Daring discourse – yes: practical considerations for cannabis use in the perioperative setting

Hance Clarke ,[1,2,3] Priodarshi Roychoudhury,[1,2] Karim S Ladha,[1,3,4] Timothy Leroux,[3,5] Joseph Fiorellino,[1,2,3] Alexander Huang,[1,2,3] Lakshmi P Kotra[3,6]

While cannabis has been consumed for thousands of years, the medical-legal landscape surrounding its use has dramatically evolved over the past decade. Canada created a legislative framework for physicians to authorize medical cannabis in 2013[1] and followed with the creation of the Cannabis Act (Bill C-45), which enabled the recreational consumption of cannabis in 2018.[2] The majority of US States have passed legislation authorizing medical cannabis[3 4] and 11 states have approved[4 5] recreational cannabis use despite the fact that at the federal level, cannabis is deemed as having no currently accepted medical use.[6] Outside of North America, the European Union recently mandated that all European citizens should have access to cannabis products within the next 3–5 years.[7]

Given the increasing acceptance of cannabis on a societal and legal level, its use by patients is not something that physicians and academics should continue to fight. Indeed, this is a losing battle that will only cause harm to our patients. Instead, we must focus our efforts on creating a safe framework within the context of society's new stance on a substance that has been prohibited for decades. There are undoubtedly negative consequences from consuming high-dose Δ^9-tetrahydrocannabinol (THC) products over a long period of time.[8] This fact, in our minds, is not debatable. However, this should not preclude us from seeking and using other forms of the plant that can potentially benefit certain disease processes.

We commend our colleagues on a nicely conducted and well-written systematic review on the use of cannabinoids for acute pain,[9] a question that is important for perioperative physicians. At the same time though, we are concerned about the relevance of this review and others to current clinical practice based on the inherent bias in the literature. In recent years, cannabis has been reviewed for the treatment of acute pain,[10] anxiety,[11 12] opioid weaning,[13] use in sport,[14] anticraving[15] and the list goes on. A quick PubMed search will reveal that over 250 systematic reviews examining various therapeutic uses for cannabis have been published over the past 5 years. Most of these systematic reviews conclude that there is an absence of, or only weak evidence to support the use of cannabis for the clinical indication being studied. The systematic reviews to date lack the inclusion of trials that use similar products being consumed by today's patient population, most trials tend to be short term with small samples sizes, and often have significant biases. If the research is conducted by a psychiatry lead research group, undoubtedly the group concludes the risk/benefit profile lands on the harms of cannabis outweighing any potential benefit of use.[16]

It is time that the academic world acknowledges the facts: 70%–80% of the research done on cannabis and funded by the Canadian Institutes of Health Research and the National Institutes of Health over the past decades have been on the harms associated with consuming THC in the adolescent and developing brains of humans and in various animal models.[17] There is little debate in the clinical world that cannabis use disorder exists,[8] that consuming cannabis during pregnancy is detrimental to the fetus[18] and that early onset schizophrenia can be induced by high-dose cannabis consumption,[19 20] with African-American males being particularly vulnerable to increases in depressive symptoms.[21] However, there is a lack of understanding by the physician and academic community with respect to the types of products available and typically authorized by physicians in todays' marketplace.

First and foremost, 'cannabis' and THC are two different substances. THC is one of the many constituents of cannabis, and although it is the most potent psychoactive substance in it, the THC concentration in cannabis products can vary significantly. Cannabis constituents, THC and cannabidiol (CBD) are among the most abundant and well-studied cannabinoids. In addition to THC and CBD, cannabis contains hundreds of organic compounds as well as, terpenes and flavonoids all of which exert their effects on the endocannabinoid (eCB) system.[22] THC is a cannabinoid receptor type 1 (CB1) agonist and a weak partial agonist at the cannabinoid receptor type 2 (CB2). CBD is not an agonist at either CB1 or CB2, it is a negative allosteric inhibitor[23] of the cannabinoid receptor and has been shown to reduce the negative effects of THC in human studies.[24] The mechanism of CBD is not well understood, it may increase eCB signaling as it has been found to increase anandamide levels. It can also increase serotonin receptor 1A activity, enhance adenosine signaling and can activate transient receptor potential cation channel subfamily V member 1 (TRPV-1) receptors, which detects thermal and nociceptive stimuli.[25] CB1 receptors are expressed throughout the brain and spinal cord in key areas responsible for pain transmission and modulation[26] as well as the gastrointestinal tract. The CB1 receptors in pain pathways offer targets for pharmacological intervention. CB2 receptors are expressed on immune tissues and cells such as thymus, tonsils, lymphocytes and macrophages. Based on the National Academies of Science review, there is evidence that cannabis products has conclusive evidence for use in the treatment for chronic pain in adults, as an anti-emetic in the treatment of chemotherapy-induced nausea and vomiting and for improving patient-reported multiple sclerosis spasticity symptoms.[27] Furthermore, there is moderate evidence for the use of cannabis products in individuals with sleep disturbance associated with obstructive sleep apnea syndrome and fibromyalgia.[27]

Physicians authorizing cannabis-based oils for medical purposes tend to initiate patients on low THC, and higher CBD strains. It is not uncommon for patients seeking medical cannabis to be started

[1]Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Ontario, Canada
[2]Anesthesia and Pain Management, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada
[3]Centre for Cannabinoid Therapeutics, University Health Network, Toronto, Ontario, Canada
[4]Department of Anesthesia, St Michael's Hospital, Toronto, Ontario, Canada
[5]The Arthritis Program, University Health Network, Toronto, Ontario, Canada
[6]Department of Pharmaceutical Sciences, University Health Network, Toronto, Ontario, Canada

Correspondence to Dr Hance Clarke, Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON M5G 2C4, Canada; hance.clarke@uhn.ca

on CBD-only oil for multiple conditions (epilepsy, social anxiety, inflammatory conditions, chronic back pain) or 1:1 concentrations with THC then being titrated into the regimen as needed for symptom improvement. Patients using cannabis for recreational purposes typically consume high-dose THC products. Epidiolex, a CBD liquid, was approved for the treatment of pediatric epilepsy conditions: Lennox-Gastault and Dravet syndromes in the USA and recently the UK.[28] Given the wide heterogeneity in products and indications, it is becoming increasingly clear that we urgently need guidelines for treating patients consuming cannabis in the perioperative setting. Unfortunately, systematic reviews of clinical trials with cannabinoids, including the current one by Abdallah *et al*,[9] do not use products available for clinical authorization or to recreational consumers.

We cannot use data from nabiximols (purified 1:1 CBD:THC plant extract) and nabilone (a synthetic cannabinoid derivative that mimics THC) exclusively for perioperative guidelines because they are different to the plant-based extracts commonly authorized by physicians. The manuscript by Abdallah *et al*[9] involves a wide range of cannabinoids, with varying chemical compositions, duration of action, the majority of which are not even clinically accessible to patients. Within the current review, Guillard *et al*[29] and Jain *et al*[30] used levonantradol which is a synthetic cannabinoid analog of dronabinol developed by Pfizer in the 1980s. This is not accessible these days and is preferred only for research into the potential therapeutic applications of cannabinoids.[31 32] A recently published retrospective matched cohort study conducted at a community-based trauma center in Colorado found that patients consuming high-dose opioids that were given dronabinol consumed less opioids than the matched cohort.[33] Let us take a closer look at a few of the studies that were included in the systematic review by Abdallah *et al*: (1) Guillard *et al* reported significantly better analgesic effects with 1 mg/kg of intramuscular pethidine compared with 1 mg, 2 mg doses of intramuscular levonantradol[29]; (2) Buggy *et al* in a randomized double-blind, placebo-controlled trial found that a single dose of 5 mg Δ^9-THC or placebo on the second postoperative day, when postoperative patient-controlled analgesia was discontinued had no effect on pain intensity at 6 hours on movement or at rest and had no effect on time to rescue analgesia for women undergoing elective abdominal hysterectomy[34]; (3) Levin *et al* reported no differences in pain scores, opioid consumption or reported drug side effects following administration of a single dose of 0.5 mg of nabilone or placebo prior to surgery, it is unfortunate that the Levin study examined a single small dose of nabilone.[35] The methodological design of each study could be criticized at a granular level and each had its own limitations but this is not the point of our discourse.

When we consider today's clinical environment, the conclusions by Abdallah *et al* are completely accurate: more research is needed. However, with this recommendation should come an important caveat, more research but no more systematic reviews. Comparing the current systematic review with a recent systematic review focused on acute pain,[10] there unfortunately was little that was added to help guide physicians in the perioperative time period regarding patients consuming cannabis. There is a lack of understanding regarding cannabis use and the potential consequences to the patient and anesthesiologist in the perioperative environment. Regardless of our willingness to accept cannabis as a modern medicine, patients are using cannabis products on a daily basis for legitimate health concerns. As such, we propose some considerations that can help physicians appropriately care for patients using cannabis:

1. *The potential for cannabis withdrawal:* for the safety of patients in the perioperative time period, we would urge our anesthesia colleagues to push for hospital-based policies in order to ensure that the patients' 'legal' authorization of their cannabis can continue into the perioperative period. There are published cases of adverse events including instances of withdrawal and harms in patients that have presented for surgery with abrupt discontinuation of their cannabis medications.[36 37] A national study of patients with a diagnosed cannabis use disorder presenting for surgery, conducted by members of our group, revealed a 2.8 increased OR of having a myocardial infarction.[38] One approach to mitigate these withdrawal problems is to allow patients to continue to consume their non-vaporized cannabis products (ie, oils or edibles) during their hospitalization period. A margin of safety can be ensured with measures such as the storage of these products in a lockbox accessible only by the patient and their care team, and by clearly documenting administration on their medication administration record. When this is not possible (such as the case of vaporized cannabis), other options should be considered. Our acute pain services routinely uses nabilone at a dose of 1–2 mg orally twice daily/thrice daily with good efficacy in patients consuming high doses of opioids or are recreational high-dose THC users on our respective acute pain services. Abrupt cessation of THC can precipitate significant withdrawal symptoms on postoperative day 0–3. Therefore, continuing access to cannabis throughout the perioperative setting may be necessary to reduce harms postoperatively for some.
2. *Remove the stigma associated with considering all cannabis products as 'weed':* the negative stigma associated with 'marijuana' use is entrenched in society. It is important to understand that patients currently consuming oil-based cannabis products (ie, oil extracts and capsules) authorized for a medical condition often begin with doses as low as 1–3 mg. This dose is several-fold lower than those consuming inhaled high-dose THC products (80–100 mg or greater). Unfortunately, the regulatory framework supporting the cannabis industry is lacking, and criticisms regarding the ability to produce a reliable and consistent product remains a valid concern. The current cannabis products are plant-derived with variable chemical compositions, thus commercial products invariably carry these variations to the point of sale. Given that none of these substances is regulated similar to other prescribed drugs (with the exception of Epidiolex), there is often significant batch-to-batch variation. We must routinely question patients within the preoperative clinic setting as we would do with any other medication to determine which of the one in five patients presenting for surgery are consuming a cannabis product.[39] We must also determine the type of product and the amount of the specific cannabinoid (ie, CBD and/or THC) being consumed by the patient in order to appropriately care for them.
3. *Education about the eCB system and cannabis products being consumed by patients:* it is imperative anesthesia providers educate themselves about their local cannabis industry and the products that are currently being consumed by patients presenting to the operating room. In a recent study, cannabis products showed variations in chemical composition simply based on the processing methods used by dif-

ferent companies.[40 41] These variations have a direct impact on the potency of cannabis products,[40] affecting when a patient consumes these products, and associated variations in receptor responses, pharmacokinetics and any co-medication-associated toxicities. In fact, cannabinoid receptor responses to THC and various cannabis-derived commercial products including those with high-dose THC content, have been found to be several-fold different in Canada.[42 43] As we move forward, products used for evidence-based trials need to meet much higher regulatory standards. We highlight the need for producing consistent and reliable medical cannabis extracts and their derivatives. Improved understanding of these products could lead to higher quality decision making in the perioperative setting.

4. *Consider the potential interactions on anesthetic care associated with the use of plant-based cannabis products*: there was a recent review published citing the potential pharmacological and anesthetic considerations associated with cannabis use.[44] This review extrapolated data from animal models which looked at cardiovascular, respiratory, cerebrovascular and pharmacological interactions with anesthetic care. A recent study examined the impact of cannabis use on perioperative care and confirmed that human data to date are markedly heterogeneous and sparse at best.[45] Over the next 5–10 years, research into the current effects of plant-based cannabis products on human physiology while under general anesthesia and perioperative care will be extremely important. Most of the research to date has been focused on the CB-1 receptors given THC is the product that continues to be highlighted to increase the risk of harm[46] and compromise patient safety. CBD appears to have an immunomodulatory and CNS depressant effect.[47] CBD's physiological effects appear at this point in time to be more benign. The pharmacokinetic profiles[48] of inhaled (peak plasma concentration 15 min) versus oral (peak plasma concentration 2 hours) cannabis should also be taken into consideration with respect to intraoperative and postoperative anesthetic care.

A 2019 report suggests that regular cannabis users require larger doses of anesthetic medications to achieve the same degree of sedation while undergoing endoscopic procedures.[49] Three times as much propofol was needed to achieve adequate sedation in cannabis users when compared with non-users (no data were given regarding when cannabis use last occurred, this difference might be exacerbated if a patient is in a withdrawal state). These higher doses of anesthetic medications have the potential for adverse consequences such as delayed awakening and hypotension. These data highlight the importance of an open dialogue with patients to gain an understanding of the type, quantity and potency of cannabis products they are consuming prior to receiving anesthesia.

Do nabiximols and nabilone reduce acute pain? According to the literature to date, perhaps not. There is no data to support the commonly held belief that cannabis can be a substitute for opioids in the acute pain setting. Furthermore, as anesthesiologists it is hard to imagine that a cannabis product would have greater efficacy than an opioid medication in the midst of an acute trauma (ie, a fracture). While there are no clinical trials suggesting that cannabis can be an opioid substitute for acute pain, there is a large body of literature suggesting that cannabis is being used by patients as an opioid substitute for chronic pain.[50 51] What we are in need of is several large-scale observational real-world evidence studies within which we know the inputs (ie, what people are actually consuming from chemical composition standpoint), which would then lead to meaningful randomized controlled trials informed by the products being consumed in the real world. Surveys of transplant recipients[52] and in the musculoskeletal[39] patient population confirm that 20% of patients are consuming cannabis-based medications unbeknownst to their healthcare providers and commonly using black market products.

The publication of systematic review after systematic review aimed at guiding clinical care should stop until literature outlining the effects of current plant-based products are published over the next 5–10 years. Mining the literature for secondary outcomes in trials not designed for the outcomes being assessed to populate a systematic review will do little to inform clinical care. Our colleagues Abdallah *et al* are absolutely correct that more research is needed. However, our group is firm that real-world data needs to be collected and outcomes evaluated on the products being used today with analytical testing of these products (to have a definitive understanding of the products being consumed). Only then will we be able to make definitive conclusions for today's perioperative patients and those in the years ahead.

Twitter Hance Clarke @drhaclarke

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ORCID iD
Hance Clarke http://orcid.org/0000-0003-4975-3823

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Correction: *Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis*

Abdallah FW, Hussain N, Weaver T, *et al*. Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis. *Reg Anesth Pain Med* 2020;45:509–19. doi:10.1136/rapm-2020-101340.

Table 1 is missing information regarding which outcomes were reported by the included studies; specifically, "black dots" are missing under the outcomes listed.

The correct table should be:

Author/ year	Surgery	N	Groups (n)	Primary outcome	Rest pain scores		Dynamic pain scores		Opioid consumption		Opioid related adverse events	Quality of recovery	Patient satisfaction
					Early	Late	Early	Late	Early	Late			
Randomized trials													
Jain *et al*[29] (1981)	Acute fracture or trauma	56	1. Levonantradol 1.5 mg (10) 2. Levonantradol 2 mg (10) 3. Levonantradol 2.5 mg (10) 4. Levonantradol 3 mg (10) 5. Control (16)	N/S	•						•		
Guillaud *et al*[14] (1983)	Renal surgery	100	1. Levonantradol 1 mg (25) 2. Levonantradol 2 mg (25) 3. Pethidine 1 mg/kg (25) 4. Control (25)	N/S	•				•		•		
Buggy *et al*[13] (2003)	Elective abdominal hysterectomy	20	1. –9-Tetrahydrocannabinol 5 mg (20) 2. Control (20)	Pain Scores	•		•		•		•		
Beaulieu *et al*[26] (2006)	Various major surgeries*	41	1. Nabilone 1 mg (11) 2. Nabilone 2 mg (9) 3. Ketoprofen 50 mg (11) 4. Control (10)	Opioid consumption at 24 hours	•		•		•		•		
Seeling *et al*[34] (2006)	Radical prostatectomy	105	1. –9-Tetrahydrocannabinol 5 mg (52) 2. Control (53)	N/S	•		•		•		•		
Ostenfeld *et al*[33] (2011)	Dental extraction	112	1. GW842166 800 mg (28) 2. GW842166 100 mg (28) 3. Ibuprofen 800 mg/ 400 mg (28) 4. Control (28)	Pain scores at 8 hours	•				•		•		
Kalliomäki *et al* [31] (2013)	Dental extraction	150	1. AZD1940 800mcg (60) 2. Naproxen 500 mg (30) 3. Control (60)	Area under the curve pain scores	•		•		•		•		
Levin *et al*[32] (2017)	Various elective surgeries	340	1. Nabilone 0.5 mg (172) 2. Control (168)	Nausea/ vomiting	•		•		•		•		
Qualitative trials													
Holdcroft *et al*[28] (2006)	Various major surgeries*	65	1. Oral cannabis 5 mg (11) 2. Oral cannabis 10 mg (30) 3. Oral cannabis 24 mg (24)	N/S	•				•		•		
Hickernell *et al*[27] (2018)	Total joint arthroplasty	259	1. Dronabinol 5 mg (81) 2. Control (178)	Nausea/ vomiting	•				•		•		
Liu *et al*[35] (2018)	Major orthopedic surgery	3793	1. Oral/inhaled cannabis (156) 2. Control (3637)	Pain scores and analgesic consumption at 24 hours	•				•		•		
Jennings *et al*[30] (2019)	Total knee arthroplasty	142	1. Oral/inhaled cannabis (71) 2. Control (71)	N/S	•		•		•		•		•

*Major surgeries included orthopedic, gynecologic, urology, plastics, and general.
Late, >24 hours; n, number of patients; N/S, not specified.

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