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SPECIAL ARTICLE

Perioperative Pain and Addiction Interdisciplinary Network (PAIN): consensus recommendations for perioperative management of cannabis and cannabinoid-based medicine users by a modified Delphi process

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Summary

In many countries, liberalisation of the legislation regulating the use of cannabis has outpaced rigorous scientific studies, and a growing number of patients presenting for surgery consume cannabis regularly. Research to date suggests that cannabis can impact perioperative outcomes. We present recommendations obtained using a modified Delphi method for the perioperative care of cannabis-using patients. A steering committee was formed and a review of medical literature with respect to perioperative cannabis use was conducted. This was followed by the recruitment of a panel of 17 experts on the care of cannabis-consuming patients. Panellists were blinded to each other's participation and were provided with rater forms exploring the appropriateness of specific perioperative care elements. The completed rater forms were analysed for consensus. The expert panel was then unblinded and met to discuss the rater form analyses. Draft recommendations were then created and returned to the expert panel for further comment. The draft recommendations were also sent to four independent reviewers (a surgeon, a nurse practitioner, and two patients). The collected feedback was used to finalise the recommendations. The major recommendations obtained included emphasising the importance of eliciting a history of cannabis use, quantifying it, and ensuring contact with a cannabis authoriser (if one exists). Recommendations also included the consideration of perioperative cannabis weaning, additional postoperative nausea and vomiting prophylaxis, and additional attention to monitoring and maintaining anaesthetic depth. Postoperative recommendations included anticipating increased postoperative analgesic requirements and maintaining vigilance for cannabis withdrawal syndrome.

Keywords: anaesthesiology; cannabinoids; cannabis; pain; perioperative care; postoperative nausea and vomiting

Editor's key points

- The number of regular cannabis users has increased significantly in recent years, with legalisation of use in some countries and increased availability in others.
- There are specific challenges that need to be considered for individuals consuming cannabis and undergoing surgery and anaesthesia, but to date there has been no comprehensive evaluation of how to best manage these patients.
- Using a modified Delphi process to evaluate current (limited) literature and reach consensus, recommendations have been made to improve perioperative outcomes.
- Recommendations include aknowledement of the potential need for increased analgesia and anti-emesis prophylaxis, but highlight the lack of robust evidence. Robust approaches to evidence generation are needed to minimise potential harms.

The United Nations estimates that approximately 200 million individuals used cannabis in 2016, an increase of 16% over the past decade.[1] This number is expected to grow as countries around the globe establish legal frameworks for both recreational and medical use. With this shift, it follows that perioperative clinicians are likely to encounter cannabis consumers with increasing frequency. The ability of cannabis to impact perioperative management extends beyond its psychoactive effects. Indeed, previous studies have demonstrated a potential for cannabis to affect numerous organ systems, including the gastrointestinal, respiratory, cardiovascular, haematological, and central nervous systems.[2–4]

Unfortunately, the rapidly changing legal landscape surrounding cannabis has outpaced rigorous scientific research. Evidence related to the management of patients using cannabis in the perioperative period is scarce. In this paper, we present recommendations for the perioperative care of cannabis-consuming patients. This guidance is the result of reviewing available medical literature[2] and of the consensus of a panel of international experts obtained using a modified Delphi technique. The modified Delphi technique used was based on the RAND/UCLA Appropriateness Method developed by the RAND Corporation, and also on the modified Delphi method used by Goel and colleagues[5] and Fitch and colleagues[6] to create consensus guidelines for the perioperative management of buprenorphine.

Cannabis and the endocannabinoid system

Cannabis contains hundreds of organic compounds, such as terpenes, flavonoids, and cannabinoids (such as Δ^9-tetrahydrocannabinol [THC] and cannabidiol [CBD]). Tetrahydrocannabinol and CBD are the most studied cannabinoid constituents of cannabis. The physiological effects of these compounds are complex and attributed mostly to their influence on the endocannabinoid system.[7]

In the endocannabinoid system, the endogenous ligands anandamide and 2-arachidonoylglycerol have been the most closely studied. Both are closely related to arachidonic acid (AA) and are synthesised from AA-containing phospholipids in cellular membranes. Endocannabinoid synthesis occurs in response to overstimulation in postsynaptic neurones as a result of an intracellular calcium rise.[8] Endocannabinoids are released from postsynaptic neurones and lead to presynaptic downregulation of excitatory signals.[9]

There has been a tremendous amount of research into the mechanism of action of exogenous THC and CBD on the human nervous system. THC is a cannabinoid receptor Type 1 (CB_1) and a cannabinoid receptor Type 2 (CB_2) partial agonist. CBD is not an agonist at either CB_1 or CB_2; rather, it is a negative allosteric modulator[10] of the cannabinoid receptor and has been shown to reduce the adverse effects of THC in human studies.[11] The precise mechanism of CBD has not been elucidated. CBD may increase endocannabinoid signalling, and has been found to increase serotonin receptor 1A activity, enhance adenosine signalling, and activate transient receptor potential cation channel Subfamily V Member 1 receptors that detect thermal and nociceptive stimuli.[12] The CB_1 receptor is found in virtually all CNS tissues, and is potentially a target of pharmacological intervention in pain pathways.[13]

As the understanding of the endocannabinoid system grows, so does its potential for developing into a reliable means of treating patients. To date, evidence suggests that cannabis products have potential use in the treatment of chronic pain, chemotherapy-induced nausea and vomiting, spasticity associated with multiple sclerosis, obstructive sleep apnoea, and fibromyalgia.[14] Research into other cannabis-related pharmacotherapy treatments for cancer pain, osteoarthritis, and opioid weaning is ongoing. Current evidence regarding these applications is inconclusive.[15–17]

It can be difficult to quantify the pharmacologically active compounds in natural cannabis that are consumed at each dosing interval. The WHO describes a typical cannabis cigarette as containing approximately 500–750 mg of cannabis.[18] The inhaled dose of CBD or Δ^9-THC in a cannabis cigarette could be approximated using estimates like this and the percentage of Δ^9-THC or CBD concentration in that cannabis product (THC/CBD dose=THC/CBD%×mg of dried cannabis). The inhaled dose is the amount of Δ^9-THC available in the entire cannabis cigarette. The actual amount of Δ^9-THC delivered to the patient varies greatly and is dependent on multiple variables, such as smoking technique and inspiratory effort.[19]

The clinical effects of cannabis vary with the quantity of cannabis consumed and the chronicity of its use.[2,3] The clinical effects of cannabis involve many organ systems, including the CNS, cardiovascular system, and respiratory system.[2,3] In the CNS, cannabis has been associated with difficulty achieving adequate depth of anaesthesia and increased cerebral blood flow, and a failure of appropriate cerebral vasodilation occurring with stressful events, such as hypercapnia and hypoxia.[20–22] Cardiovascular concerns include beta-adrenergic-mediated tachycardia—with acute use possibly associated with a greater incidence of myocardial ischaemia in at-risk individuals.[23–28] Orthostatic hypotension and bradycardia have been associated with heavy acute and chronic cannabis use.[29] In the respiratory system, smoked cannabis has been associated with increased airway reactivity.[30–33] Other perioperative cannabis-related concerns described in the literature and relevant to perioperative care include postoperative shivering, drug interaction (e.g. warfarin, NSAIDs, and opioids), reduced postoperative sleep quality, and greater postoperative pain.[2,3,34]

Aims

An expert Delphi-based method was used to develop and evaluate a set of recommendations to help guide the care of patients consuming cannabis in the perioperative period. These recommendations focused on strategies with the potential to improve post-surgical outcomes for patients consuming cannabis. Strategies that we present are derived from questions and discussion of the following interventions and concerns: weaning from cannabis, substituting nabiximols or nabilone for normal cannabis intake and using them to treat withdrawal, screening for cannabis misuse and withdrawal, intraoperative monitoring, analgesia, induction and maintenance of anaesthesia, postoperative nausea and vomiting (PONV), patient use of cannabis while hospitalised, and discharge contact with their cannabis authoriser. It is acknowledged that not all of the recommendations presented will be applicable in all jurisdictions, as cannabis legislation and product availability vary; however, there are many ubiquitous concerns regarding this patient population addressed by the strategies presented here.

This practice advisory was created following the 22-step checklist recommended by the essential Reporting Items for Practice Guidelines in Healthcare (RIGHT) group for the Enhancing the Quality and Transparency of Health Research (EQUATOR) network.[35] A research and ethics board (REB) waiver was obtained from the REB at the University Health Network before commencing this project.

Target population

The expert panel determined that the current consensus statements presented here are primarily targeted at patients consuming recreational cannabis before surgery with a particular focus on patients consuming inhaled cannabis or oral cannabis. They also agreed that these consensus statements could be applied to patients consuming clinician-authorised cannabis. However, when considering the perioperative care of patients consuming clinician-authorised cannabis products, the expert panel acknowledged the necessity of collaboration between the perioperative care team and the medical cannabis authoriser.

End users and settings

These recommendations are primarily intended for perioperative care providers, such as anaesthesiologists, surgeons, pharmacists, nurse practitioners, and nurses. They may also be of interest to care providers who also have a role in patient's preoperative and post-hospital discharge care, such as family physicians.

Clinical practice development groups

Systematic review team

A review of medical literature, 'The impact of perioperative cannabis use: a narrative scoping review', was completed before the expert panel's finalisation.[2] This review was directed at understanding the scope of cannabis perioperative management strategies and other existing evidence relating to perioperative cannabis use by patients.

Steering committee

A steering committee was created to develop this project, recruit an expert panel, collect and analyse data, and compile and draft summary recommendations. This committee was composed of four anaesthesiologists with expertise in treating

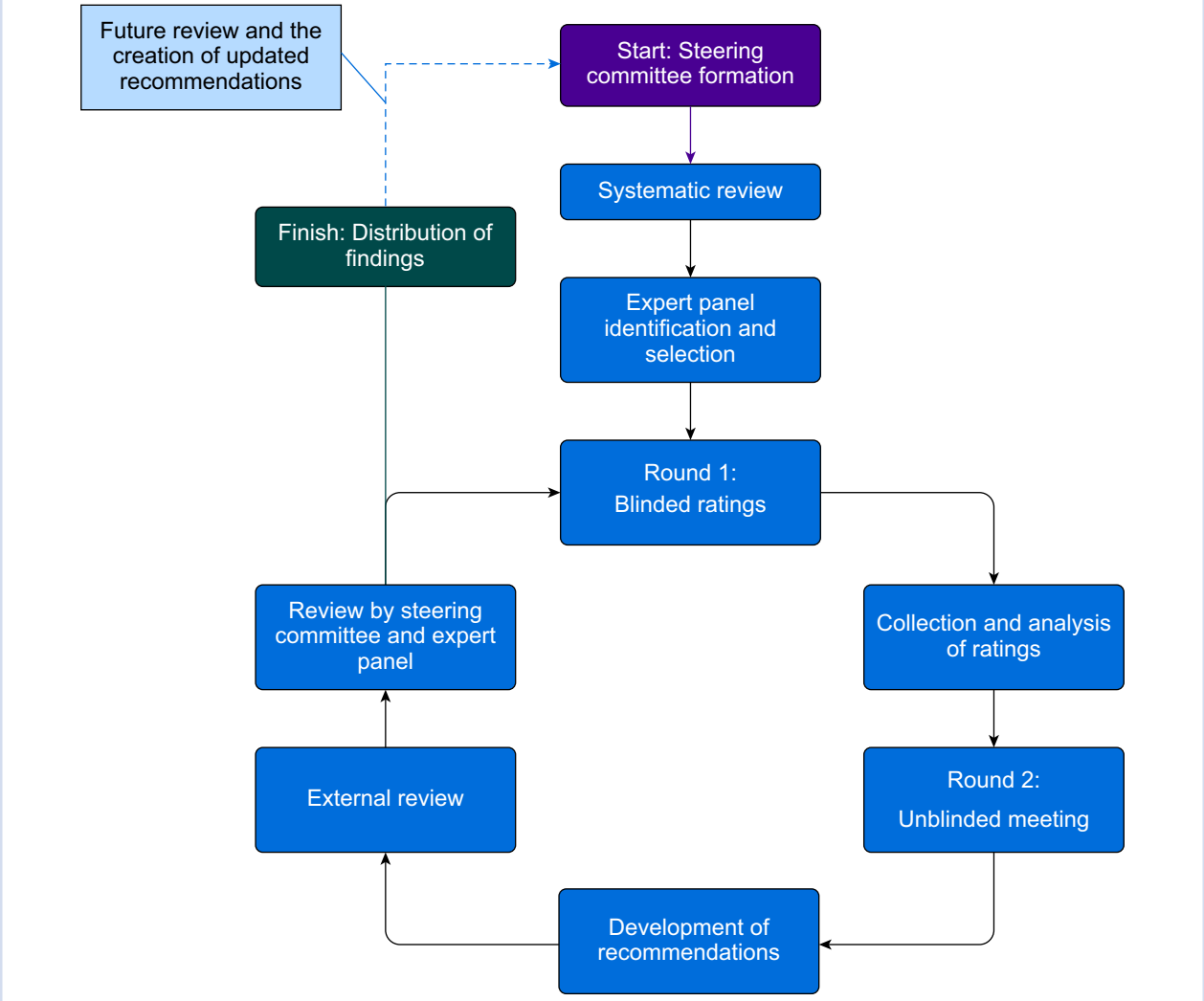

Fig 1. Outline of the recommendation development process. The potential to propose additional blinded ratings to address major disagreements between the panel and reviewers is shown. Also displayed is the potential to review the distributed findings and revise them as practice and evidence evolves.

patients consuming cannabis. The panel members also had an interest, or experience, in creating consensus-based recommendations. Details on the creation of the steering committee can be found in the study protocol, 'Perioperative Pain and Addiction Interdisciplinary Network (PAIN): protocol for the perioperative management of cannabis and cannabinoid-based medicines using a modified Delphi process' by McLaren-Blades and colleagues.[36]

Expert consensus panel

Experts were defined as individuals possessing experience with teaching, development, research, or clinical practice related to cannabis or perioperative medicine. Experts were sought from diverse clinical and geographical backgrounds with prospective panel members being identified by the review of relevant published research and peer recommendations. Seventeen experts were included in the final panel. Eight different countries of clinical practice and seven different clinical specialties were represented by the expert panel.[36]

Clinical practice advisory development process

The steering committee developed the practice guidelines by the steps outlined in Fig. 1. Fig. 1 also notes the potential to repeat and review this advisory, as the medical culture and evidence around patient perioperative cannabis use continue to evolve. Rater forms were created by the steering committee and given to each member of the expert panel. The expert panel was blinded to each other's participation until all rater forms were completed (Fig. 1, 'Round 1'). The expert panellists were later unblinded to each other, so the analysis and areas of consensus found in the rater form data could be discussed (Fig. 1, 'Round 2'). Instructions for panellists, including examples from a completed rater form, can be found in

Supplementary document A1. Excerpts of survey rater forms from the preoperative, intraoperative, and postoperative questionnaires can be found in Supplementary documents A2. A total of 1649 items were rated by each panellist during survey Round 1.

Evidence

The narrative scoping review conducted by members of our group found a limited number of studies that could directly inform the management of cannabis users presenting for surgery.[2] This review evaluated articles collected on November 28, 2018 using a systematic search protocol under the supervision of an information specialist. The initial search strategy focused on human studies examining the management of perioperative cannabis. However, given the limited number of studies identified, the scope of the review was broadened to include therapeutic uses of cannabis in the perioperative period and to physiological effects related to cannabis that would be of relevance to the perioperative clinician. Overall, the evidence surrounding perioperative cannabis management was weak as determined by the Grading of Recommendations Assessment, Development and Evaluation tool.[37] The results of the review were distributed to all expert panel participants with the rater forms (Fig. 1, 'Round 1') and were published elsewhere.[2]

Healthcare questions

Using the Population, Intervention, Comparator, and Outcome format, healthcare questions regarding perioperative cannabis use were identified. This formed the basis for the rater forms used in Round 1 (rater form excerpts can be found in Supplementary document A2).

Populations

Surgical patients consuming inhaled cannabis or cannabis edibles recreationally, or without health professional guidance, were primarily considered in the rater forms and later panel discussions. The interventions, comparators and outcomes listed below guided the creation of the document.

Interventions

(i) Any diagnostic or therapeutic procedure.
(ii) Preoperative weaning of current cannabis dose.
(iii) Nabilone and nabiximols replacement of daily cannabis dose for prevention or treatment of cannabis withdrawal or for weaning current cannabis dose.
(iv) Initiating adjunct analgesia.
(v) Initiating regional anaesthesia.
(vi) Providing additional anaesthetic to ensure adequate depth of anaesthesia.
(vii) Providing additional PONV prophylaxis.
(viii) Initiating outpatient cannabis authoriser involvement in the perioperative period.

Comparators

(i) Different CBD and THC doses of inhaled (smoked and vaped) cannabis.
(ii) Different CBD and THC doses of cannabis oils.
(iii) Cannabis products of unknown CBD or THC content.
(iv) Recreational and therapeutic cannabis use.

Outcomes

(i) Adequacy of postoperative analgesia.
(ii) PONV.
(iii) Adequate depth of anaesthesia.
(iv) Exacerbation of underlying disorder treated by cannabis: recreational (self-treatment and misuse) or prescribed (e.g. oncological or neurogenic pain).
(v) Perioperative morbidity associated with cannabis use (cannabis withdrawal syndrome [CWS]).

Consensus

Each item (clinical question) on the expert panel rater form was scaled from 1 to 9, creating three terciles (1–3, 4–6, and 7–9). A panellist rating of 1–3 indicated that a panellist thought the item was inappropriate, 4–6 indicated an item was of unknown harm or benefit, and a rating of 7–9 indicated an item appropriate. For consensus, the initial Round 1 rater form item had to have a median score in one of the extreme terciles (1–3 or 7–9) and have no more than two panellists selecting rater scores in the opposite tercile.

Clinical practice advisory

Consensus definitions: CBD and THC dominance, and significant cannabis consumption

CBD and THC dominance

Recommendations. The pharmacological effects of cannabis are predominantly considered to be mediated by its CBD and THC content. Considering a cannabis product as THC or CBD dominant can help to direct recommendations within the context of cannabis products being extremely diverse in their absolute THC and CBD content, and their ratio of CBD to THC. For this practice, advisory dominance is determined by considering which of these compounds (THC or CBD) is predominantly responsible for the therapeutic and adverse clinical profile of a cannabis product.

The expert panel determined that cannabis product CBD or THC dominance is decided by whichever of the two was present in a higher concentration, and that balanced products (CBD-to-THC ratio of 1:1) should always be considered THC dominant. The unit of measure should be the same for both CBD and THC when reviewing CBD-to-THC ratios (usually milligrams).

The expert panel also agreed that a cannabis product could be also considered CBD dominant when the ratio of CBD to THC is greater than 10:1. When the ratio of CBD to THC is less than 10:1, a product could be considered THC dominant.

Evidence and rationale for recommendations. The expert panel and steering committee agreed that for the creation of the perioperative recommendations presented here, it was important to consider whether CBD or THC might dominate the clinical effects of the cannabis being consumed. Cannabis formulations and their CBD-to-THC-content ratios are very heterogeneous. This makes it difficult to make discreet clinical recommendations regarding them. CBD may possibly attenuate and antagonise some of the

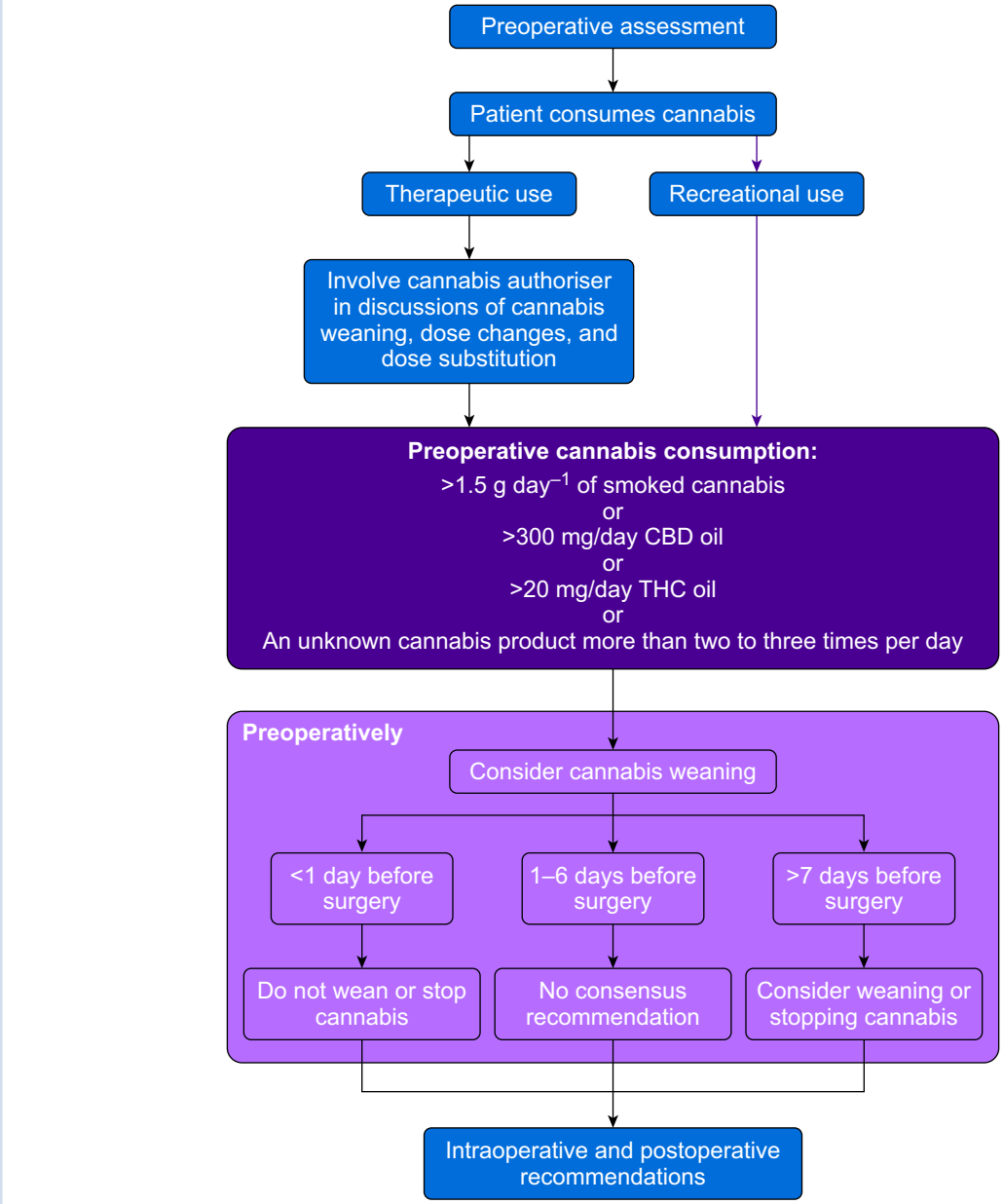

Fig 2. Summary of preoperative recommendations for preoperative patients presenting for surgery. CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol.

clinical effects of THC, such as memory impairment, paranoid symptoms, and appetite.[38–42] Cannabis consumers also correlate increasing THC content and decreasing CBD content, with the potency of cannabis they consume.[43] Nabilone is a synthetic (THC) cannabinoid whose effects are primarily mediated by its action on CB_1 receptors, whereas nabiximols is a cannabis extract containing an almost 1:1 ratio of THC to CBD.[44,45] Both of these therapies in the context of cannabis substitution (and THC/CBD dominance) were considered when creating this practice advisory and will be reviewed later in these recommendations.

Defining significant cannabis consumption in the perioperative period

Recommendations

Significant cannabis consumption (screening quantities to prompt further discussion of perioperative management) for these recommendations would be described as being greater than (i) 1.5 g day^{-1} of inhaled cannabis, (ii) 300 mg day^{-1} CBD oil, and (iii) 20 mg day^{-1} THC oil. The panel also acknowledged that consuming a cannabis product more than two to three times per day with an unknown CBD or THC content should

also be considered as significant when making cannabis-related perioperative care decisions.

Evidence and rationale for recommendations

Determining a 'significant', 'high', or 'low' cannabis dose is extremely difficult when the many different variables amongst patients, products, and therapeutic cannabis indications are acknowledged. When considering dosage, it was useful for the expert panel to consider conditions that treatment with cannabis and cannabinoid medications (nabilone, nabiximols, dronabinol, and CBD) are more widely accepted. These conditions included CWS, chronic pain, Lennox–Gastaut syndrome, and chemotherapy-induced nausea and vomiting. Cannabis dosages used for task performance studies, such as driving, were also considered.[14,32–34,46–58] Because of the variability of many of these dosages, the experience of the expert panel finalised what doses these recommendations would consider being significant in the perioperative period.

Preoperative period consensus recommendations

Preoperative assessment and planning

Recommendations. Routine screening (inquiry) of patients within the preoperative clinic setting to identify cannabis consumption before surgery is recommended. Estimating daily cannabis intake and the duration of cannabis use is also appropriate and recommended. The method of consuming cannabis should also be identified. For those patients consuming cannabis more than once per day, it is appropriate to screen for cannabis use disorder (CUD). When planning anaesthesia for patients consuming cannabis, extra consideration should be given to regional anaesthesia as long as it is otherwise not contraindicated. On the day of surgery, it is important to record the time cannabis was last consumed.

Evidence and rationale for recommendations. Patient perioperative cannabis consumption may affect perioperative outcomes, and therefore, it is important to identify and quantify it. The expert panel agreed that for perioperative planning and assessment, grams per day is a simple method to quantify dried cannabis consumption and would be used for the recommendations presented here.

Cannabis products are sold accounting for mass of dried product (grams) and CBD and THC content. CBD and THC content in dried cannabis is usually expressed as a percentage of the product's mass (%) or as milligrams of CBD or THC per gram of product (mg g^{-1}). CBD and THC in cannabis oils and edibles are usually presented in milligrams.[59] Using this information, our recommendations suggest that cannabis product consumption be quantified in grams per day (g day^{-1}), or as milligrams of CBD or THC per day (CBD mg day^{-1} or THC mg day^{-1}).

Several validated screening tools are available for CUD, such as the revised Cannabis Use Disorder Identification Test.[60] The expert panel recognised that daily cannabis consumption may warrant screening for CUD and possible referral to an addiction medicine or psychiatry service.

Preoperative cannabis weaning

Recommendations

Provided there are more than 7 days before surgery, cannabis tapering or cessation could be considered if a patient is consuming more than (i) 1.5 g day^{-1} of smoked cannabis, (ii) 300 mg day^{-1} CBD oil, and (iii) 20 mg day^{-1} THC oil. Patients consuming a cannabis product more than two to three times per day with an unknown CBD or THC content should also be considered for weaning. These patients should not be considered for cannabis weaning or cessation 24 h or less before surgery. These recommendations are summarised in Fig. 2.

A goal of reducing consumption to less than the inclusion doses for weaning (as mentioned in the Recommendations section above) could be considered as a reasonable initial target. For example, if a patient consumes 2 g day^{-1} of inhaled cannabis, weaning to 1.5 g day^{-1} is a sensible initial target. Preoperative weaning to lower doses or cessation can be considered given sufficient time and if the patient remains motivated to do so. Patients consuming cannabis products of unknown CBD/THC content should be encouraged to start a cannabis product of a known CBD/THC content and re-evaluated. Weaning should be a collaborative effort with the rate of the cannabis taper guided by the patient's tolerance of their dose reduction.

Surgery should not be delayed for re-evaluation or weaning. Very high doses of cannabis or frequencies of cannabis use (two to three times the doses and frequencies listed previously for consideration of weaning) should prompt discussion amongst the perioperative care team of the potential benefits of a specialist review (e.g. pain medicine, addiction medicine, or psychiatry) in the preoperative period.

Evidence and rationale for recommendations

The expert panel arrived at no consensus regarding recommendations for tapering cannabis 1–6 days before surgery. The panel agreed that weaning 7 or more days before surgery could be done safely and be of possible benefit to patients. The panel also agreed that reducing cannabis consumption may decrease adverse outcomes possibly associated with cannabis use and analgesic tolerance, CWS, uncertainty with EEG-derived depth of anaesthesia monitoring (e.g. bispectral index [BIS] or entropy monitoring), and PONV. The panel was concerned that tapering or cessation of cannabis within a day of surgery may add an increased risk of CWS and possibly exacerbate associated underlying medical conditions (e.g. chronic pain and anxiety).[61] Lastly, the panel agreed that if clinician-authorised cannabis was to be weaned, the authorising healthcare professional should be included in the weaning or cessation discussion.

Human and animal studies have demonstrated low potential for developing CWS with CBD administration.[62,63] Aggressive weaning of CBD products should be done with expert guidance, as CWS may still occur and CBD may mask some of the adverse effects associated with THC.[49] Weaning CBD consumption while maintaining THC consumption is not encouraged, as the adverse effects of THC use could be exacerbated.

The panel agreed that there was a glaring paucity of evidence regarding cannabis weaning targets and perioperative outcomes. Their recommendations of which patients may

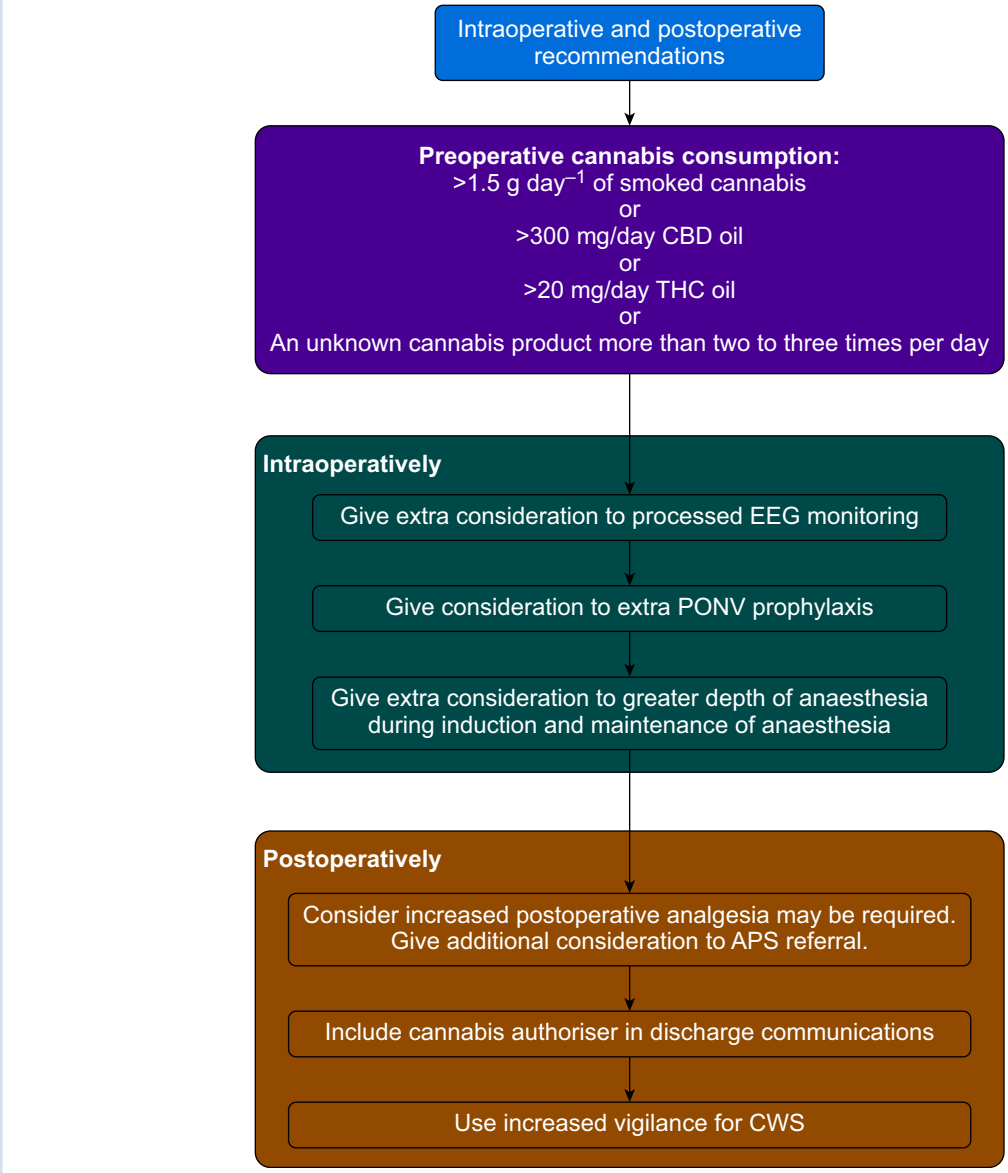

Fig 3. Summary of intraoperative and postoperative recommendations for preoperative patients presenting for surgery. Examples of processed electroencephalography (EEG) monitoring include bispectral analysis and entropy. APS, acute pain service; CWS, cannabis withdrawal syndrome; PONV, postoperative nausea and vomiting. CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol.

benefit from weaning and weaning targets were primarily based on the scarce medical evidence available and the collective clinical experience of the expert panel.

Intraoperative period consensus recommendations

Contraindications to analgesia

Recommendations. Patient perioperative cannabis use is not a contraindication to (i) NSAIDs, (ii) opioids, (iii) i.v. or regional local anaesthetic, (iv) ketamine, (v) gabapentin or pregabalin, (vi) dexmedetomidine, and (vii) acetaminophen/paracetamol.

Evidence and rationale for recommendations. No contraindications to the perioperative administration of the analgesic agents described previously were evident. There may be interactions between the endocannabinoid system and some of the analgesic agents described. The clinical significance of this in the perioperative period is uncertain.

Cytochrome P-450 (CYP-450) enzymes are the primary metabolisers of exogenous CBD and THC, and smoked cannabis induces CYP1A2-mediated theophylline metabolism.[64,65] Cannabidiol may also inhibit CYP2C19 and CYP3A4 of the P-450 system.[66] Cannabinoids may possibly prolong the half-lives and increase the effects of drugs, such as acetaminophen, warfarin, some benzodiazepines, and some opioids, because of their effects on the CYP-450 system.[2,67] Studies of CBD, THC, and P-450 induction and inhibition seem to describe a small risk of significant drug interactions

with drugs metabolised by these systems.[2,64] However, current evidence of cannabis and analgesia interaction is limited and more research is needed.

Cannabinoids (THC and CBD) have been demonstrated to inhibit cyclooxygenase (COX) enzymes in *in vitro* and animal studies.[68] Animal studies have suggested that chronic THC use in humans may cause a reduced response to some NSAIDs, such as celecoxib, ketorolac, indomethacin, and Aspirin.[69] However, although there is evidence that any NSAID that influences the COX-2 system can affect the endogenous cannabinoid system, there is no clear evidence of antagonism, synergy, or additive effects of cannabinoids and NSAIDs, especially in humans.[68,70]

The expert panel agreed that local anaesthetics and regional anaesthetic techniques are not contraindicated and may warrant additional consideration because of the uncertainties around long-term cannabis use and its effects on the respiratory system and CNS, and uncertainties regarding depth of anaesthesia, depth of anaesthesia monitoring, and analgesic tolerance.[32,71]

PONV prophylaxis

Recommendation

Considered additional PONV prophylaxis for patients is consuming more than (i) 1.5 g day^{-1} of smoked cannabis, (ii) 300 mg day^{-1} CBD oil, and (iii) 20 mg day^{-1} THC oil. Patients consuming a cannabis product more than two to three times per day with an unknown CBD or THC content should also be considered for additional PONV prophylaxis.

These recommendations can be found in Fig. 3.

Evidence and rationale for recommendations

Cannabinoids are acknowledged as a useful adjunct in the treatment of chemotherapy-induced nausea and vomiting, but have been trialled less successfully in the prevention of PONV.[72–74]

Some cannabis-consuming patients develop severe refractory cyclic nausea and vomiting attributed to cannabinoid hyperemesis syndrome (CHS). CHS may be linked to cannabis-influenced dysfunction of central and enteric CB_1 receptors.[75] Patients can also develop nausea and stomach pain associated with CWS. CWS begins presenting in cannabis-consuming patients after a period of 48 h of abstinence from cannabis.[3,49]

Anti-emetic therapy is generally poorly effective in patients suffering from CHS, although some success has been reported with butyrophenone (e.g. haloperidol and droperidol) treatment. Destination therapy for persons with CHS is abstinence from cannabis. Care for acute CWS is supportive with administration of gabapentin, nabilone, nabiximols, or dronabinol possibly being beneficial.[3,49] PONV in patients with CWS or CHS could contribute to morbidity and diagnostic uncertainty regarding other causes of nausea and vomiting.

The expert panel acknowledged the limited evidence available supporting this recommendation, but determined that the administration of additional PONV prophylaxis to patients who consumed significant quantities of cannabis was of potential benefit and unlikely to result in harm.

Anaesthetic depth and depth of anaesthesia monitoring

Recommendations

For patients consuming more than (i) 1.5 g day^{-1} of inhaled cannabis, (ii) 300 mg day^{-1} CBD oil, and (iii) 20 mg day^{-1} THC oil, or (iv) patients consuming a cannabis product more than two to three times per day with an unknown CBD or THC content, it should be considered that the patient may require additional anaesthetic to achieve an adequate depth of anaesthesia during the induction and maintenance of anaesthesia. Additional consideration towards using processed depth of anaesthesia EEG monitoring should also be considered for these patients.

These recommendations can be found in Fig. 3.

Evidence and rationale for recommendations

Research has suggested that patients consuming cannabis may require more anaesthetic to achieve adequate depth of anaesthesia and may display tolerance to volatile anaesthetic agents propofol and opioids.[2,3,71] Human and animal studies have had some inconsistent findings. Animal studies of the acute administration of cannabinoids to dogs, mice, and rabbits results in lower anaesthetic requirement and prolonged anaesthesia for these animals.[2,71] However, human trials have demonstrated increased propofol and volatile agents being required to achieve BIS readings less than 60 in self-reported cannabis smokers and in volunteers administered nabiximols.[2,3]

Being cognisant that patients consuming cannabis could have greater anaesthetic requirements, it is sensible to have additional anaesthetic medication available for induction and maintenance and to use depth of anaesthesia monitoring. The expert panel agreed that acute cannabis intoxication and chronicity of cannabis use be considered when planning anaesthesia, as acutely intoxicated ('high') patients may require less anaesthetic (and have prolonged emergence) and that chronic cannabis use may predispose to greater anaesthetic tolerance.

Postoperative period consensus recommendations

Postoperative analgesia

Recommendations. It is appropriate to consider that postoperative analgesic requirements may be higher in patients consuming greater than (i) 1.5 g day^{-1} inhaled cannabis, (ii) 300 mg day^{-1} CBD-dominant oil, and (iii) 20 mg day^{-1} THC-dominant cannabis oil. Patients consuming a cannabis product with an unknown CBD or THC content more than two to three times per day should also be considered to have potentially greater postoperative analgesic requirements.

These recommendations can be found in Fig. 3.

Evidence and rationale for recommendations. Expert clinician experience and a few studies suggest that patients that habitually consume cannabis have greater postoperative pain.[76–78] Some preclinical studies have suggested that there may be a synergistic effect between opioids and cannabinoids, and that THC-associated analgesia may be partially mediated by delta- and kappa-opioid receptors. However, evidence supporting cannabis and the treatment of postoperative pain is lacking.[2,3]

As discussed previously in the 'Intraoperative period consensus recommendations' sections 'Contraindications to analgesia' and 'Anaesthetic depth and depth of anaesthesia monitoring', cannabis users may possibly have tolerance to the effects of certain NSAIDs and opioids. Additionally, cannabinoids may affect the metabolism of some analgesics, such as certain opioids, acetaminophen, and benzodiazepines. However, robust evidence of the significance of these effects in humans is lacking.

The expert panel also recognised the importance of considering other non-cannabis-related causes of increased postoperative pain. They acknowledged that withdrawal from an analgesic or anxiolytic cannabis regime might theoretically contribute to increased postoperative pain perception. It was further recognised that CWS and the removal of cannabis as an external locus of control (a chemical coping mechanism) could theoretically contribute to increased distress and decreased tolerance of pain. The expert panel agreed that patient referral to an acute pain service should be done on a case-by-case basis with cannabis use as a possible additional consideration in the referral process.

Monitoring for cannabis withdrawal

Recommendations

It is appropriate to consider that CWS symptoms may occur in postoperative patients who consume greater than (i) 1.5 g day^{-1} inhaled cannabis, (ii) 300 mg day^{-1} CBD-dominant oil, and (iii) 20 mg day^{-1} THC-dominant cannabis oil. It should also be considered that patients consuming a cannabis product with an unknown CBD or THC content more than two to three times per day might also develop CWS symptoms in the postoperative period. These recommendations can be found in Fig. 3.

The symptoms of CWS are unlikely to occur in patients consuming 300 mg day^{-1} (one cigarette), or less, of smoked CBD-dominant cannabis.

Evidence and rationale for recommendations

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM V) criteria for the diagnosis of CWS include the abrupt cessation of prolonged or heavy cannabis use accompanied by three or more symptoms of the following: irritability or anger, anxiety, insomnia, decreased appetite, restlessness, altered mood, and a physical symptom causing significant discomfort (such as abdominal pain, tremors, sweating, fever, chill, or headache). The symptoms of CWS occur 24–72 h after cannabis cessation peaking in the first week and lasting 1–2 weeks. 'Heavy cannabis use' is not defined in the diagnostic criteria of the DSM V.[79] Regular cannabis use is associated with a downregulation and desensitisation of cortical and subcortical CB_1 receptors, which begin to reverse after 48 h of abstinence before returning to normal in approximately 4 weeks.[49] Cannabis users with opioid dependence are less likely to experience CWS, and naltrexone administration has been observed to reduce the self-administration of cannabis and related positive subjective effects in active cannabis users.[49]

CWS could potentially contribute to morbidity in the postoperative period. Vigilance for CWS symptoms should be included in relevant perioperative care plans. This is especially true if a patient's daily cannabis intake is not replaced or continued in the postoperative period. Suspected CWS should provoke referral to a psychiatry service. Tools available for assessing CWS include the Cannabis Withdrawal Scale.[45] Admission for elective surgery may also provide an opportune time for cannabis education, and patients could be involved in self-monitoring for CWS.

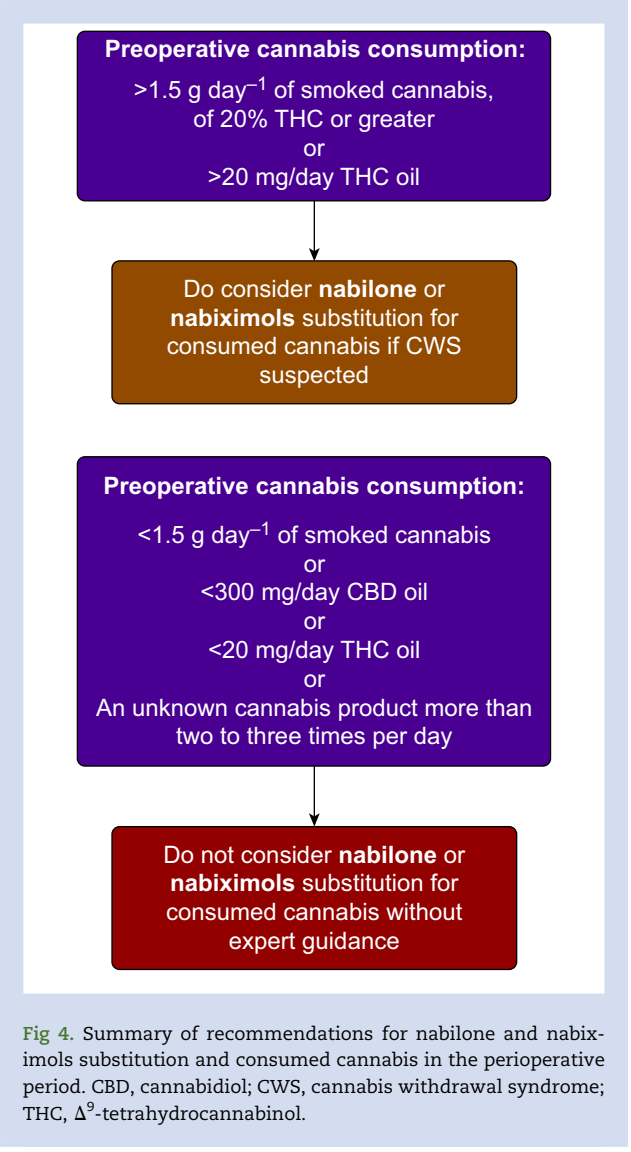

Fig 4. Summary of recommendations for nabilone and nabiximols substitution and consumed cannabis in the perioperative period. CBD, cannabidiol; CWS, cannabis withdrawal syndrome; THC, Δ^9-tetrahydrocannabinol.

Nabilone and nabiximols administration

Recommendations

There was no consensus amongst the expert panel as to whether nabilone and nabiximols are an appropriate substitution for inhaled cannabis, cannabis oils, and cannabis edibles when weaning from cannabis in the preoperative period in patients not diagnosed with CWS.

It is most appropriate to consider nabilone or nabiximols substitution for a patient's previously administered inhaled cannabis or cannabis oil if they are having CWS symptoms in the postoperative period.

It is not appropriate to supplement or substitute nabilone or nabiximols for inhaled cannabis or cannabis oil in the postoperative period for patients regularly consuming less

than (i) 1.5 g day^{-1} smoked cannabis, (ii) 300 mg day^{-1} CBD-dominant oil, and (iii) 20 mg day^{-1} THC-dominant cannabis oil. Nabilone or nabiximols supplementation/substitution is also not appropriate for patients consuming a cannabis product with an unknown CBD or THC content less than two to three times per day.

It is appropriate to consider nabilone substitution for patients with CWS symptoms in the postoperative period if preoperatively they were consuming more than 1.5 g day^{-1} of high-THC (>20%) smoked cannabis or more than 20 mg day^{-1} of THC oil.

Patients with suspected CWS should be referred to psychiatry or addiction medicine care providers. These clinicians can help initiate or guide the treatment of CWS with nabilone or nabiximols in perioperative patients, and explore other treatment options for CWS.

These recommendations are summarised in Fig. 4.

Evidence and rationale for recommendations

Nabilone is a synthetic analogue of Δ^9-THC. It has anxiolytic, anti-emetic, and analgesic properties. It is associated with adverse effects, such as drowsiness, dizziness, vertigo, postural hypotension, and dry mouth. It has good oral bioavailability (96%) and an elimination half-life of 2 h.[44,80] Nabiximols is a medication derived from *Cannabis sativa* plants containing the plant CBD, THC, and some of its terpenoids. It is administered via a buccal spray with absorption through the buccal mucosa.[45]

There is evidence that nabilone and nabiximols can reduce the symptoms of CWS and reduce cannabis craving in persons with CUD, akin to nicotine replacement in tobacco smokers. However, the most appropriate dosages for these interventions are not known.[57,81,82] cannabis withdrawal syndrome might cause further harm in those perioperative patients receiving treatment for CUD, as CWS is a major determinant of relapse.[45]

The expert panel agreed that these products were not suitable for patients consuming cannabis products with minimal THC content. The panel also agreed that if these products are used as a substitution for cannabis therapy, expert guidance in the form of clinicians familiar with prescribing or authorising cannabis, nabilone, or nabiximols should be sought (e.g. pain specialists, psychiatrists, and addiction medicine specialists). The expert panel did not come to consensus regarding the dosages of these medications to be used when substituting, but agreed that the already accepted dosages for these medications should not be exceeded.

Consumption of inhaled cannabis, cannabis oil, and ingested cannabis while hospitalised

Recommendations

It may be appropriate to consider continued administration of cannabis oil or ingested cannabis while admitted to a general post-surgical ward in keeping with evidence-based care, institutional regulations, and national legislation. It is not appropriate to consume inhaled or vaped cannabis on any hospital ward.

Evidence and rationale for recommendations

In a study of law enforcement officers working at two outdoor concerts exposed to smoked cannabis, THC and its metabolites were detectible in personal air samples taken from around the officers and were detectible in 34% of the 29 participating officers' urine, but were not found in any of their blood samples. Officers in the study also complained of minor symptoms they attributed to cannabis exposure.[83] Studies, such as this, demonstrate that patients consuming inhaled cannabis may have a localised effect on other nearby personnel and patients. It might be assumed that smoked cannabis, like smoked tobacco, may be a hospital fire hazard.[84]

The expert panel agreed that cannabis oils and edibles might be appropriate on a general post-surgical ward, such as when continuing an appropriate therapeutic cannabis regime or to avoid CWS. The panel did not reach consensus regarding the administration of cannabis oils and edibles on ICUs, high-dependency units, or step-down units.

Post-discharge contact with cannabis authoriser

Recommendations

Perioperative care providers should include a patient's cannabis authoriser (if an authoriser exists) in discharge planning (review), if they feel it is appropriate to do so. This is especially true for patients consuming greater than (i) 1.5 g day^{-1} smoked cannabis, (ii) 300 mg day^{-1} CBD-dominant oil, and (iii) 20 mg day^{-1} THC-dominant cannabis oil, or if a post-surgical patient's authorised cannabis dose has been stopped, changed, or substituted (e.g. with nabilone or nabiximols).

Evidence and rationale for recommendations

Communication amongst hospital healthcare providers has an impact on post-surgical outcomes, including hospital readmission.[85] By extension, the quality of communication between in-hospital healthcare providers and outpatient healthcare providers also impacts post-discharge outcomes.[86] cannabis authorisers may be general practitioners, nurse practitioners, oncologists, and pain physicians. As a participant in patient post-surgical care, cannabis authorisers should be included in discharge communications.

The expert panel agreed that these recommendations were most applicable to patients on higher doses of cannabis and for those previously on high doses of cannabis that had been weaned or had substitutions for their previous cannabis dosages. Potentially beneficial information in the discharge communication might include changes to cannabis therapy, suggestions for alternative therapies, or other clinical observations (e.g. CWS, suspected CUD, and failure to meet therapeutic goals) requiring follow-up by the cannabis authoriser.

Additional consensus recommendations

Ambulatory surgery

Recommendations. The recommendations presented in this document are appropriate for patients undergoing ambulatory surgery. Recreational cannabis use should not exempt patients from having ambulatory surgery. If the patient is consuming a clinician-authorised cannabis product, additional dialogue with the cannabis authoriser should be sought before modifying or discontinuing a patient's usual cannabis regime before ambulatory surgery.

Evidence and rationale for recommendations. The expert panel agreed that these guidelines are appropriate for ambulatory surgery. There is a paucity of evidence on how cannabis use affects ambulatory surgery outcomes. Isolated cannabis use, without other patient risk factors of poor ambulatory surgery outcomes (e.g. poor functional status), is not generally considered a contraindication to receiving ambulatory surgery.[87] Standard metrics for safe discharge after ambulatory surgery, such as stable vital signs, adequate analgesia, a return to preoperative cognitive function, and the ability to stand and walk unassisted, should still be utilised.[88] There was consensus amongst the expert panel at the survey Round 2 meeting (Fig. 1) that there was insufficient evidence for cannabis use to be a contraindication for ambulatory surgery and that the care recommendations presented here are relevant for these patients.

Review and quality assurance

A two-step process was used to create a set of practice recommendations for surgical patients consuming cannabis. The draft set of recommendations derived from this process were recirculated to the expert panel and to independent reviewers with relevant experience—a surgeon, a nurse practitioner, and two patients. Any reviewer comments were explicitly addressed before the final recommendations document. Specific comments that were addressed are detailed in the 'Rationale for recommendations' sections of this document.

Limitations and future direction

The heterogeneity of cannabis formulations and products makes concise perioperative recommendations challenging. This is compounded by uncertainty surrounding the significance of cannabis dosing and dosing equivalency between cannabis products. Varied product legality and the frequent off-label use of cannabis products also contribute to gaps in research and knowledge regarding cannabis. A paucity of RCTs examining patients consuming cannabis in the perioperative period necessitates more research to guide care providers. Our panel did not develop quality metrics to evaluate the implementation of the recommendations presented here. Further work is needed to track perioperative outcomes of cannabis users presenting for surgery. Ultimately, as new and existing cannabis preparations are used and the evidence regarding them grows, these guidelines will require review and regular updating.

Authors' contributions

Conception and design of the Delphi methodology and protocol underlying the clinical recommendations development process: AM-B, KL, AG, HC
Data collection, analysis, and summarisation: AM-B, IK, BS, RS
Writing of protocol: AM-B, KL, AG, YK, HC
Writing of paper: AM-B, KL, AG, MJB, PF-S, SH, YK, KK, BLF, NJL, JL, HM, JN, AR, L-AR, HS, ASi, ASu, RT, SY, HC
Independent reviewers: TSL, SSJL, MG, PC
Expert panel: MJB, PF-S, SH, YK, KK, BLF, NJL, SY, JL, HM, JN, AR, L-AR, HS, ASi, ASu, RT

Declarations of interest

KL is a co-principal investigator of an observational study of medical cannabis funded by Shoppers Drug Mart (Canada). AR is currently employed as Chief Medical Officer for PureForm Global, in which she owns stocks. L-AR has been a member of the Scientific Advisory Board for Nycomed (Denmark) and the Omeros Corporation (USA). He has also conducted studies supported by grants from Ferring Pharmaceuticals (Denmark). BLF has received funding and research-related donations from Canopy, Aurora, Pfizer, Bioprojet, BrainsWay, Aphria, ACS, Alkermes, and GW Pharmaceuticals. His research is supported by a clinician scientist award from the Department of Family and Community Medicine of the University of Toronto. HS is an affiliated member of the Michael G. DeGroote Centre for Medicinal Cannabis Research and is involved in several studies regarding post-surgical cannabis consumption, with one study being funded by the Canadian Institutes of Health Research. SY has received honoraria payment from Canopy Health for her lectures and work on a clinical study advisory board. NJL has received Merck Sharp & Dohme income for non-cannabis-related speaking engagements and Vifor Pharma-sponsored non-cannabis-related training. PF-S has held consultancy and educational meetings with Spectrum Therapeutics, Grunenthal, and Kyowa Kirin in addition to authoring cannabis-related reviews and the peripheral μ-opioid receptor antagonist guidelines. He has also done consultancies for Kingdom Therapeutics and CBD Science. RT is a member of the Tilray, Canopy Growth, Allergan, Lundbeck, and Indivior advisory boards; has received unrestricted education grants from Canopy Growth, Otsuka, Pfizer, Purdue (Pickering, Canada), Shire, Jansen, Sunovion, Lundbeck, and Allergan; and has received speaking honoraria regarding opioids, pain medicine, or addiction from Indivior, Pfizer, Otsuka, Allergan, and Lundbeck. SH has received personal fees associated with Medoc Limited and Rafa Limited, and has been involved in research supported by Disarm Therapeutics. HC was a previous advisor for Scientus Pharma (Whitby, Canada), and has been involved with advisory boards for Canopy Growth (Smiths Falls, Canada), AbbVie Corp. (Dorval, Canada), and Medical Cannabis by Shoppers Drug Mart (Toronto, Canada). The other authors declared no conflicts of interest regarding the creation of the recommendations.

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Appendix A. Supplementary data

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