and wide-ranging expertise.

We initially reached out to these prospective expert panellists by emailing solicitation letters describing the project and the timelines involved (Appendix 2). Prospective panellists were then asked to complete and return a conflict of interest form (Appendix 3) along with their indication of interest in the project. Conflicts of Interest were reviewed by the Steering Committee and prospective panellists with potential conflicting industry affiliations were removed from the final shortlist. Possible incentives for participation in this process included (1) the opportunity to be selected into a diverse group (2) unique educational opportunities and (3) increased internal and external visibility (1).

Ethics

All participants will be informed that by responding to the questionnaire, they have indicated their consent to participate in the study and have their de-identified responses included in associated analyses. All data

will be preserved on paper (under lock and key) as well as a computer (which is password protected) in a locked office, in accordance with standard guidelines. Only the steering committee will have access to the data, which will be destroyed after 5 years in accordance with local guidelines.

Delphi Procedures (Data Collection and Data Analysis)

We will administer paper questionnaires that will be delivered as attachments to expert panellists by email. Panellists will be asked to print out the questionnaires and complete them on paper. The email will include an instruction form (Appendix 4) that includes a table of contents and a sample exercise grid. Furthermore, a systematic review completed by the steering committee will be provided to panellists as a resource for supplement existing knowledge and experience in this topic. To reduce the likelihood of attrition bias, we will notify the panel that authorship of the final guideline document will be offered only to participants that complete the entire Delphi process.

Round 1 & 2 of Delphi Procedure

The Delphi process will consist of 2 survey rounds. The first round will consist of questionnaires that will be completed remotely by all panellists. Panellists will be blinded to each other's participation in the first round to prevent any communication that may lead to bias in the ratings. The first survey round will extend to 3 weeks, with the first week dedicated to addressing any concerns raised by panellists. In this round, panellists will first be asked to rate the appropriateness of continuing or stopping buprenorphine where: 1 = Very Appropriate to Stop Buprenorphine and 9 = Very Appropriate to Continue Buprenorphine at the same or reduced dose. Next, panelists will be asked to rate the appropriateness of reducing vs maintaining dosage, where: 1 = Very Appropriate to reduce Buprenorphine dosage; and 9 = Very Appropriate to Continue Buprenorphine at the same dosage. Panellists will also be asked to identify potential deletions, modifications, or points of clarification upon return of the rating forms. Panellists will then scan and return their rating forms with unique personal identifier codes on each page.

In order to identify thresholds for agreement, we will include pre-determined information about buprenorphine dose, formulation, diagnosis (Pain and/or OUD), risk of exacerbation of underlying disorder, expected surgical pain, and availability of regional anaesthetic technique in the final list of indications. These 840 indications will reflect the complete perioperative period, including strategies for communication with the outpatient provider and utilization of multimodal analgesia.

After completion of round 1, a 2-week Analysis Period will ensue, in which two blinded independent analysts will extract de identified data from rating forms and input data into two mutually exclusive databases. De-identified results including scores for each indication (including median and mode scores, interquartile ranges, indications with universal consensus, and qualitative feedback) along with a narrative report of the findings will be remitted to individual panellists to review prior to round 2 of the Delphi Process. The second-round meeting will be conducted in person and over teleconference given the geographic diversity of expert panellists. Any ambiguous indications, or external factors not previously considered will be aggregated for discussion during this round. Panellists will have the opportunity to discuss addition or removal of indications (items) at this point. If indications are deemed to be insufficient (not capturing the breadth of the theme) or overly inclusive (extreme granularity of indications) then the steering committee will offer a second round of rating after inclusion or exclusion of culprit items. If duplicate indications exist, where possible, the steering committee will aim to combine indications.

Definition of Consensus

In any Delphi process, decision rules are determined in advance to both define and determine consensus. Consensus on a topic is usually determined if a certain number or percentage of the votes falls within a prescribed range. The Steering Committee has *a priori* decided on its definition of consensus in order to avoid bias. Using the European Union BIOMED Concerted Action on Appropriateness for surgical procedures as referenced in the RAND/UCLA Appropriateness Method User's Manual (32).

We define consensus (agreement) in 2 ways: 1) Appropriate treatment defined as a clustering of scores with a median score in the high end of the scale (7-9) without 'disagreement' (i.e. more than 2 panellists' scores

in the low end of the scale, 1-3) and 2) Inappropriate treatment defined as a clustering of scores with a median score in the low end of the scale (1-3) without 'disagreement' (i.e. more than 2 panellists' scores in the high end of the scale, 7-9).

Development of Guidelines and Recommendations

A final operational manual with decision rules for each indication will be presented to panellists during the second-round meeting, with accompanying explanatory documents as necessary. Panellists will be asked to rank and order the recommendations to rationalize the number of items included in the final guideline as per the EQUATOR network's reporting tool for practice guidelines in healthcare (RIGHT) (36). An email questionnaire will aim to obtain a final majority agreement on the synthesis of comments after the 2nd round of the Delphi process. It is expected that clear and concise rationale will accompany individual recommendation statements.

Review and Quality Assurance

We plan to use a 2-step process in order to develop and refine an internationally agreed upon guideline for the perioperative management of patients maintained on buprenorphine. Initially, a draft guideline will undergo independent review by members external to the steering committee. Any comments will be addressed explicitly in the final guideline document. A questionnaire will be emailed out to panellists after the second round to solicit suggestions for improvement in future iterations.

The guideline document should reflect the needs of patients who have co-occurring disorders where possible, therefore facilitating its use in as many perioperative scenarios as possible. The final consensus guidelines will be submitted to a perioperative journal and championed by individual panellists at their home institutions.

To test the acceptability of the proposed guidelines due to varying geography and practice patterns, we will seek annual comments and suggestions from regional and national users of the guideline. The guideline document should be reviewed annually in order to reflect shifting evidence and expert opinion.

Funding and management of interests

No funding sources will be used in any stage of the guideline development. Individual steering committee members and panellists were made to complete conflict of interest forms prior to involvement in this process. Any prospective steering committee members or panellists with perceived conflicts of interests were not included at any point of the guideline development. Original declaration forms outlining conflict of interest are available upon request to the first author of the study (Akash Goel).

Limitations of the Guideline

Increasingly, providers are beginning to see off-label prescription of sublingual buprenorphine for patients with pain disorders. Furthermore, there are several new formulations of buprenorphine emerging. As evidence emerges and new formulations of buprenorphine are developed, these guidelines will require updating in the future hopefully on an annual basis.

Delphi Study Status

The first round of the Delphi process will begin in October, with an in-person, second round meeting scheduled in November 2018. Data collection and analysis will occur after the second-round meeting if panellists and the steering committee are satisfied that all important questions have been addressed. A paper reporting the results of the Delphi process will be submitted for publication in early 2019 followed by conference presentations. Data collection will start in October 2018 and anticipated to be completed by December 2018.

Author Statement

Akash Goel, Joel Weissman and Harsha Shanthanna developed the Delphi Protocol and methodology

Akash Goel and Saam Azargive developed and modified Round 1 panel rating forms

Akash Goel, Karim Ladha, Wiplove Lamba, Scott Duggan, John Hanlon, Tania Di Renna, Philip Peng and Hance Clarke were involved in the development of the research question and formulation of the Delphi Protocol as part of the Steering Committee

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Table 1. *Summary of major existing guidelines for perioperative management of buprenorphine*

Title	Date	Major Peri-operative recommendations
Brummett et al (Michigan Guidelines) (29)	2007	1. Where moderate to severe pain is expected, cancel surgery in patients still taking buprenorphine, return the patient to the buprenorphine provider, and transition them to short-acting opioids for >5 days prior to surgery 2. Coordinate follow-up postoperatively with buprenorphine provider 3. Anticipate the patient's course will be similar to an opioid tolerant patient 4. Consider adjuncts – Acetaminophen and/or NSAIDs 5. In cases where minimal to no pain is expected, continue buprenorphine for post operative pain
Anderson et al (1)	2017	1. Where moderate to severe pain is expected, cancel surgery such that buprenorphine is weaned off before surgery and short-acting opioids are used to replace it. 2. A plan for follow-up and reinstitution of therapy should be established 3. Anticipate patient's opioids requirements will be similar to an opioid-tolerant patient 4. Consider adjuncts – NSAIDs, membrane stabilizers, acetaminophen, local anaesthetics, regional anesthetic techniques 5. Ensure appropriate outpatient follow-up with buprenorphine provider
Sen et al (28)	2016	1. Discontinue buprenorphine 72H before operative procedure, or replace buprenorphine with methadone 2. Expect additional opioid doses for acute pain control 3. Discharge on pure opioid induction protocol of buprenorphine in conjunction with primary provider
Jonan et al (30)	2018	1. Utilize non-opioid adjuncts, regional Anesthesia, and local anesthetic infiltration by surgeon where possible. 2. Where low post operative pain is expected, continue buprenorphine perioperatively without taper 3. Where intermediate pain is expected, discontinue buprenorphine 3 days prior to procedure, consider high dose PCA, and consider ICU admission for respiratory monitoring 4. Where High pain is expected, discontinue buprenorphine 3-5 days prior to procedure, consider pure opioid agonist to manage withdrawal, and consider ICU for respiratory monitoring
Childers and Arnold (25)	2012	1. Adjuvant analgesics and interventional procedures should be provided if available 2. Hold buprenorphine and start short acting opioid agonists if expecting moderate to severe pain 3. Re-initiate buprenorphine in the post-operative period with the buprenorphine provider 4. Where mild to moderate pain is expected, consider treating pain with buprenorphine alone, or use short-acting opioid agonists at higher doses 5. Consider replacing buprenorphine with methadone for opioid addiction where ongoing pain management is expected
Bryson (26)	2014	1. Ideally, buprenorphine should be discontinued 72H before surgery, then restarted once patient no longer has acute pain requiring narcotic analgesics 2. If the plan is to continue buprenorphine, use short-acting opioid analgesics to achieve pain control, expecting higher than normal effective doses. Divide buprenorphine maintenance dose and administer every 6-8 hours 3. If the plan is to stop the buprenorphine, use standard opioids for analgesia, conduct a slow taper over 2 weeks or an abrupt taper over 3 days, remaining buprenorphine free for 72 hours before surgery 4. If the relapse rate is too high, replace maintenance dose of buprenorphine with methadone before surgery, and use another short-acting opioid and analgesic for breakthrough pain
Berry et al. (Vermont Guidelines) (27)	2015	1. Reduce buprenorphine dose to 8mg SL on the day of surgery 2. Use oxycodone or other full agonists to make up opiate debt + typical post operative course management 3. Expect longer than normal pain management regimen in the post operative period 4. Buprenorphine doses above 10mg daily will block opioid analgesics for pain
Lembke et al. (Editorial) (31)	2018	1. Continue buprenorphine in the perioperative period for patients taking 12mg SL or less 2. Taper buprenorphine to 12 mg SL 2-3 days pre-op 3. Multimodal analgesia, Regional techniques where possible 4. Higher than normal doses of opioids to treat pain for 2-4 days post-op

Dear Prospective Panelist,

We are writing to you to because you have been nominated for a special expert consensus panel. This Panel will be establishing guidelines on the perioperative management of patients who are taking buprenorphine for the management of pain and/or substance use disorder.

We will be embarking on this project because current evidence provides little guidance as to how best to manage this group of patients. Our group has conducted a systematic review of the existing evidence and we hope to use this for the basis of conducting a 2-staged Delphi process resulting in consensus on appropriateness of continuing or stopping buprenorphine in the perioperative period.

This process involves the following steps and timeline:

Task	**Timeline**
Review of existing literature (Complete)	Complete
Nomination of experts in Addiction medicine, pain medicine, and Anesthesiology Obtain CVs, Conflict of Interest Forms (Delphi)	By September
Confirmation of Panel by Core Committee **Dissemination of Core Materials to Expert Panel**	By September 15
Review of evidence by expert panel (remotely done)	By September 31st
Review of consensus statements (remotely done)	By September 31st
Submission of consensus statements, and collation of data	By September 31st
Meeting by Teleconference/In-person to review consensus and/or conflicts	By October 31st
Development of consensus	By December 30th
Publication of consensus document	By January 2019

As part of the nomination process, we are seeking recognized experts as part of the Canadian Society of Addiction Medicine (CSAM), CPS (Canadian Pain Society) and CAS (Canadian Anesthesiologists' Society). You were nominated based on the following 4 criteria:

Leadership in the specialty
Absence of conflicts of interest
Geographic diversity
Diversity of practice setting

We would be delighted to have you serve on this panel, and would be happy to answer any questions you may have about the process. Please return your CVs and COI forms to me by August 4 if you are interested in pursuing this opportunity.

Sincerely,

The Steering Committee

CANADIAN BUPRENORPHINE CONSENSUS GUIDELINES

CONFLICT OF INTEREST DISCLOSURE FORM

The following are examples of conflicts of interest:

- Any direct financial interest in a for-profit entity such as a pharmaceutical organization, medical devices company, communications firm, or other financial supporter
- Current or recent participation in a clinical trial sponsored by the Organization
- Membership with a speakers bureau
- Holding of a patent for a product referred to in the CPD activity or marketed by a commercial organization
- Receiving honoraria to speak on behalf of a pharmaceutical organization or medical communication company, including talks for which the individual has been contracted but has not yet received payment for
- Financial relationships with program-sponsoring organizations that are non-pharmaceutical or non–health care organizations (eg, insurance companies, financial institutions, government, for-profit organizations, other non-profit organizations)

O I, _____ declare no conflict of interest

O I, _____ declare the following conflicts of interest
(Please list below)

Signature _____-

Name _____

Title _____

Perioperative Management of Buprenorphine Products

Panel Instructions

Dear Panellist,

Thank you for your participation in the national guideline development for managing patients taking buprenorphine products in the perioperative period. Below you will find some definitions and instructions for how to fill out the panel rating forms.

There are 840 indications that you will be required to rate.

How does the Modified Delphi process work?
There are 2 rounds of ratings – the first round is done in a 'blinded' fashion where panellists are not aware of who the other panellists are, and are not meant to discuss their thoughts with each other. They are to fill out rater forms and return them to the **moderator**. There will be a second round where panellists will meet in person and teleconference to discuss discrepancies in their rating and aim to obtain consensus on conflicting areas.

How are the rating forms organized?
There are 3 **chapters** that are focused on the diagnosis of the patient prior to surgery
1. OPIOID USE DISORDER ONLY (No co-occurring pain disorder) – 280 indications
2. OPIOID USE DISORDER AND PAIN DISORDER – 280 indications
3. PAIN DISORDER ONLY (No co-occurring opioid use disorder) – 280 indications

These chapters are then divided into various **sections** that are organized by stage of the patient experience:
1. *PRE-OP PLANNING – Buprenorphine Strategies*
2. *POST-OP PAIN – Buprenorphine in patients experiencing post op pain*
3. *POST-OP PAIN – Analgesic adjuncts to manage pain (i.e. NSAIDS, Tylenol etc)*
4. *POST-OP PAIN –Opioids to manage pain (i.e. fentanyl, hydromorphone)*
5. *DISCHARGE – Discharge strategies*
6. *OUTPATIENT PROVIDER INVOLVEMENT – indications for involving outpatient provider in these settings*

PERIOPEARTIVE BUPRENORPHINE MANAGEMENT – PRIVATE AND CONFIDENTIAL – PLEASE DO NOT SHARE

What is the definition of 'Appropriateness'?

The RAND/UCLA appropriateness method (which we are using in this guideline development process) allows panellists to rate appropriateness of therapy from 1-9. Median scores of all panellists will be obtained, and consensus definitions will be provided during the second round (in person/teleconference meeting of panel)

Instructions on how to use the Rater forms:

1) **Print out the forms**
2) **Read the Chapter on the top of the page** – I.e. Chapter 1, Section 1.1 reads: "Opioid Use Disorder Only (No Concurrent Pain Disorder)" – this indicates to the panellist to consider patients with opioid use disorder ONLY and no concurrent pain disorder when rating an indication
3) **Read across the top of the table** - You will see two big categories, patients who are at LOW risk of 'Chapter 1' Disorder Exacerbation and HIGH risk of Chapter 1 Disorder Exacerbation. This directs panellists to stratify patients based on the definitions provided to them and their own experience.
4) **Read down the left most column of the table –** The left most column labels the Section within the chapter – "pre-operative planning". As the panellist scrolls down the left-most column, they will notice that it is divided based on certain clinical characteristics – for example, what dose of buprenorphine the patient is on, how much post-operative pain is expected, and whether a regional anesthesia technique (i.e. nerve block, epidural) is feasible for the surgery for a variety of plausible scenarios.
5) **Read Across the INDICATION ROW –**
   Indications are dichotomized. This row indicates the options available to the panellist when rating from 1-9. For example, the first appropriateness rating available to the panellist is Appropriateness of Continuing Buprenorphine with the numbers 1 to 9 below them. This directs the panellist to choose a score for the indication, with a score of '9' being closest to – 'It is most appropriate to Continue Buprenorphine', and a score of '1' being closest to 'It is most appropriate to stop Buprenorphine'. Any scores in between indicates a lack of certainty around the indication.
   Panelists are urged to use the extremes of the rating scale.
6) **Use a black pen** only to **circle** the most appropriate score for the indication.
7) **Scan and Email** your forms to agoel@hsph.harvard.edu

PERIOPEARTIVE BUPRENORPHINE MANAGEMENT – PRIVATE AND CONFIDENTIAL – PLEASE DO NOT SHARE

Example – Refer to the colour coding to clarify – this form can only be viewed online or if printed in colour

Example

_CHAPTER 1: OPIOID USE DISORDER ONLY (NO CO-OCCURRING PAIN DISORDER)_____PANELIST # __ ROUND 1__

Page 1

Definitions: High Risk of Exacerbation includes concurrent mood disorder, duration of therapy <1 year, positive urine drug screen within 1 year

Chapter 1: Opioid Use Disorder (OUD)

Section 1.1: Pre-Op Planning

INDICATION ROW	LOW-MODERATE Risk of Exacerbation: Appropriateness of: Continue Buprenorphine Therapy (9) vs Stop (1)	LOW-MODERATE Risk of Exacerbation: Appropriateness of Maintain (1) vs. Reducing Buprenorphine (9) Dose	HIGH Risk of Exacerbation: Appropriateness of: Continuing Buprenorphine Therapy (9) vs. Stop (1)	HIGH Risk of Exacerbation: Appropriateness of: Maintain (1) vs. Reducing Buprenorphine Dose (9)	*(Indication Number)*
A. Patient is on **0-8mg** SL Buprenorphine Daily	——————→	——————→	←—————→	←—————→	*Leave Blank*
Severe Post Op Pain expected in an elective case					
a) With Regional Anesthesia	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	*1-4*
b) WithOUT Regional Anesthesia	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	*5-8*

For a score of 9 on this indication, refer to colour coded elements of the rater box (above) and the composite outcome (below)

For patients who meet the following criteria:

1) Opioid Use Disorder and No concurrent Pain Disorder
2) Low-Moderate Risk of Relapse of underlying disorder
3) Taking 0-8 mg of SL buprenorphine daily
4) Presenting for surgery where regional anesthesia technique is possible
5) Given surgical/patient factors, likely to experience severe post-operative pain

I believe that it is most appropriate to continue buprenorphine (Score 9 out of 9) at the pre-operative dose (No reduction) (Score 1 out of 9)

Definition of 'Risk of Exacerbation': Please see definitions under specific chapters headings in the panel rating forms

PRIVATE AND CONFIDENTIAL PANEL INSTRUCTIONS – PLEASE DO NOT SHARE

BMJ Open

Peri-operative Pain and Addiction Interdisciplinary Network (PAIN)
The Perioperative management of Buprenorphine: Protocol for a modified Delphi process

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Title: Perioperative Pain and Addiction Interdisciplinary Network (PAIN)
The Perioperative management of Buprenorphine: Protocol for a modified Delphi process

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None of the authors declared a conflict of interest

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Buprenorphine, Surgery, Substance Use Disorder, Chronic Pain, Perioperative Management, Perioperative Guidelines

Perioperative Pain and Addiction Interdisciplinary Network (PAIN)
The Perioperative management of Buprenorphine: Protocol for a modified Delphi process

Akash Goel, Saam Azargive, Joel Weissman, Harsha Shanthanna, Karim Ladha, Wiplove Lamba, Scott Duggan, John Hanlon, Tania Di Renna, Philip Peng, Hance Clarke

Abstract

Introduction
The ongoing opioid epidemic has necessitated increasing prescriptions of buprenorphine, which is evidence-based treatment for opioid use disorder, and also shown to reduce harms associated with unsafe opioid administration. A systematic review of perioperative management strategies for patients taking buprenorphine concluded that there was little guidance for managing buprenorphine perioperatively. The aim of this project is to develop consensus guidelines on the optimal perioperative management strategies for this group of patients. In this paper we present the design for a modified Delphi technique that will be used to gain consensus among patients and multidisciplinary experts in addiction, pain, community and perioperative medicine.

Methods and Analysis

A national panel of experts was identified by perioperative, pain, and/or addiction systematic review authorship, established international profile in perioperative, pain and/or addiction research, community clinical excellence, and by peer referral. A steering group will develop a first round a list of indications to be rated by the panel of national experts, patients, and allied health care professionals. In round 1, the expert panel will rate the appropriateness of each individual item and provide additional suggestions for revisions, additions, or deletions. The definition for consensus will be set *a priori*. Consensus will be gauged for both appropriateness and inappropriateness of treatment strategies. Where agreement is not reached and items are suggested for addition/deletion/modification, round 2 will take place over teleconference in order to obtain consensus.

Ethics and Dissemination
Institutional REB provided a waiver for this modified Delphi protocol. We plan on developing a national guideline for the management of patients taking buprenorphine in the perioperative period that will be generalizable across 3 sets of pre-operative diagnoses including Opioid Use Disorder and/or Co-occurring Pain Disorders. The findings will be published in peer-reviewed publications and conference presentations.

Article Summary (Strengths and Limitations)

1. Existing Perioperative Strategies to manage patients on buprenorphine are based on expert opinion and regional practices
2. We will employ a modified Delphi Protocol optimizing medical and geographical diversity of panellists to ensure the development of a trustworthy set of guidelines
3. We will aim to include patient and allied-health care experts on our panel to ensure that the Delphi process and guideline development is patient-centered
4. Agreement and Disagreement will be measured by apriori agreed upon consensus criteria
5. Given that new buprenorphine products are being released and diagnostic scales are being constantly re-evaluated, we will aim to re-visit our guidelines regularly

Introduction

Buprenorphine has been used for opioid detoxification, addiction therapy, acute pain and chronic pain management since 2002 (1). Its unique pharmacological properties and wide safety profile

have made it increasingly prescribed in the chronic pain and addiction patient population. The number of patients on buprenorphine treatment is increasing (2,3). Since its approval in 2002, the number of buprenorphine/naloxone tablets sold increased from 8 million in 2005 to over 145 million in 2009. Emerging studies have shown that increasing Medicaid coverage for Buprenorphine-naloxone has resulted in an overall increase in people filing prescriptions for buprenorphine-naloxone (4).

Until now, inadequate pain management is the main impetus for the perioperative discontinuation of buprenorphine. Recent evidence suggests that its perioperative discontinuation may hinder harm reduction by destabilizing patients with opioid use disorder (5). For example, transitioning a patient off buprenorphine to a full agonist opioid will permit free access to opioid receptors for the purposes of analgesia, but will not address the substance use disorder that may worsen as a result (5). Emerging evidence suggests that certain subsets of patients are less likely to experience deterioration of their substance use disorder (6,7) no matter which strategy is pursued (continue or discontinue). Furthermore, there remain grave public health concerns over improper use and/or disposal of full mu-agonists that are prescribed in the peri-operative period.

Currently, the quality of evidence regarding perioperative management of patients on buprenorphine is weak. A systematic review conducted by Goel et al (In press) revealed that the number of studies to address the perioperative dilemma is limited, and few directly evaluated the question of continuation versus discontinuation of buprenorphine (8-24). Few studies make considerations for the possibility of relapse in cases where there has been a history of Opioid Use Disorder (OUD). Many studies highlighted the importance of multimodal and regional anesthesia techniques. Furthermore, the only RCT combined patients taking buprenorphine and methadone into one group (25), limiting the study's applicability to the important question: Should buprenorphine be continued in the perioperative period or not? It is important that the perioperative physician consider and balance the issue of pain control vs. patient destabilization. In fact, the destabilization of a patient with a previous substance abuse problem risks the patient returning to their previous life struggle; this has significant negative consequences including the possibility of peri- and postoperative overdose/death.

There is a need to develop specific guidance on how to manage OUD perioperatively. Until now, 8 major guidelines (1, 26-32) were built on the backbone of anesthesiologists' opinions and existing case reports (8-24) (Table 1 of Appendix 1). Many of the existing guidelines propose discontinuation of buprenorphine before surgery, especially where high-pain is expected. However, more recently, editorialized guidelines have proposed continuation of buprenorphine depending on the pre-operative dose and indication (32). Moreover, there is disagreement on the best discharge strategies for patients taking buprenorphine, irrespective of diagnosis. While most guidelines agree upon major principles such as multimodal analgesia, there is no consensus on which strategies are more likely to succeed. Overall, there is disagreement on optimal pre-, intra-, and post-operative strategies for managing buprenorphine in patients with OUD and/or chronic pain disorders.

Given the lack of RCTs, the strength of a Delphi process is to bring geographically and medically diverse experts together and determine where there is agreement in the perioperative management of buprenorphine. Furthermore, this process ensures the integration of multidisciplinary and patient opinions, resulting in more patient-centered and trustworthy guidelines.

Aim

We will aim to use a national expert consensus Delphi-based survey technique to develop and evaluate a set of recommendations that address perioperative buprenorphine management strategies. We will seek to focus on the following factors: 1) Indication for Buprenorphine therapy, 2) Risk of worsening of substance use disorder and/or co-occurring pain disorder, 3) Expected pain after surgery, 4) Feasibility of perioperative regional anesthesia technique, 5) Utility of adjunct analgesia and 6) Dose and formulation of buprenorphine therapy. We will follow the 22-

step checklist recommended by the RIGHT group (33) for the EQUATOR network.

Methods and Design

This study will use a modified Delphi technique, which was developed by the RAND corporation (34) in order to address complex problems that cannot be solved without a group of experts. The Delphi technique involves anonymous voting and controlled feedback in order to generate discussion and eventual consensus on controversial topics. The Delphi method reduces the likelihood of situations in which group consensus is dominated by the perspectives of a strong minority (35).

An International Research Steering Committee has developed the list of indications, and we plan to conduct 2 Delphi rounds in which experts rate appropriateness of buprenorphine management. Panel responses will be de-identified, compiled, analyzed and summarized before being returned to panelists. The summary report will entail qualitative and quantitative details about individual panelists' responses compared to their counterparts. It is expected that the panelist can then review their responses in light of the replies of other panelists prior to a round 2 in-person discussion and re-rating.

Steering Committee

An International Steering Committee (Harvard University, University of Toronto, McMaster University, Queen's University) was formed to develop and conduct this project and consists of representation from various disciplines (Anaesthesiology, Family Practice, Epidemiology, Addictions Medicine, Pain Medicine), geographical areas (Canada, United States) and research expertise (Delphi, health services, and quantitative methods). A literature review including a systematic review was conducted by the steering committee to understand the scope of management strategies published to date. The protocol and associated methods were established and agreed upon through in-person, telephone, and email communication. Important functional domains of the research question were considered by the steering committee after completion of the literature review (i.e. Pre-Operative Management, Post-operative buprenorphine management, inpatient use of opioids and adjuncts for analgesia, involvement of outpatient providers, and discharge planning). These domains are represented as 'sections' in the final questionnaire. Reference was made to previous and published Delphi studies (35,36). There were 3 drafts reviewed by the Steering committee, and a final draft after a self-test by the steering committee provided a further set of comments and suggestions.

Generation of the Chapters with Indications (Items)

The indications and domains identified from the systematic review (37) were examined along with the available evidence from existing recommendations on this topic (1, 26-32). Furthermore, case experience from addiction and pain physicians was used to complete a panel rater-form based on the RAND questionnaires used in existing studies (34). The form was generated in order to reflect the essential processes involved in the perioperative experience of patients maintained on Buprenorphine. In total, 840 indications will be divided into 3 chapters of pre-operative diagnoses. – 1. Opioid Use Disorder Only, 2. Opioid Use Disorder with Co-occurring Pain Disorder, 3. Pain Disorder Only. Panellists will indicate their preference for various perioperative strategies (continue, reduce, stop) by systematically rating these indications from chapters 1 to 3.

Selection of National Panel of Experts (Participants and Recruitment)

'Experts' were defined as individuals involved in the management, development, research, teaching or analysis of clinical perioperative buprenorphine strategies. Because the Delphi group size depends more on optimizing group dynamics to obtain consensus than statistical analysis, we aimed for a panel size based on original Delphi methodology from the RAND study (34) (optimal panel size of 9 and no greater than 15). We set an a priori estimate of panellist attrition rate (20%) and aimed to select up to 15 panellists for Round 1 (the maximum recommended by the RAND authors).

To identify experts in the field of addiction and perioperative medicine, we reviewed authorship of published guidelines and case reports of buprenorphine management in the perioperative period; we identified established national and regional profiles in addiction, pain, or perioperative medicine; we solicited peer recommendations from individuals on boards of the National Canadian Pain, Addiction, and Anaesthesiology Societies (CSAM, CPS, CAS). We sought to diversify our panel by selecting panellists with practice experience in all the Canadian provinces, membership on professional societies, and wide-ranging expertise.

We initially reached out to these prospective expert panellists by emailing solicitation letters describing the project and the timelines involved (Appendix 2). Prospective panellists were then asked to complete and return a conflict of interest form (Appendix 3) along with their indication of interest in the project. Conflicts of Interest were reviewed by the Steering Committee and prospective panellists with potential conflicting industry affiliations were removed from the final shortlist. Possible incentives for participation in this process included (1) the opportunity to be selected into a diverse group (2) unique educational opportunities and (3) increased internal and external visibility (1).

Patient and Public Involvement

We included a patient on our steering committee and expert panel in order to develop a research question and outcome measures that were informed by patient priorities, experience, and preferences. Furthermore, inclusion of a nurse practitioner also allowed the panellists to consider the values and preferences of the target population.

Ethics

All participants will be informed that by responding to the questionnaire, they have indicated their consent to participate in the study and have their de-identified responses included in associated analyses. All data will be preserved on paper (under lock and key) as well as a computer (which is password protected) in a locked office, in accordance with standard guidelines. Only the steering committee will have access to the data, which will be destroyed after 5 years in accordance with local guidelines.

We obtained an official waiver from our institutional REB for the conduct of this protocol. The REB deemed our Delphi protocol not to be research as defined in the Tri-Council Policy Statement, and therefore, did not fall under the purview of the REB.

Delphi Procedures (Data Collection and Data Analysis)

We will administer paper questionnaires that will be delivered as attachments to expert panellists by email. Panellists will be asked to print out the questionnaires and complete them on paper. The email will include an instruction form (Appendix 4) that includes a table of contents and a sample exercise grid. Furthermore, a systematic review completed by the steering committee will be provided to panellists as a resource for supplement existing knowledge and experience in this topic. To reduce the likelihood of attrition bias, we will notify the panel that authorship of the final guideline document will be offered only to participants that complete the entire Delphi process.

Round 1 & 2 of Delphi Procedure

The Delphi process will consist of 2 survey rounds. The first round will consist of questionnaires that will be completed remotely by all panellists. Panellists will be blinded to each other's participation in the first round to prevent any communication that may lead to bias in the ratings. The first survey round will extend to 3 weeks, with the first week dedicated to addressing any concerns raised by panellists. In this round, panellists will first be asked to rate the appropriateness of continuing or stopping buprenorphine where: 1 = Very Appropriate to Stop Buprenorphine and 9 = Very Appropriate to Continue Buprenorphine at the same or reduced dose. Next, panelists will be asked to rate the appropriateness of reducing vs maintaining dosage, where: 1 = Very Appropriate to reduce Buprenorphine dosage; and 9 = Very Appropriate to Continue Buprenorphine at the same dosage. Panellists will also be asked to identify potential deletions, modifications, or points of clarification upon return of the rating forms. Furthermore,

they will be urged to consider patient populations that will require individualized approaches to the management of their buprenorphine dose in the perioperative period. Panellists will then scan and return their rating forms with unique personal identifier codes on each page.

In order to identify thresholds for agreement, we will include pre-determined information about buprenorphine dose, formulation, diagnosis (Pain and/or OUD), risk of exacerbation of underlying disorder, expected surgical pain, and availability of regional anaesthetic technique in the final list of indications. These 840 indications will reflect the complete perioperative period, including strategies for communication with the outpatient provider and utilization of multimodal analgesia.

After completion of round 1, a 2-week Analysis Period will ensue, in which two blinded independent analysts will extract de identified data from rating forms and input data into two mutually exclusive databases. De-identified results including scores for each indication (including median and mode scores, interquartile ranges, indications with universal consensus, and qualitative feedback) along with a narrative report of the findings will be remitted to individual panellists to review prior to round 2 of the Delphi Process. The second-round meeting will be conducted in person and over teleconference given the geographic diversity of expert panellists. Any ambiguous indications, or external factors not previously considered will be aggregated for discussion during this round. Panellists will have the opportunity to discuss addition or removal of indications (items) at this point. If indications are deemed to be insufficient (not capturing the breadth of the theme) or overly inclusive (extreme granularity of indications) then the steering committee will offer a second round of rating after inclusion or exclusion of culprit items. If duplicate indications exist, where possible, the steering committee will aim to combine indications.

Definition of Consensus

In any Delphi process, decision rules are determined in advance to both define and determine consensus. Consensus on a topic is usually determined if a certain number or percentage of the votes falls within a prescribed range. The Steering Committee has *a priori* decided on its definition of consensus in order to avoid bias. Using the European Union BIOMED Concerted Action on Appropriateness for surgical procedures as referenced in the RAND/UCLA Appropriateness Method User's Manual (34).

We define consensus (agreement) in 2 ways: 1) Appropriate treatment defined as a clustering of scores with a median score in the high end of the scale (7-9) without 'disagreement' (i.e. more than 2 panellists' scores in the low end of the scale, 1-3) and 2) Inappropriate treatment defined as a clustering of scores with a median score in the low end of the scale (1-3) without 'disagreement' (i.e. more than 2 panellists' scores in the high end of the scale, 7-9).

Development of Guidelines and Recommendations

A final operational manual with decision rules for each indication will be presented to panellists during the second-round meeting, with accompanying explanatory documents as necessary. Panellists will be asked to rank and order the recommendations to rationalize the number of items included in the final guideline as per the EQUATOR network's reporting tool for practice guidelines in healthcare (RIGHT) (33). An email questionnaire will aim to obtain a final majority agreement on the synthesis of comments after the 2nd round of the Delphi process. It is expected that clear and concise rationale will accompany individual recommendation statements.

Review and Quality Assurance

We plan to use a 2-step process in order to develop and refine an internationally agreed upon guideline for the perioperative management of patients maintained on buprenorphine. Initially, a draft guideline will undergo independent review by members external to the steering committee. Any comments will be addressed explicitly in the final guideline document. A questionnaire will be emailed out to panellists after the second round to solicit suggestions for improvement in future iterations.

The guideline document should reflect the needs of patients who have co-occurring disorders where possible, therefore facilitating its use in as many perioperative scenarios as possible. The final consensus guidelines will be submitted to a perioperative journal and championed by individual panellists at their home institutions.

To test the acceptability of the proposed guidelines due to varying geography and practice patterns, we will seek annual comments and suggestions from regional and national users of the guideline. The guideline document should be reviewed annually in order to reflect shifting evidence and expert opinion.

Funding and management of interests

No funding sources will be used in any stage of the guideline development. Individual steering committee members and panellists were made to complete conflict of interest forms prior to involvement in this process. Any prospective steering committee members or panellists with perceived conflicts of interests were not included at any point of the guideline development. Original declaration forms outlining conflict of interest are available upon request to the first author of the study (Akash Goel).

Limitations of the Guideline

Increasingly, providers are beginning to see off-label prescription of sublingual buprenorphine for patients with pain disorders. Furthermore, there are several new formulations of buprenorphine emerging. As evidence emerges and new formulations of buprenorphine are developed, these guidelines will require updating in the future hopefully on an annual basis.

Delphi Study Status

The first round of the Delphi process will begin in October, with an in-person, second round meeting scheduled in November 2018. Data collection and analysis will occur after the second-round meeting if panellists and the steering committee are satisfied that all important questions have been addressed. A paper reporting the results of the Delphi process will be submitted for publication in early 2019 followed by conference presentations. Data collection will start in October 2018 and anticipated to be completed by December 2018.

Author Statement

Akash Goel, Joel Weissman and Harsha Shanthanna developed the Delphi Protocol and methodology

Akash Goel and Saam Azargive developed and modified Round 1 panel rating forms

Akash Goel, Karim Ladha, Wiplove Lamba, Scott Duggan, John Hanlon, Tania Di Renna, Philip Peng and Hance Clarke were involved in the development of the research question and formulation of the Delphi Protocol as part of the Steering Committee

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Title	Date	Major Peri-operative recommendations
Anderson et al	2017	1. Where moderate to severe pain is expected, cancel surgery such that buprenorphine is weaned off before surgery and short-acting opioids are used to replace it. 2. A plan for follow-up and reinstitution of therapy should be established 3. Anticipate patient's opioids requirements will be similar to an opioid-tolerant patient 4. Consider adjuncts – NSAIDs, membrane stabilizers, acetaminophen, local anaesthetics, regional anesthetic techniques 5. Ensure appropriate outpatient follow-up with buprenorphine provider
Sen et al	2016	1. Discontinue buprenorphine 72H before operative procedure, or replace buprenorphine with methadone 2. Expect additional opioid doses for acute pain control 3. Discharge on pure opioid induction protocol of buprenorphine in conjunction with primary provider
Jonan et al	2018	1. Utilize non-opioid adjuncts, regional Anesthesia, and local anesthetic infiltration by surgeon where possible. 2. Where low post operative pain is expected, continue buprenorphine perioperatively without taper 3. Where intermediate pain is expected, discontinue buprenorphine 3 days prior to procedure, consider high dose PCA, and consider ICU admission for respiratory monitoring 4. Where High pain is expected, discontinue buprenorphine 3-5 days prior to procedure, consider pure opioid agonist to manage withdrawal, and consider ICU for respiratory monitoring
Childers and Arnold	2012	1. Adjuvant analgesics and interventional procedures should be provided if available 2. Hold buprenorphine and start short acting opioid agonists if expecting moderate to severe pain 3. Re-initiate buprenorphine in the post-operative period with the buprenorphine provider 4. Where mild to moderate pain is expected, consider treating pain with buprenorphine alone, or use short-acting opioid agonists at higher doses 5. Consider replacing buprenorphine with methadone for opioid addiction where ongoing pain management is expected
Bryson	2014	1. Ideally, buprenorphine should be discontinued 72H before surgery, then restarted once patient no longer has acute pain requiring narcotic analgesics 2. If the plan is to continue buprenorphine, use short-acting opioid analgesics to achieve pain control, expecting higher than normal effective doses. Divide buprenorphine maintenance dose and administer every 6-8 hours 3. If the plan is to stop the buprenorphine, use standard opioids for analgesia, conduct a slow taper over 2 weeks or an abrupt taper over 3 days, remaining buprenorphine free for 72 hours before surgery 4. If the relapse rate is too high, replace maintenance dose of buprenorphine with methadone before surgery, and use another short-acting opioid and analgesic for breakthrough pain
Berry (Vermont Guidelines)	2015	1. Reduce buprenorphine dose to 8mg SL on the day of surgery 2. Use oxycodone or other full agonists to make up opiate debt + typical post operative course management 3. Expect longer than normal pain management regimen in the post operative period 4. Buprenorphine doses above 10mg daily will block opioid analgesics for pain
Lembke et al. (Editorial)	2018	1. Continue buprenorphine in the perioperative period for patients taking 12mg SL or less 2. Taper buprenorphine to 12 mg SL 2-3 days pre-op 3. Multimodal analgesia, Regional techniques where possible 4. Higher than normal doses of opioids to treat pain for 2-4 days post-op

Dear Prospective Panelist,

We are writing to you to because you have been nominated for a special expert consensus panel. This Panel will be establishing guidelines on the perioperative management of patients who are taking buprenorphine for the management of pain and/or substance use disorder.

We will be embarking on this project because current evidence provides little guidance as to how best to manage this group of patients. Our group has conducted a systematic review of the existing evidence and we hope to use this for the basis of conducting a 2-staged Delphi process resulting in consensus on appropriateness of continuing or stopping buprenorphine in the perioperative period.

This process involves the following steps and timeline:

Task	**Timeline**
Review of existing literature (Complete)	Complete
Nomination of experts in Addiction medicine, pain medicine, and Anesthesiology Obtain CVs, Conflict of Interest Forms (Delphi)	By September
Confirmation of Panel by Core Committee **Dissemination of Core Materials to Expert Panel**	By September 15
Review of evidence by expert panel (remotely done)	By September 31st
Review of consensus statements (remotely done)	By September 31st
Submission of consensus statements, and collation of data	By September 31st
Meeting by Teleconference/In-person to review consensus and/or conflicts	By October 31st
Development of consensus	By December 30th
Publication of consensus document	By January 2019

As part of the nomination process, we are seeking recognized experts as part of the Canadian Society of Addiction Medicine (CSAM), CPS (Canadian Pain Society) and CAS (Canadian Anesthesiologists' Society). You were nominated based on the following 4 criteria:

Leadership in the specialty
Absence of conflicts of interest
Geographic diversity
Diversity of practice setting

We would be delighted to have you serve on this panel, and would be happy to answer any questions you may have about the process. Please return your CVs and COI forms to me by August 4 if you are interested in pursuing this opportunity.

Sincerely,

The Steering Committee

CANADIAN BUPRENORPHINE CONSENSUS GUIDELINES

CONFLICT OF INTEREST DISCLOSURE FORM

The following are examples of conflicts of interest:

- Any direct financial interest in a for-profit entity such as a pharmaceutical organization, medical devices company, communications firm, or other financial supporter
- Current or recent participation in a clinical trial sponsored by the Organization
- Membership with a speakers bureau
- Holding of a patent for a product referred to in the CPD activity or marketed by a commercial organization
- Receiving honoraria to speak on behalf of a pharmaceutical organization or medical communication company, including talks for which the individual has been contracted but has not yet received payment for
- Financial relationships with program-sponsoring organizations that are non-pharmaceutical or non–health care organizations (eg, insurance companies, financial institutions, government, for-profit organizations, other non-profit organizations)

O I, _____ declare no conflict of interest

O I, _____ declare the following conflicts of interest (Please list below)

Signature _____-

Name _____

Title _____

Perioperative Management of Buprenorphine Products

Panel Instructions

Dear Panellist,

Thank you for your participation in the national guideline development for managing patients taking buprenorphine products in the perioperative period. Below you will find some definitions and instructions for how to fill out the panel rating forms.

There are 840 indications that you will be required to rate.

How does the Modified Delphi process work?
There are 2 rounds of ratings – the first round is done in a 'blinded' fashion where panellists are not aware of who the other panellists are, and are not meant to discuss their thoughts with each other. They are to fill out rater forms and return them to the **moderator**. There will be a second round where panellists will meet in person and teleconference to discuss discrepancies in their rating and aim to obtain consensus on conflicting areas.

How are the rating forms organized?
There are 3 **chapters** that are focused on the diagnosis of the patient prior to surgery
1. OPIOID USE DISORDER ONLY (No co-occurring pain disorder) – 280 indications
2. OPIOID USE DISORDER AND PAIN DISORDER – 280 indications
3. PAIN DISORDER ONLY (No co-occurring opioid use disorder) – 280 indications

These chapters are then divided into various **sections** that are organized by stage of the patient experience:
1. *PRE-OP PLANNING – Buprenorphine Strategies*
2. *POST-OP PAIN – Buprenorphine in patients experiencing post op pain*
3. *POST-OP PAIN – Analgesic adjuncts to manage pain (i.e. NSAIDS, Tylenol etc)*
4. *POST-OP PAIN –Opioids to manage pain (i.e. fentanyl, hydromorphone)*
5. *DISCHARGE – Discharge strategies*
6. *OUTPATIENT PROVIDER INVOLVEMENT – indications for involving outpatient provider in these settings*

PERIOPEARTIVE BUPRENORPHINE MANAGEMENT – PRIVATE AND CONFIDENTIAL – PLEASE DO NOT SHARE

What is the definition of 'Appropriateness'?

The RAND/UCLA appropriateness method (which we are using in this guideline development process) allows panellists to rate appropriateness of therapy from 1-9. Median scores of all panellists will be obtained, and consensus definitions will be provided during the second round (in person/teleconference meeting of panel)

Instructions on how to use the Rater forms:

1) **Print out the forms**
2) **Read the Chapter on the top of the page** – I.e. Chapter 1, Section 1.1 reads: "Opioid Use Disorder Only (No Concurrent Pain Disorder)" – this indicates to the panellist to consider patients with opioid use disorder ONLY and no concurrent pain disorder when rating an indication
3) **Read across the top of the table** - You will see two big categories, patients who are at LOW risk of 'Chapter 1' Disorder Exacerbation and HIGH risk of Chapter 1 Disorder Exacerbation. This directs panellists to stratify patients based on the definitions provided to them and their own experience.
4) **Read down the left most column of the table –** The left most column labels the Section within the chapter – "pre-operative planning". As the panellist scrolls down the left-most column, they will notice that it is divided based on certain clinical characteristics – for example, what dose of buprenorphine the patient is on, how much post-operative pain is expected, and whether a regional anesthesia technique (i.e. nerve block, epidural) is feasible for the surgery for a variety of plausible scenarios.
5) **Read Across the INDICATION ROW –**
   Indications are dichotomized. This row indicates the options available to the panellist when rating from 1-9. For example, the first appropriateness rating available to the panellist is Appropriateness of Continuing Buprenorphine with the numbers 1 to 9 below them. This directs the panellist to choose a score for the indication, with a score of '9' being closest to – 'It is most appropriate to Continue Buprenorphine', and a score of '1' being closest to 'It is most appropriate to stop Buprenorphine'. Any scores in between indicates a lack of certainty around the indication.

   Panelists are urged to use the extremes of the rating scale.
6) **Use a black pen** only to **circle** the most appropriate score for the indication.
7) **Scan and Email** your forms to agoel@hsph.harvard.edu

PERIOPEARTIVE BUPRENORPHINE MANAGEMENT – PRIVATE AND CONFIDENTIAL – PLEASE DO NOT SHARE

Example – Refer to the colour coding to clarify – this form can only be viewed online or if printed in colour

Example

_CHAPTER 1: OPIOID USE DISORDER ONLY (NO CO-OCCURRING PAIN DISORDER)_____PANELIST # __ ROUND 1__

Page 1

Definitions: High Risk of Exacerbation includes concurrent mood disorder, duration of therapy <1 year, positive urine drug screen within 1 year

Chapter 1: Opioid Use Disorder (OUD)

Section 1.1: Pre-Op Planning

INDICATION ROW	LOW-MODERATE Risk of Exacerbation: Appropriateness of: Continue Buprenorphine Therapy (9) vs Stop (1)	LOW-MODERATE Risk of Exacerbation: Appropriateness of Maintain (1) vs. Reducing Buprenorphine (9) Dose	HIGH Risk of Exacerbation: Appropriateness of: Continuing Buprenorphine Therapy (9) vs. Stop (1)	HIGH Risk of Exacerbation: Appropriateness of: Maintain (1) vs. Reducing Buprenorphine Dose (9)	*(Indication Number)*
A. Patient is on **0-8mg** SL Buprenorphine Daily	——————→	——————→	←—————→	←—————→	*Leave Blank*
Severe Post Op Pain expected in an elective case					
a) With Regional Anesthesia	1 2 3 4 5 6 7 8 **9**	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	*1-4*
b) WithOUT Regional Anesthesia	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	*5-8*

For a score of 9 on this indication, refer to colour coded elements of the rater box (above) and the composite outcome (below)

For patients who meet the following criteria:

1) Opioid Use Disorder and No concurrent Pain Disorder
2) Low-Moderate Risk of Relapse of underlying disorder
3) Taking 0-8 mg of SL buprenorphine daily
4) Presenting for surgery where regional anesthesia technique is possible
5) Given surgical/patient factors, likely to experience severe post-operative pain

I believe that it is most appropriate to continue buprenorphine (Score 9 out of 9) at the pre-operative dose (No reduction) (Score 1 out of 9)

Definition of 'Risk of Exacerbation': Please see definitions under specific chapters headings in the panel rating forms

PRIVATE AND CONFIDENTIAL PANEL INSTRUCTIONS – PLEASE DO NOT SHARE

BMJ Open

Perioperative Pain and Addiction Interdisciplinary Network (PAIN): Protocol of a Practice Advisory for the Perioperative Management of Buprenorphine using a Modified Delphi Process

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Title: Perioperative Pain and Addiction Interdisciplinary Network (PAIN): Protocol of a Practice Advisory for the Perioperative Management of Buprenorphine using a Modified Delphi Process

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None of the authors declared a conflict of interest

Key Words

Buprenorphine, Surgery, Substance Use Disorder, Chronic Pain, Perioperative Management, Perioperative Guidelines

Perioperative Pain and Addiction Interdisciplinary Network (PAIN): Protocol of a Practice Advisory for the Perioperative Management of Buprenorphine using a Modified Delphi Process

Akash Goel, Saam Azargive, Joel Weissman Harsha Shanthanna, Karim Ladha, Wiplove Lamba, Scott Duggan, John Hanlon, Tania Di Renna, Philip Peng, Hance Clarke

Abstract

Introduction

The ongoing opioid epidemic has necessitated increasing prescriptions of buprenorphine, which is evidence-based treatment for opioid use disorder, and also shown to reduce harms associated with unsafe opioid administration. A systematic review of perioperative management strategies for patients taking buprenorphine concluded that there was little guidance for managing buprenorphine perioperatively. The aim of this project is to develop consensus guidelines on the optimal perioperative management strategies for this group of patients. In this paper we present the design for a modified Delphi technique that will be used to gain consensus among patients and multidisciplinary experts in addiction, pain, community and perioperative medicine.

Methods and Analysis

A national panel of experts was identified by perioperative, pain, and/or addiction systematic review authorship, established international profile in perioperative, pain and/or addiction research, community clinical excellence, and by peer referral. A steering group will develop a first round a list of indications to be rated by the panel of national experts, patients, and allied health care professionals. In round 1, the expert panel will rate the appropriateness of each individual item and provide additional suggestions for revisions, additions, or deletions. The definition for consensus will be set *a priori*. Consensus will be gauged for both appropriateness and inappropriateness of treatment strategies. Where agreement is not reached and items are suggested for addition/deletion/modification, round 2 will take place over teleconference in order to obtain consensus.

Ethics and Dissemination

Institutional REB provided a waiver for this modified Delphi protocol. We plan on developing a national guideline for the management of patients taking buprenorphine in the perioperative period that will be generalizable across 3 sets of pre-operative diagnoses including Opioid Use Disorder and/or Co-occurring Pain Disorders. The findings will be published in peer-reviewed publications and conference presentations.

Article Summary (Strengths and Limitations)

1. Existing Perioperative Strategies to manage patients on buprenorphine are based on expert opinion and regional practices
2. We will employ a modified Delphi Protocol optimizing medical and geographical diversity of panellists to ensure the development of a trustworthy set of guidelines
3. We will aim to include patient and allied-health care experts on our panel to ensure that the Delphi process and guideline development is patient-centered
4. Agreement and Disagreement will be measured by a priori agreed upon consensus criteria
5. Given that new buprenorphine products are being released and diagnostic scales are being constantly re-evaluated, we will aim to re-visit our guidelines regularly

Introduction

Buprenorphine has been used for medically supervised withdrawal, historically referred to as detoxification, opioid use disorder (OUD), acute pain and chronic pain management since 2002 (1). Its unique pharmacological properties and wide safety profile have made it increasingly prescribed in the chronic pain and OUD patient population. The number of patients on buprenorphine treatment is increasing (2,3). Since its approval in 2002, the number of buprenorphine/naloxone tablets sold increased from 8 million in 2005 to over 145 million in 2009. Emerging studies have shown that increasing Medicaid coverage for Buprenorphine-naloxone has resulted in an overall increase in people filing prescriptions for buprenorphine-naloxone (4).

Until now, inadequate pain management is the main impetus for the perioperative discontinuation of buprenorphine. Recent evidence suggests that its perioperative discontinuation may hinder harm reduction by destabilizing patients with OUD (5). For example, transitioning a patient off buprenorphine to a full agonist opioid will permit free access to opioid receptors for the purposes of analgesia, but will not address the OUD that may worsen as a result (5). Emerging evidence suggests that certain subsets of patients are less likely to experience deterioration of their OUD (6,7) no matter which strategy is pursued (continue or discontinue). Furthermore, there remain grave public health concerns over improper use and/or disposal of full mu-agonists that are prescribed in the peri-operative period.

Currently, the quality of evidence regarding perioperative management of patients on buprenorphine is weak. A systematic review conducted by Goel et al revealed that the number of studies to address the perioperative dilemma is limited, and few directly evaluated the question of continuation versus discontinuation of buprenorphine (8-24). Few studies make considerations for the possibility of relapse in cases where there has been a history of OUD. Many studies highlighted the importance of multimodal and regional anesthesia techniques. Furthermore, the only RCT combined patients taking buprenorphine and methadone into one group (25), limiting the study's applicability to the important question: Should buprenorphine be continued in the perioperative period or not? It is important that the perioperative physician consider and balance the issue of pain control vs. patient destabilization. In fact, the destabilization of a patient with an OUD risks the patient returning to the drug; this has significant negative consequences including the possibility of peri- and postoperative overdose/death.

There is a need to develop specific guidance on how to manage OUD perioperatively. Until now, 8 major guidelines (1, 26-32) were built on the backbone of anesthesiologists' opinions and existing case reports (8-24) (Table 1 of Appendix 1). Many of the existing guidelines propose discontinuation of buprenorphine before surgery, especially where high-pain is expected. However, more recently, editorialized guidelines have proposed continuation of buprenorphine depending on the pre-operative dose and indication (32). Moreover, there is disagreement on the best discharge strategies for patients taking buprenorphine, irrespective of diagnosis. While most guidelines agree upon major principles such as multimodal analgesia, there is no consensus on which strategies are more likely to succeed. Overall, there is disagreement on optimal pre-, intra-, and post-operative strategies for managing buprenorphine in patients with OUD and/or chronic pain disorders.

Given the lack of RCTs, the strength of a Delphi process is to bring geographically and medically diverse experts together and determine where there is agreement in the perioperative management of buprenorphine. Furthermore, this process ensures the integration of multidisciplinary and patient opinions, resulting in more patient-centered and trustworthy guidelines.

Aim

We will aim to use a national expert consensus Delphi-based survey technique to develop and evaluate a set of recommendations that address perioperative buprenorphine management strategies. We will seek to focus on the following factors: 1) Indication for Buprenorphine therapy, 2) Risk of worsening of OUD and/or co-occurring pain disorder, 3) Expected pain after surgery, 4) Feasibility of perioperative regional anesthesia technique, 5) Utility of adjunct analgesia and 6) Dose and formulation of buprenorphine therapy. We will follow the 22-step checklist recommended

by the RIGHT group (33) for the EQUATOR network.

Methods and Design

This study will use a modified Delphi technique, which was developed by the RAND corporation (34) in order to address complex problems that cannot be solved without a group of experts. The Delphi technique involves anonymous voting and controlled feedback in order to generate discussion and eventual consensus on controversial topics. The Delphi method reduces the likelihood of situations in which group consensus is dominated by the perspectives of a strong minority (35).

An International Research Steering Committee (Perioperative Pain and Addiction Network) has developed the list of indications, and we plan to conduct 2 Delphi rounds in which experts rate appropriateness of buprenorphine management. Panel responses will be de-identified, compiled, analyzed and summarized before being returned to panelists. The summary report will entail qualitative and quantitative details about individual panelists' responses compared to their counterparts. It is expected that the panelist can then review their responses in light of the replies of other panelists prior to a round 2 in-person discussion and re-rating.

Steering Committee

An International Steering Committee (Harvard University, University of Toronto, McMaster University, Queen's University) was formed to develop and conduct this project and consists of representation from various disciplines (Anaesthesiology, Family Practice, Epidemiology, Addictions Medicine, Pain Medicine), geographical areas (Canada, United States) and research expertise (Delphi, health services, and quantitative methods), referred to collectively as the Perioperative Pain and Addiction Network (PAIN). A literature review including a systematic review was conducted by the steering committee to understand the scope of management strategies published to date. The protocol and associated methods were established and agreed upon through in-person, telephone, and email communication. Important functional domains of the research question were considered by the steering committee after completion of the literature review (i.e. Pre-Operative Management, Post-operative buprenorphine management, inpatient use of opioids and adjuncts for analgesia, involvement of outpatient providers, and discharge planning). These domains are represented as 'sections' in the final questionnaire. Reference was made to previous and published Delphi studies (35,36). There were 3 drafts reviewed by the Steering committee, and a final draft after a self-test by the steering committee provided a further set of comments and suggestions.

Generation of the Chapters with Indications (Items)

The indications and domains identified from the systematic review (37) were examined along with the available evidence from existing recommendations on this topic (1, 26-32). Furthermore, case experience from addiction and pain physicians was used to complete a panel rater-form based on the RAND questionnaires used in existing studies (34). The form was generated in order to reflect the essential processes involved in the perioperative experience of patients maintained on Buprenorphine. In total, 840 indications will be divided into 3 chapters of pre-operative diagnoses. - 1. Opioid Use Disorder Only, 2. Opioid Use Disorder with Co-occurring Pain Disorder, 3. Pain Disorder Only. Panellists will indicate their preference for various perioperative strategies (continue, reduce, stop) by systematically rating these indications from chapters 1 to 3.

Selection of National Panel of Experts (Participants and Recruitment)

'Experts' were defined as individuals involved in the management, development, research, teaching or analysis of clinical perioperative buprenorphine strategies. Because the Delphi group size depends more on optimizing group dynamics to obtain consensus than statistical analysis, we aimed for a panel size based on original Delphi methodology from the RAND study (34) (optimal panel size of 9 and no greater than 15). We set an a priori estimate of panellist attrition rate (20%) and aimed to select up to 15 panellists for Round 1 (the maximum recommended by the RAND authors).

To identify experts in the field of addiction and perioperative medicine, we reviewed authorship of published guidelines and case reports of buprenorphine management in the perioperative period; we identified established national and regional profiles in addiction, pain, or perioperative medicine; we solicited peer recommendations from individuals on boards of the National Canadian Pain, Addiction, and Anaesthesiology Societies (CSAM, CPS, CAS). We sought to diversify our panel by selecting panellists with practice experience in all the Canadian provinces, membership on professional societies, and wide-ranging expertise.

We initially reached out to these prospective expert panellists by emailing solicitation letters describing the project and the timelines involved (Appendix 2). Prospective panellists were then asked to complete and return a conflict of interest form (Appendix 3) along with their indication of interest in the project. Conflicts of Interest were reviewed by the Steering Committee and prospective panellists with potential conflicting industry affiliations were removed from the final shortlist. Possible incentives for participation in this process included (1) the opportunity to be selected into a diverse group (2) unique educational opportunities and (3) increased internal and external visibility (1).

Patient and Public Involvement

We included a patient on our steering committee and expert panel in order to develop a research question and outcome measures that were informed by patient priorities, experience, and preferences. Furthermore, inclusion of a nurse practitioner also allowed the panellists to consider the values and preferences of the target population.

Ethics

All participants will be informed that by responding to the questionnaire, they have indicated their consent to participate in the study and have their de-identified responses included in associated analyses. All data will be preserved on paper (under lock and key) as well as a computer (which is password protected) in a locked office, in accordance with standard guidelines. Only the steering committee will have access to the data, which will be destroyed after 5 years in accordance with local guidelines.

We obtained an official waiver from our institutional REB for the conduct of this protocol. The REB deemed our Delphi protocol not to be research as defined in the Tri-Council Policy Statement, and therefore, did not fall under the purview of the REB.

Delphi Procedures (Data Collection and Data Analysis)

We will administer paper questionnaires that will be delivered as attachments to expert panellists by email. Panellists will be asked to print out the questionnaires and complete them on paper. The email will include an instruction form (Appendix 4) that includes a table of contents and a sample exercise grid. Furthermore, a systematic review completed by the steering committee will be provided to panellists as a resource for supplement existing knowledge and experience in this topic. To reduce the likelihood of attrition bias, we will notify the panel that authorship of the final guideline document will be offered only to participants that complete the entire Delphi process.

Round 1 & 2 of Delphi Procedure

The Delphi process will consist of 2 survey rounds. The first round will consist of questionnaires that will be completed remotely by all panellists. Panellists will be blinded to each other's participation in the first round to prevent any communication that may lead to bias in the ratings. The first survey round will extend to 3 weeks, with the first week dedicated to addressing any concerns raised by panellists. In this round, panellists will first be asked to rate the appropriateness of continuing or stopping buprenorphine where: 1 = Very Appropriate to Stop Buprenorphine and 9 = Very Appropriate to Continue Buprenorphine at the same or reduced dose. Next, panelists will be asked to rate the appropriateness of reducing vs maintaining dosage, where: 1 = Very Appropriate to reduce Buprenorphine dosage; and 9 = Very Appropriate to Continue Buprenorphine at the same dosage. Panellists will also be asked to identify potential deletions, modifications, or points of clarification upon return of the rating forms. Furthermore, they will be urged to consider patient populations that will require individualized approaches to the management of their buprenorphine dose in the perioperative period. Panellists will then scan and return their rating forms with unique personal identifier codes on each page.

In order to identify thresholds for agreement, we will include pre-determined information about buprenorphine dose, formulation, diagnosis (Pain and/or OUD), risk of exacerbation of underlying disorder, expected surgical pain, and availability of regional anaesthetic technique in the final list of indications. These 840 indications will reflect the complete perioperative period, including strategies for communication with the outpatient provider and utilization of multimodal analgesia.

After completion of round 1, a 2-week Analysis Period will ensue, in which two blinded independent analysts will extract de identified data from rating forms and input data into two mutually exclusive databases. De-identified results including scores for each indication (including median and mode scores, interquartile ranges, indications with universal consensus, and qualitative feedback) along with a narrative report of the findings will be remitted to individual panellists to review prior to round 2 of the Delphi Process. The second-round meeting will be conducted in person and over teleconference given the geographic diversity of expert panellists. Any ambiguous indications, or external factors not previously considered will be aggregated for discussion during this round. Panellists will have the opportunity to discuss addition or removal of indications (items) at this point. If indications are deemed to be insufficient (not capturing the breadth of the theme) or overly inclusive (extreme granularity of indications) then the steering committee will offer a second round of rating after inclusion or exclusion of culprit items. If duplicate indications exist, where possible, the steering committee will aim to combine indications.

Definition of Consensus

In any Delphi process, decision rules are determined in advance to both define and determine consensus. Consensus on a topic is usually determined if a certain number or percentage of the votes falls within a prescribed range. The Steering Committee has *a priori* decided on its definition of consensus in order to avoid bias. Using the European Union BIOMED Concerted Action on Appropriateness for surgical procedures as referenced in the RAND/UCLA Appropriateness Method User's Manual (34).

We define consensus (agreement) in 2 ways: 1) Appropriate treatment defined as a clustering of scores with a median score in the high end of the scale (7-9) without 'disagreement' (i.e. more than

2 panellists' scores in the low end of the scale, 1-3) and 2) Inappropriate treatment defined as a clustering of scores with a median score in the low end of the scale (1-3) without 'disagreement' (i.e. more than 2 panellists' scores in the high end of the scale, 7-9).

Development of Guidelines and Recommendations

A final operational manual with decision rules for each indication will be presented to panellists during the second-round meeting, with accompanying explanatory documents as necessary. Panellists will be asked to rank and order the recommendations to rationalize the number of items included in the final guideline as per the EQUATOR network's reporting tool for practice guidelines in healthcare (RIGHT) (33). An email questionnaire will aim to obtain a final majority agreement on the synthesis of comments after the 2nd round of the Delphi process. It is expected that clear and concise rationale will accompany individual recommendation statements.

Review and Quality Assurance

We plan to use a 2-step process in order to develop and refine an internationally agreed upon guideline for the perioperative management of patients maintained on buprenorphine. Initially, a draft guideline will undergo independent review by members external to the steering committee. Any comments will be addressed explicitly in the final guideline document. A questionnaire will be emailed out to panellists after the second round to solicit suggestions for improvement in future iterations.

The guideline document should reflect the needs of patients who have co-occurring disorders where possible, therefore facilitating its use in as many perioperative scenarios as possible. The final consensus guidelines will be submitted to a perioperative journal and championed by individual panellists at their home institutions.

To test the acceptability of the proposed guidelines due to varying geography and practice patterns, we will seek annual comments and suggestions from regional and national users of the guideline. The guideline document should be reviewed annually in order to reflect shifting evidence and expert opinion.

Funding and management of interests

No funding sources will be used in any stage of the guideline development. Individual steering committee members and panellists were made to complete conflict of interest forms prior to involvement in this process. Any prospective steering committee members or panellists with perceived conflicts of interests were not included at any point of the guideline development. Original declaration forms outlining conflict of interest are available upon request to the first author of the study (Akash Goel).

Limitations of the Guideline

Increasingly, providers are beginning to see off-label prescription of sublingual buprenorphine for patients with pain disorders. Furthermore, there are several new formulations of buprenorphine emerging. As evidence emerges and new formulations of buprenorphine are developed, these guidelines will require updating in the future hopefully on an annual basis.

Delphi Study Status

The first round of the Delphi process will begin in October, with an in-person, second round meeting scheduled in November 2018. Data collection and analysis will occur after the second-round meeting if panellists and the steering committee are satisfied that all important questions have been addressed. A paper reporting the results of the Delphi process will be submitted for publication in early 2019 followed by conference presentations. Data collection will start in October 2018 and anticipated to be completed by December 2018.

Author Statement

Akash Goel, Joel Weissman and Harsha Shanthanna developed the Delphi Protocol and methodology

Akash Goel and Saam Azargive developed and modified Round 1 panel rating forms

Akash Goel, Karim Ladha, Wiplove Lamba, Scott Duggan, John Hanlon, Tania Di Renna, Philip Peng and Hance Clarke were involved in the development of the research question and formulation of the Delphi Protocol as part of the Steering Committee

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Title	Date	Major Peri-operative recommendations
Anderson et al	2017	1. Where moderate to severe pain is expected, cancel surgery such that buprenorphine is weaned off before surgery and short-acting opioids are used to replace it. 2. A plan for follow-up and reinstitution of therapy should be established 3. Anticipate patient's opioids requirements will be similar to an opioid-tolerant patient 4. Consider adjuncts – NSAIDs, membrane stabilizers, acetaminophen, local anaesthetics, regional anesthetic techniques 5. Ensure appropriate outpatient follow-up with buprenorphine provider
Sen et al	2016	1. Discontinue buprenorphine 72H before operative procedure, or replace buprenorphine with methadone 2. Expect additional opioid doses for acute pain control 3. Discharge on pure opioid induction protocol of buprenorphine in conjunction with primary provider
Jonan et al	2018	1. Utilize non-opioid adjuncts, regional Anesthesia, and local anesthetic infiltration by surgeon where possible. 2. Where low post operative pain is expected, continue buprenorphine perioperatively without taper 3. Where intermediate pain is expected, discontinue buprenorphine 3 days prior to procedure, consider high dose PCA, and consider ICU admission for respiratory monitoring 4. Where High pain is expected, discontinue buprenorphine 3-5 days prior to procedure, consider pure opioid agonist to manage withdrawal, and consider ICU for respiratory monitoring
Childers and Arnold	2012	1. Adjuvant analgesics and interventional procedures should be provided if available 2. Hold buprenorphine and start short acting opioid agonists if expecting moderate to severe pain 3. Re-initiate buprenorphine in the post-operative period with the buprenorphine provider 4. Where mild to moderate pain is expected, consider treating pain with buprenorphine alone, or use short-acting opioid agonists at higher doses 5. Consider replacing buprenorphine with methadone for opioid addiction where ongoing pain management is expected
Bryson	2014	1. Ideally, buprenorphine should be discontinued 72H before surgery, then restarted once patient no longer has acute pain requiring narcotic analgesics 2. If the plan is to continue buprenorphine, use short-acting opioid analgesics to achieve pain control, expecting higher than normal effective doses. Divide buprenorphine maintenance dose and administer every 6-8 hours 3. If the plan is to stop the buprenorphine, use standard opioids for analgesia, conduct a slow taper over 2 weeks or an abrupt taper over 3 days, remaining buprenorphine free for 72 hours before surgery 4. If the relapse rate is too high, replace maintenance dose of buprenorphine with methadone before surgery, and use another short-acting opioid and analgesic for breakthrough pain
Berry (Vermont Guidelines)	2015	1. Reduce buprenorphine dose to 8mg SL on the day of surgery 2. Use oxycodone or other full agonists to make up opiate debt + typical post operative course management 3. Expect longer than normal pain management regimen in the post operative period 4. Buprenorphine doses above 10mg daily will block opioid analgesics for pain
Lembke et al. (Editorial)	2018	1. Continue buprenorphine in the perioperative period for patients taking 12mg SL or less 2. Taper buprenorphine to 12 mg SL 2-3 days pre-op 3. Multimodal analgesia, Regional techniques where possible 4. Higher than normal doses of opioids to treat pain for 2-4 days post-op

Dear Prospective Panelist,

We are writing to you to because you have been nominated for a special expert consensus panel. This Panel will be establishing guidelines on the perioperative management of patients who are taking buprenorphine for the management of pain and/or substance use disorder.

We will be embarking on this project because current evidence provides little guidance as to how best to manage this group of patients. Our group has conducted a systematic review of the existing evidence and we hope to use this for the basis of conducting a 2-staged Delphi process resulting in consensus on appropriateness of continuing or stopping buprenorphine in the perioperative period.

This process involves the following steps and timeline:

Task	**Timeline**
Review of existing literature (Complete)	Complete
Nomination of experts in Addiction medicine, pain medicine, and Anesthesiology Obtain CVs, Conflict of Interest Forms (Delphi)	By September
Confirmation of Panel by Core Committee **Dissemination of Core Materials to Expert Panel**	By September 15
Review of evidence by expert panel (remotely done)	By September 31st
Review of consensus statements (remotely done)	By September 31st
Submission of consensus statements, and collation of data	By September 31st
Meeting by Teleconference/In-person to review consensus and/or conflicts	By October 31st
Development of consensus	By December 30th
Publication of consensus document	By January 2019

As part of the nomination process, we are seeking recognized experts as part of the Canadian Society of Addiction Medicine (CSAM), CPS (Canadian Pain Society) and CAS (Canadian Anesthesiologists' Society). You were nominated based on the following 4 criteria:

Leadership in the specialty
Absence of conflicts of interest
Geographic diversity
Diversity of practice setting

We would be delighted to have you serve on this panel, and would be happy to answer any questions you may have about the process. Please return your CVs and COI forms to me by August 4 if you are interested in pursuing this opportunity.

Sincerely,

The Steering Committee

Clinical Practice Advisory for Perioperative Management of Buprenorphine

CONFLICT OF INTEREST DISCLOSURE FORM

The following are examples of conflicts of interest:

- Any direct financial interest in a for-profit entity such as a pharmaceutical organization, medical devices company, communications firm, or other financial supporter
- Current or recent participation in a clinical trial sponsored by the Organization
- Membership with a speakers bureau
- Holding of a patent for a product referred to in the CPD activity or marketed by a commercial organization
- Receiving honoraria to speak on behalf of a pharmaceutical organization or medical communication company, including talks for which the individual has been contracted but has not yet received payment for
- Financial relationships with program-sponsoring organizations that are non-pharmaceutical or non–health care organizations (eg, insurance companies, financial institutions, government, for-profit organizations, other non-profit organizations)

O I, Hance Clarke MD PhD declare no conflict of interest

O I, _____ declare the following conflicts of interest (Please list below)

Signature _____-

Name Hance Clarke

Title Director Pain Services / TGH

Perioperative Management of Buprenorphine Products

Panel Instructions

Dear Panellist,

Thank you for your participation in the national guideline development for managing patients taking buprenorphine products in the perioperative period. Below you will find some definitions and instructions for how to fill out the panel rating forms.

There are 840 indications that you will be required to rate.

How does the Modified Delphi process work?
There are 2 rounds of ratings – the first round is done in a 'blinded' fashion where panellists are not aware of who the other panellists are, and are not meant to discuss their thoughts with each other. They are to fill out rater forms and return them to the **moderator**. There will be a second round where panellists will meet in person and teleconference to discuss discrepancies in their rating and aim to obtain consensus on conflicting areas.

How are the rating forms organized?
There are 3 **chapters** that are focused on the diagnosis of the patient prior to surgery
1. OPIOID USE DISORDER ONLY (No co-occurring pain disorder) – 280 indications
2. OPIOID USE DISORDER AND PAIN DISORDER – 280 indications
3. PAIN DISORDER ONLY (No co-occurring opioid use disorder) – 280 indications

These chapters are then divided into various **sections** that are organized by stage of the patient experience:
1. *PRE-OP PLANNING – Buprenorphine Strategies*
2. *POST-OP PAIN – Buprenorphine in patients experiencing post op pain*
3. *POST-OP PAIN – Analgesic adjuncts to manage pain (i.e. NSAIDS, Tylenol etc)*
4. *POST-OP PAIN –Opioids to manage pain (i.e. fentanyl, hydromorphone)*
5. *DISCHARGE – Discharge strategies*
6. *OUTPATIENT PROVIDER INVOLVEMENT – indications for involving outpatient provider in these settings*

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What is the definition of 'Appropriateness'?

The RAND/UCLA appropriateness method (which we are using in this guideline development process) allows panellists to rate appropriateness of therapy from 1-9. Median scores of all panellists will be obtained, and consensus definitions will be provided during the second round (in person/teleconference meeting of panel)

Instructions on how to use the Rater forms:

1) **Print out the forms**
2) **Read the Chapter on the top of the page** – I.e. Chapter 1, Section 1.1 reads: "Opioid Use Disorder Only (No Concurrent Pain Disorder)" – this indicates to the panellist to consider patients with opioid use disorder ONLY and no concurrent pain disorder when rating an indication
3) **Read across the top of the table** - You will see two big categories, patients who are at LOW risk of 'Chapter 1' Disorder Exacerbation and HIGH risk of Chapter 1 Disorder Exacerbation. This directs panellists to stratify patients based on the definitions provided to them and their own experience.
4) **Read down the left most column of the table –** The left most column labels the Section within the chapter – "pre-operative planning". As the panellist scrolls down the left-most column, they will notice that it is divided based on certain clinical characteristics – for example, what dose of buprenorphine the patient is on, how much post-operative pain is expected, and whether a regional anesthesia technique (i.e. nerve block, epidural) is feasible for the surgery for a variety of plausible scenarios.
5) **Read Across the INDICATION ROW –**
   Indications are dichotomized. This row indicates the options available to the panellist when rating from 1-9. For example, the first appropriateness rating available to the panellist is Appropriateness of Continuing Buprenorphine with the numbers 1 to 9 below them. This directs the panellist to choose a score for the indication, with a score of '9' being closest to – 'It is most appropriate to Continue Buprenorphine', and a score of '1' being closest to 'It is most appropriate to stop Buprenorphine'. Any scores in between indicates a lack of certainty around the indication.

   Panelists are urged to use the extremes of the rating scale.
6) **Use a black pen** only to **circle** the most appropriate score for the indication.
7) **Scan and Email** your forms to agoel@hsph.harvard.edu

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Example – Refer to the colour coding to clarify – this form can only be viewed online or if printed in colour

Example

_CHAPTER 1: OPIOID USE DISORDER ONLY (NO CO-OCCURRING PAIN DISORDER)_____PANELIST # __ ROUND 1__

Page 1

Definitions: High Risk of Exacerbation includes concurrent mood disorder, duration of therapy <1 year, positive urine drug screen within 1 year

Chapter 1: Opioid Use Disorder (OUD)

Section 1.1: Pre-Op Planning

INDICATION ROW	LOW-MODERATE Risk of Exacerbation: Appropriateness of: Continue Buprenorphine Therapy (9) vs Stop (1)	LOW-MODERATE Risk of Exacerbation: Appropriateness of Maintain (1) vs. Reducing Buprenorphine (9) Dose	HIGH Risk of Exacerbation: Appropriateness of: Continuing Buprenorphine Therapy (9) vs. Stop (1)	HIGH Risk of Exacerbation: Appropriateness of: Maintain (1) vs. Reducing Buprenorphine Dose (9)	*(Indication Number)*
A. Patient is on **0-8mg** SL Buprenorphine Daily	——————→	——————→	←—————→	←—————→	*Leave Blank*
Severe Post Op Pain expected in an elective case					
a) With Regional Anesthesia	1 2 3 4 5 6 7 8 **9**	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	*1-4*
b) WithOUT Regional Anesthesia	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 5 6 7 8 9	*5-8*

For a score of 9 on this indication, refer to colour coded elements of the rater box (above) and the composite outcome (below)

For patients who meet the following criteria:

1) Opioid Use Disorder and No concurrent Pain Disorder
2) Low-Moderate Risk of Relapse of underlying disorder
3) Taking 0-8 mg of SL buprenorphine daily
4) Presenting for surgery where regional anesthesia technique is possible
5) Given surgical/patient factors, likely to experience severe post-operative pain

I believe that it is most appropriate to continue buprenorphine (Score 9 out of 9) at the pre-operative dose (No reduction) (Score 1 out of 9)

Definition of 'Risk of Exacerbation': Please see definitions under specific chapters headings in the panel rating forms

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