






# ASRA Pain Medicine consensus guidelines on the management of the perioperative patient on cannabis and cannabinoids

Shalini Shah <sup>1</sup>, Eric S Schwenk <sup>2</sup>, Rakesh V Sondekoppam <sup>3</sup>, Hance Clarke <sup>4</sup>, Mark Zakowski<sup>5</sup>, Rachel S Rzasa-Lynn<sup>6</sup>, Brent Yeung<sup>7</sup>, Kate Nicholson<sup>8</sup>, Gary Schwartz<sup>9,10</sup>, W Michael Hooten <sup>11</sup>, Mark Wallace<sup>12</sup>, Eugene R Viscusi <sup>2</sup>, Samer Narouze <sup>13</sup>

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/rapm-2022-104013>).

For numbered affiliations see end of article.

## Correspondence to

Dr Shalini Shah, Department of Anesthesiology, UC Irvine Healthcare, Orange, CA 92868, USA; [ssshah1@hs.uci.edu](mailto:ssshah1@hs.uci.edu)

Received 27 August 2022  
Accepted 8 November 2022

## ABSTRACT

**Background** The past two decades have seen an increase in cannabis use due to both regulatory changes and an interest in potential therapeutic effects of the substance, yet many aspects of the substance and their health implications remain controversial or unclear.

**Methods** In November 2020, the American Society of Regional Anesthesia and Pain Medicine charged the Cannabis Working Group to develop guidelines for the perioperative use of cannabis. The Perioperative Use of Cannabis and Cannabinoids Guidelines Committee was charged with drafting responses to the nine key questions using a modified Delphi method with the overall goal of producing a document focused on the safe management of surgical patients using cannabinoids. A consensus recommendation required  $\geq 75\%$  agreement.

**Results** Nine questions were selected, with 100% consensus achieved on third-round voting. Topics addressed included perioperative screening, postponement of elective surgery, concomitant use of opioid and cannabis perioperatively, implications for parturients, adjustment in anesthetic and analgesics intraoperatively, postoperative monitoring, cannabis use disorder, and postoperative concerns. Surgical patients using cannabinoids are at potential increased risk for negative perioperative outcomes.

**Conclusions** Specific clinical recommendations for perioperative management of cannabis and cannabinoids were successfully created.

## INTRODUCTION

This clinical practice guideline on the perioperative use of cannabis is designed to be a tool to help clinicians make evidence-based decisions regarding the perioperative management of patients who consume cannabis, who are presenting for surgery with increasing frequency. While many of the perioperative risks and challenges related to perioperative cannabis, such as how to advise patients preoperatively, the effects of cannabis on anesthetic medications, and the interaction between cannabis, opioids, and pain, have been described in the literature, there is no single document that summarizes all of these concerns and provides evidence-based recommendations. Flexibility in this clinical practice

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a wide variability in consumption patterns among the US population (recreational, medicinal, frequent, infrequent) as well as in formulations (cannabidiol, tetrahydrocannabinol, or combination). Although cannabis is reputed to have medicinal and psychoactive effects, its implications in the perioperative care setting are still largely unknown.

## WHAT THIS STUDY ADDS

⇒ The guidelines offer critical education about terminology, pharmacology, and clinical implications associated with cannabinoid therapy in the perioperative period.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identifying current evidence-based aspects and knowledge gaps of cannabinoid therapy should facilitate both clinicians and researchers in improving the care of patients in the perioperative period.

guideline is intended to enable person-centered decision-making that takes into account an individual's expected health outcomes and well-being within the context of various regulatory environments. This document covers preoperative, intraoperative, and acute postoperative care considerations and several questions specifically focus on issues related to regional anesthesia and acute pain, which are the focus of the readers of this journal. The guidelines are not intended to limit or deny care nor affect the rights of patients or providers nor do they define standard of care. They are not intended to replace clinical judgment. In the imperfect setting of heterogenous data, limited data, controversial topics, and bias inherent to expert opinion, compliance with the recommendations may not result in improved outcomes compared with personalized medicine. This guideline is also not intended to prompt the rapid tapering or discontinuation of cannabinoids or opioids for patients, nor is it intended to serve as a law, regulation, and/or policy



► <http://dx.doi.org/10.1136/rapm-2022-104193>



© American Society of Regional Anesthesia & Pain Medicine 2023. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Shah S, Schwenk ES, Sondekoppam RV, et al. *Reg Anesth Pain Med* Epub ahead of print: [please include Day Month Year]. doi:10.1136/rapm-2022-104013

that dictates clinical practice or a substitute for US Food and Drug Administration (FDA)-approved labeling.<sup>1</sup>

## BACKGROUND

Cannabis is the most commonly used psychotropic substance after alcohol and the most common recreational drug used in the USA with about 10% of the population (27.6 million people) reporting monthly use in 2018 according to the US Substance Abuse and Mental Health Services Administration (SAMHSA).<sup>2,3</sup> To contextualize the risk of cannabis, SAMHSA approximates 1 in 10 people who use marijuana will become addicted; when they start before the age of 18, the rate of addiction rises to 1 in 6.<sup>3</sup> Legalization and decriminalization of cannabis over the last decade has led to increased interest and literature on the subject, and has given rise to overt legal use and commercialization.<sup>4</sup> With the rising prevalence of both medical and recreational cannabis use in the general population, anesthesiologists, surgeons, and perioperative physicians must have an understanding of the effects of cannabis on physiology in order to provide safe perioperative care. There is a critical need to summarize the existing cannabis literature in order to provide perioperative physicians and others with tools to address the challenges that arise from managing patients taking cannabis and cannabinoids.<sup>5</sup>

The purpose of this document is to provide background on cannabinoid terminology and relevant pharmacology as well as expert guidelines on perioperative management of patients who consume cannabis and cannabinoids in order to improve clinical

care and future research and provide guidance to regulatory agencies to fully understand the impact of cannabis on anesthesia and pain care. This document covers preoperative, intraoperative, and acute post operative care considerations.

## Definitions and terminology

Explanation of terminology will not only help clarify the subsequent discussions in this document but will assist physicians in their interactions with patients as well as understanding of the literature related to cannabis. Informed and accessible discussion with patients supports improved patient communication and trust and may contribute to improved outcomes.

A glossary of the most common and relevant terms for medical cannabis and related uses are presented in [table 1](#).

## Cannabinoid pharmacology

Cannabis plants include several species, the most common of which are *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabinoids are chemicals derived from cannabis (phytocannabinoids), such as cannabidiol (CBD) and  $\Delta^9$ -tetrahydrocannabinol (THC); synthetic medications, such as nabilone, dronabinol, nabiximols; and endogenous cannabinoids that stimulate cannabinoid receptors, such as arachidonoyl ethanolamine (anandamide, AEA) or 2-arachidonoylglycerol (2-AG).

**Table 1** Cannabis terminology\*

Term	Description
Cannabis	All plant materials, components, and derivative products of the cannabis plant, including flowers, leaves, seeds, stalks, and other materials and cannabis resins, extractions, and other derivative products. Cannabis is listed in Schedule 1 of the Controlled Substances Act in the USA.
Marijuana, marihuana	Historical slang with Mexican roots adopted in the 1930s during the American prohibition efforts. Marijuana continues to be used interchangeably with cannabis in reference to plant strains containing high THC. Given the racial stigma, the word marijuana is becoming less used in favor of cannabis.
Hemp	Describes a collection of cannabis cultivars with specific properties, namely high production of fiber and seeds with minimal production of THC.
Cultivars (varieties, strains)	Distinct cultivars of the cannabis plant having unique genetic signature and expressing distinct chemical composition. Colloquially referred to as strains.
Cannabis extracts	Highly concentrated preparations of cannabis which are produced via a variety of manufacturing techniques.
Terpenes	Aromatic compounds that exist in unique profiles in different strains and may provide some therapeutic benefits.
Cannabinoid-based medicines	A general term used to describe therapeutic cannabis or cannabinoid-based products in which cannabinoids are the primary active pharmaceutical ingredient. This term is applied regardless of origin as plant-derived or synthetic cannabinoids.
Pharmaceutical or prescription cannabinoids	Cannabinoid-based treatments that have been approved as medical treatments for specific indications. Examples include nabilone (Cesamet), dronabinol (Marinol), cannabidiol (CBD; Epidiolex), and nabiximols (1:1 preparation of THC:CBD, eg, Sativex, not available in the USA).
Medical cannabis	Cannabis-based treatments that are not approved medical treatments but have been legalized and regulated for patient access. Medical cannabis is differentiated from non-medical cannabis by a unique access program and a required medical authorization.
Recreational cannabis use	Non-medical use for pleasure or leisure
Recent cannabis use	Use within the past 30 days
Heavy cannabis use	Daily or near-daily use
Endocannabinoids	Endogenous cannabinoids produced by the body and active at cannabinoid receptors. The most well-known endocannabinoids are anandamide and 2-arachidonoylglycerol
Phytocannabinoids	Cannabinoids that are produced by the cannabis plant, primarily in the female flower. More than 100 unique cannabinoids have been identified. Common phytocannabinoids include $\Delta^9$ -THC, CBD, cannabinol, and cannabigerol.
$\Delta^9$ -THC	THC is the primary cannabinoid in almost all varieties of cannabis. THC is the primary psychoactive agent and contributes the most therapeutic effects as well as adverse effects and intoxication of cannabis.
CBD	CBD is usually the other well-characterized cannabinoid found in cannabis. It has potential analgesic, anti-epileptic, anxiolytic, and anti-inflammatory properties, which inspired the selective breeding of cannabis strains with high concentrations of CBD and minimal THC concentration.

\*Information extracted from references [307](#) [308](#).  
CBD, cannabidiol;  $\Delta^9$ -THC,  $\Delta^9$ -tetrahydrocannabinol.

## $\Delta$ 9-tetrahydrocannabinol

THC and CBD are among the most well-studied cannabinoids. CBD was identified in 1940 while THC was first identified in 1964.<sup>6</sup> THC is the main psychoactive compound of the cannabis plant. THC concentration varies in different cannabis-based products ranging from 5% in marijuana to 80% in hashish oil.<sup>7,8</sup>

### THC pharmacodynamics and mechanism of action

THC acts as a partial agonist at the cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) and has high affinity at CB1 compared with CB2.<sup>9,10</sup> Both CB1 and CB2 receptors are G-protein-coupled receptors. Activation of cannabinoid receptors inhibits adenylate cyclase activity with subsequent reduction of intracellular cyclic adenosine monophosphate (cAMP) level or promotes mitogen-activated protein kinase activity. Decreased cAMP level leads to activation of voltage-gated potassium channels and inhibition of Calcium channels, thus inhibiting neurotransmitters release.<sup>11</sup>

Within the spinal cord, CB1 receptors have been localized to multiple areas involved in nociceptive processing including the superficial dorsal horn, the dorso-lateral funiculus, and lamina X.<sup>12</sup> The activation of CB1 receptors in central nociceptive processing regions and primary afferents inhibits the release of neurotransmitters via decreased calcium conductance and increasing potassium conductance, which forms the possible anatomical basis for the analgesic action of cannabinoid agonists.<sup>13</sup>

CB1 receptor activation mediates the psychoactive properties cannabis, including changes in mood or consciousness, memory processing, and motor control.<sup>14</sup> In animal studies, THC activation of CB1 receptors produces a “tetrad” effect: suppression of locomotor activity, hypothermia, immobility in the ring test, and antinociception in the tail-flick or hot-plate test.<sup>10</sup>

CB1 receptor agonism mediates an increase in neurotransmitter release of acetylcholine, glutamate, and dopamine in rat prefrontal cortex.<sup>15–17</sup> THC-induced dopamine release in the endocannabinoid system has been postulated as a potential mechanism of action for brain reward.<sup>16,18</sup>

THC has many other non CB1-receptor-mediated and CB2-receptor-mediated effects. Other receptors that THC modulates include G-protein receptor 55 and transient receptor potential cation channels (eg, transient receptor potential cation channel subfamily V (TRPV) members: TRPV1, TRPV2, TRPA1) and the serotonin receptors, 5-hydroxytryptamine (5-HT).<sup>19,20</sup> TRPV1 is imperative for detection and regulation of temperature and pain perception.<sup>21</sup>

### THC pharmacokinetics

Inhalation or smoking is the most common form of consumption.<sup>22</sup> Other routes of administration include vaporization, oral spray, edibles, tinctures, other oromucosal/sublingual routes (eg, capsules and lozenges), transdermal topicals (cannabis-infused lotions and oils), and rectal routes.<sup>22,23</sup>

Smoking cannabis produces rapid absorption, shorter duration of action and higher blood concentration of THC.<sup>24–27</sup> Absorption and bioavailability of THC depends on the type of smoking device, the depth of inhalation, puff duration, smoking habits (breath-holding), and the composition of cigarettes.<sup>28</sup> Vaporization offers a potential risk-reduction tool with a similar pharmacological profile as smoking.<sup>29</sup>

In contrast to smoking as a method of delivery, oral absorption of cannabis is slow, variable, and highly dependent on the fat content of associated food ingestion.<sup>30,31</sup> Based on bioavailability

alone, the conversion factor between inhalation and oral absorption has been estimated at 2.5.<sup>32</sup> Oral ingestion undergoes extensive hepatic first-pass metabolism with bioavailability of 10%–20%.<sup>33</sup>

THC has high plasma protein binding and large volume of distribution.<sup>28,34</sup> The plasma concentration of THC can follow two-compartment, three-compartment, or four-compartment models.<sup>28,35–37</sup> THC is metabolized in the liver via microsomal hydroxylation and oxidation by cytochrome P450 (CYP) enzymes 2C9, 2C19, and 3A4. THC is metabolized into an active form 11-OH-THC. Additional breakdown then results in 11-nor-9-carboxy-THC, the inactive metabolite.<sup>24</sup>

### Cannabidiol

CBD is a non-intoxicating phytocannabinoid and has been associated with analgesic, anti-inflammatory, anticonvulsant, anxiolytic, and antipsychotic effects.<sup>7</sup> Although CBD has been shown to have potent anticonvulsant effects in humans, there are no studies supporting analgesic effects in humans. A recent study showed that 400 mg of CBD was not superior to placebo with respect to analgesia in patients presenting in the emergency room with acute low back pain.<sup>38</sup> CBD may work synergistically with THC to produce its analgesic effect while decreasing psychoactive and cognitive side effects, such as sedation and memory impairment.<sup>39</sup> CBD has proven to be well tolerated, showing low toxicity in several studies. Common side effects of CBD include somnolence, fatigue, and change in appetite and sleep pattern.<sup>40</sup>

### CBD pharmacodynamics and mechanisms of action

CBD has low affinity for both CB1 and CB2 receptors. It acts as a negative allosteric modulator of the CB1 receptor and as a weak inverse agonist of the CB2 receptor.<sup>41–43</sup> CBD also interacts with other non-cannabinoid targets, including serotonin 1A receptors, vanilloid receptor 1 (TRPV1), and adenosine A2A receptors, all of which regulate the perception of pain.<sup>7</sup> The inverse agonist activity at the CB2 receptor may explain the anti-inflammatory effects of CBD.<sup>10</sup>

CBD may also act as antagonist of the orphan receptor GPR 55.<sup>44</sup> Moreover, CBD can act as an allosteric modulator of the  $\mu$ - and  $\delta$ -opioid receptors.<sup>45</sup> The antipsychotic effects of CBD may be explained by enhancing anandamide signaling through inhibition of its reuptake and enzymatic deactivation.<sup>46</sup>

### CBD pharmacokinetics

CBD, like THC, undergoes extensive hepatic first-pass metabolism with *per os* (PO) consumption, with animal models demonstrating a range of 10%–13%.<sup>47</sup> Only one study has reported the bioavailability of CBD in humans (31% following smoking), and half-life depends on dose and route of administration. CBD undergoes phase I and phase II metabolism. CBD is metabolized predominantly by CYP enzymes CYP3A4 and CYP2C19. Consequently, drugs that inhibit or induce these CYP enzymes would increase or decrease CBD levels, respectively. Phase II metabolism occurs through uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9 and 2B7.<sup>24,48</sup>

Similar to that of THC, CBD plasma level decreases rapidly after smoking and follows a multiphasic pattern. The half-life of CBD has been estimated to be 27–35 hours after smoking or inhalation and 2–5 days after oral administration.<sup>49,50</sup>

CBD is excreted both in urine and feces. Unlike THC, a large portion of CBD is excreted unchanged in the feces.<sup>24,25</sup> The most abundant metabolites are the inactive hydroxylated 7

(or 11)-carboxy derivatives of CBD, with the active 7 (or 11)-hydroxy CBD as a minor metabolite.<sup>51</sup>

### Cannabinoid drug interactions

The most clinically significant cannabinoid drug interactions are additive pharmacodynamic interactions when co-administered with other agents with similar physiological effects. In the presence of cannabinoids, sedation may be increased with administration other central nervous system depressants, benzodiazepines, opioids, alcohol, and antihistamines, while tachycardia may increase with tricyclic stimulants, sympathomimetics, and antidepressants.<sup>52</sup>

As noted, THC is metabolized predominantly by CYP3A4 and CYP2C9, while CBD is metabolized predominantly by CYP3A4 and CYP2C19. Therefore, drugs that inhibit or induce these CYP enzymes would increase or decrease THC and CBD levels, respectively.<sup>24 48</sup> Cannabinoids can competitively inhibit their own metabolizing enzymes, especially with sensitive substrates.<sup>53 54</sup>

Both THC and CBD may inhibit CYP3A4 and CYP2D6, with CBD having the most potent action. Moreover, CBD is a potent inhibitor of CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.<sup>55 56</sup> CBD is also a potent inhibitor of UGT1A9 and UGT2B7. Accordingly, plasma levels of UGT1A9 substrates, such as diflunisal, propofol, or fenofibrate and UGT2B7 substrates, such as gemfibrozil, lamotrigine, morphine, or lorazepam, may be increased when coadministered with CBD.<sup>57</sup>

In addition to the pharmacodynamic synergistic effects that cannabis has with coadministered opioids, there are potential pharmacokinetic interactions as well.<sup>58 59</sup> In the perioperative setting, special attention should be paid to potential cannabinoid interactions with warfarin, direct oral anticoagulants, and clopidogrel (table 2).<sup>60–62</sup> Common cannabinoid drug interactions are summarized in table 3.<sup>63–67</sup>

## METHODS

The initiation of these guidelines began with the submission of a proposal to the American Society of Regional Anesthesia and Pain Medicine (ASRA Pain Medicine) jointly by the cannabis and perioperative medicine special interest groups within the society on November 29, 2020. The proposal was reviewed and approved first by the Guidelines and Regulatory Advocacy Committee and subsequently by the Board of Directors. The

members of the steering committee who created the proposal included SS, ESS, and SN. The steering committee selected potential writing committee members based on national reputation, publishing history on the topic of cannabis, and/or clinical expertise in managing patients taking cannabinoids. The Perioperative Use of Cannabis and Cannabinoids Guidelines Committee was charged with drafting responses to the key questions created by the steering committee with the overall goal of producing a document that focuses on the safe management of surgical patients taking cannabinoids. The ASRA Pain Medicine board and the steering committee provided clear directions that the committee's objective was neither to endorse nor oppose cannabinoid use but rather to provide evidence-based guidelines that are practical for the average anesthesiologist or other perioperative physicians managing patients already taking cannabinoids.

Once the initial roster of the committee was determined, the initial meeting took place on January 5, 2021. Two members present at the initial meeting later notified the steering committee they would not be able to continue in their roles, and one was replaced. The steering committee assigned 2–3 members to each question based on expertise and availability. After initial written responses including recommendations with levels of certainty were submitted to the steering committee, they were edited, and a modified Delphi method was used in which all committee members voted on the recommendations via email with possible responses of 'approve', 'approve with changes', or 'disapprove'. Individual responses were sent to the steering committee only and were not shared with other committee members. It was determined prior to voting that 75% agreement was needed to reach consensus for a given recommendation. After the first round of voting, it was determined that 2 of the question responses required substantial modification such that a second round of voting for those two questions was needed. Any changes suggested by committee members were considered by the steering committee and incorporated if agreed on. The results of each round of voting, including a summary of the narrative comments from committee members, are shown in online supplemental appendix table 6. The document was then approved by the ASRA Pain Medicine guidelines committee, and subsequently the board of directors.

Literature searches for each question were performed using PubMed, Embase, and the Cochrane Database of Systematic Reviews. Reference lists of relevant publications were also searched. Specific search terms and strategies used were designed

**Table 2** Cannabinoid drug Interactions with anticoagulants and antiplatelets used with permission from Samer Narouze, MD, PhD<sup>60–62</sup>

Cannabinoids drug interactions with anticoagulants and antiplatelets		
Drug	Effect	Intervention
Warfarin	THC and CBD can cause competitive inhibition of CYP2C9 and inhibit metabolism of the S-warfarin isomer, leading to supratherapeutic international normalized ratio levels.	▶ Check INR within 3 days
DOACs (direct-acting oral anticoagulants)	CBD and possibly THC can increase DOACs level due to competitive inhibition of P-glycoproteins, and to a lesser extent CYP3A4.	▶ Close monitoring ▶ Consider using other anticoagulants or discontinue CBD/THC
Clopidogrel	CBD and possibly THC can increase clopidogrel level due to the competitive inhibition of CYP2C19.	▶ Consider using another antiplatelet
Heparin/fondaparinux	No known interactions as these agents are processed by endothelial and renal cells and not metabolized by CYP enzymes, UGT, or P-glycoprotein.	
Platelets	Immune thrombocytopenia with synthetic cannabis.	▶ Unlikely to have significant clinical effects ▶ Immune thrombocytopenia is rare
CBD, cannabidiol; THC, tetrahydrocannabinol.		

**Table 3** Summary of cannabinoid-drug interactions used with permission from Samer Narouze, MD, PhD<sup>63–67</sup>

Enzyme	Drugs	Effects and interventions
<b>CYP2C9</b>		
CYP2C9 inducers	<ul style="list-style-type: none"> <li>▶ Antiarrhythmics: amiodarone</li> <li>▶ Anticonvulsants: valproic acid</li> <li>▶ Antidepressants: fluoxetine</li> <li>▶ Fluconazole, metronidazole, sulfamethoxazole</li> </ul>	<ul style="list-style-type: none"> <li>▶ Decrease THC level</li> <li>▶ Unlikely to have significant effect on CBD</li> </ul>
CYP2C9 inhibitors	<ul style="list-style-type: none"> <li>▶ Carbamazepine, rifampin</li> </ul>	<ul style="list-style-type: none"> <li>▶ Increase THC level</li> <li>▶ Unlikely to have significant effect on CBD</li> </ul>
CYP2C9 substrates	<ul style="list-style-type: none"> <li>▶ Warfarin</li> <li>▶ <b>Buprenorphine</b></li> <li>▶ Non-steroidal anti-inflammatory drugs (NSAIDs): celecoxib, naproxen,</li> <li>▶ Anticonvulsants: phenobarbital, phenytoin</li> <li>▶ Fluvastatin, rosiglitazone, rosuvastatin, sulfonyleureas, losartan, valsartan</li> </ul>	<ul style="list-style-type: none"> <li>▶ CBD and possibly THC may increase drug levels</li> <li><i>Interventions:</i></li> <li>▶ Decrease dose of substrate</li> <li>▶ Monitor for toxicity and side effects</li> <li>▶ Check INR within 3 days</li> </ul>
<b>CYP2C19</b>		
CYP2C19 inducers	<ul style="list-style-type: none"> <li>▶ Anticonvulsants: carbamazepine, phenytoin, phenobarbital</li> <li>▶ Rifampin, rifampicin, ketoconazole, St. John's wort</li> </ul>	<ul style="list-style-type: none"> <li>▶ Decrease CBD and THC levels</li> </ul>
CYP2C19 inhibitors	<ul style="list-style-type: none"> <li>▶ Antidepressants: fluoxetine, fluvoxamine</li> <li>▶ Chloramphenicol, felbamate, isoniazid</li> <li>▶ Protease inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>▶ Increase CBD and THC levels</li> </ul>
CYP2C19 substrates	<ul style="list-style-type: none"> <li>▶ Antidepressants: amitriptyline, citalopram, bupropion</li> <li>▶ Anticonvulsants: clobazam, diazepam, phenytoin, phenobarbital</li> <li>▶ Antiplatelets: clopidogrel</li> <li>▶ Proton pump Inhibitors: omeprazole, pantoprazole</li> </ul>	<ul style="list-style-type: none"> <li>▶ CBD and THC may increase drug levels</li> <li><i>Interventions:</i></li> <li>▶ Decrease dose of substrate</li> <li>▶ Monitor for toxicity</li> <li>▶ Consider using alternative antiplatelet instead of clopidogrel</li> </ul>
<b>CYP2D6</b>		
CYP2D6 Substrates	<ul style="list-style-type: none"> <li>▶ <b>Opioids: codeine, morphine, hydrocodone, tramadol</b></li> <li>▶ Anticonvulsants: valproate</li> <li>▶ Antidepressants: amitriptyline, citalopram, nortriptyline</li> <li>▶ Antipsychotics: clozapine, haloperidol, risperidone</li> <li>▶ Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone</li> <li>▶ <math>\beta</math>-blockers: carvedilol, metoprolol</li> </ul>	<ul style="list-style-type: none"> <li>▶ CBD&gt;THC may increase drug levels.</li> <li><i>Interventions:</i></li> <li>▶ Decrease dose of substrate</li> <li>▶ Monitor for toxicity and side effects</li> <li>▶ Monitor for opioids augmentation</li> <li>▶ Monitor QTc for antidepressants and antiarrhythmics</li> </ul>
<b>CYP3A4</b>		
CYP3A4 Inducers	<ul style="list-style-type: none"> <li>▶ Anticonvulsants: carbamazepine, phenytoin, phenobarbital, topiramate</li> <li>▶ Cimetidine, pioglitazone, rifampin, St. John's wort</li> </ul>	<ul style="list-style-type: none"> <li>▶ Decrease CBD and THC levels</li> </ul>
CYP3A4 Inhibitors	<ul style="list-style-type: none"> <li>▶ Antiarrhythmic: amiodarone, dronedarone, quinidine, diltiazem, verapamil</li> <li>▶ Anticonvulsants: valproate</li> <li>▶ Antifungals: ketoconazole, itraconazole, posaconazole</li> <li>▶ Macrolides: clarithromycin, erythromycin</li> <li>▶ Protease inhibitors</li> <li>▶ Tyrosine kinase inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>▶ Increase CBD and THC levels</li> </ul>
CYP3A4 Substrates	<ul style="list-style-type: none"> <li>▶ <b>Opioids: fentanyl, alfentanil, methadone</b></li> <li>▶ • Benzodiazepines: midazolam</li> <li>▶ Calcium channel blockers: amlodipine, felodipine</li> <li>▶ Calcineurin inhibitor: cyclosporine, tacrolimus</li> <li>▶ PDE5 inhibitors: sildenafil</li> <li>▶ Propafenone</li> <li>▶ Statins</li> <li>▶ Zaleplon, zopiclone, zolpidem</li> </ul>	<ul style="list-style-type: none"> <li>▶ Increase CBD and THC levels</li> </ul>
<b>UGT1A9 (Phase II)</b>		
UGT1A9 Substrates	<ul style="list-style-type: none"> <li>▶ Analgesics/NSAIDs: acetaminophen, ibuprofen, diflunisal</li> <li>▶ Anesthetics: propofol</li> <li>▶ Anticonvulsants: valproate</li> <li>▶ Antipsychotics: haloperidol</li> <li>▶ DOACs: dabigatran</li> <li>▶ Canagliflozin, dapagliflozin, irinotecan, mycophenolate mofetil, regorafenib, sorafenib</li> </ul>	<ul style="list-style-type: none"> <li>▶ CBD increases substrate levels</li> <li><i>Interventions:</i></li> <li>▶ Consider decreasing substrate dose</li> <li>▶ Monitor for side effects or toxicity</li> </ul>
<b>UGT2B7 (Phase II)</b>		
UGT2B7 substrates	<ul style="list-style-type: none"> <li>▶ <b>Opioids: hydromorphone, morphine, buprenorphine</b></li> <li>▶ NSAIDs: ibuprofen, naproxen.</li> <li>▶ Benzodiazepines: lorazepam</li> <li>▶ Anticonvulsants: carbamazepine, valproate, lamotrigine</li> <li>▶ Statins: lovastatin, simvastatin</li> <li>▶ Ezetimibe, losartan</li> </ul>	
<b>p-glycoprotein (transport protein)</b>		

Continued

Table 3 Continued

Enzyme	Drugs	Effects and interventions
P-glycoprotein substrates	<ul style="list-style-type: none"> <li>▶ DOACs: dabigatran, apixaban, rivaroxaban</li> <li>▶ Digoxin, loperamide</li> </ul>	<ul style="list-style-type: none"> <li>▶ CBD and possibly THC may be a substrate and inhibitor of P-glycoprotein</li> </ul> <p><i>Intervention:</i></p> <ul style="list-style-type: none"> <li>▶ Decrease dose of substrate</li> <li>▶ Monitor for toxicity and side effects</li> </ul>

CBD, cannabidiol; INR, international normalized ratio ; THC, tetrahydrocannabinol.

by the working group assigned to each question. There were no limitations applied to the searches.

Recommendation grades assigned were based on the US Preventive Services Task Force (USPSTF) definitions of evidence strength, which specifies grade A-D or I for insufficient evidence to recommend. A level of certainty was also assigned to the statements (tables 4 and 5).<sup>68</sup> This system has been used in previous ASRA guidelines documents<sup>69,70</sup> and allows flexibility for high-grade recommendations to be made despite a lack of level 1 studies in the literature. The ASRA Pain Medicine Board of Directors reviewed and approved this document on August 8, 2022.

#### Question 1: Should all surgical and procedural patients requiring anesthesia be screened for cannabinoids preoperatively and if so, what information should be obtained?

The American Society of Anesthesiologists (ASA) standards for preanesthesia care state that before delivery of anesthetic care, the anesthesiologist is responsible for determining the medical status of the patient and developing a plan of anesthesia care, including ‘... the medical history, including previous anesthetic experiences and medical therapy.’<sup>71</sup> The ASA statement encompasses any and all medically relevant substances, including cannabinoids, regardless of whether they are medicinal, recreationally used, or illicitly obtained.

Cannabinoids are the most used addictive substances globally<sup>2</sup>; therefore, physicians should screen for them during the preoperative evaluation. All patients should be questioned about cannabinoid use, dose and frequency, route of administration, and time of last use. A review of 28 studies with 65,720 participants by the USPSTF in 2020 found no evidence for benefits or harms from screening for drug use.<sup>72</sup> However, this review did not specifically address perioperative screening where the implications of cannabinoid use may be more acute. Cannabinoids

can produce significant physiologic changes and can potentially interact with anesthetics that can lead to complications.<sup>73,74</sup> Drug screening by laboratory analysis of urine, saliva, blood, or hair generally detects only THC or carboxy-THC and is not recommended unless clinically indicated, such as for acute intoxication.

In addition to screening for cannabinoid use and verifying details as stated above, perioperative physicians should evaluate patients for acute intoxication. Practitioners should be aware of cannabinoid interactions with other medications, anesthetics, and physiologic changes. Literature has shown that acute cannabis intoxication could be detrimental in the perioperative period (see also sections questions 2, 3, and 8). It may be useful to use a standardized tool to screen preoperatively for cannabis use. The Cannabis Use Disorder Test has been validated and used to identify cannabis use disorder (CUD).<sup>75</sup>

Recreational cannabis and cannabinoids have the potential to be mixed or laced with other substances, including pesticides, heavy metals, and carcinogens, which could have significant effects on perioperative outcomes.<sup>76,77</sup>

A recent retrospective cohort study showed an association between chronic cannabinoid use and a 20% increase in incidence of postoperative nausea and vomiting (PONV).<sup>78</sup> Because prophylaxis for PONV may be initiated preoperatively, screening for cannabinoid use can help identify patients at higher risk. Patients taking cannabinoids preoperatively may also report increased postoperative pain levels, which could affect perioperative management.<sup>73</sup> This is discussed in more detail later in the document.

Unfortunately, few studies have addressed potential interactions between cannabinoids and anesthetic agents, and there is little consistency among the various preparations regarding dosage and CBD/THC ratio. A derivative of cannabis,  $\Delta^8$ -THC, is currently being produced and sold in the USA through a legal loophole. There is a paucity of research on this substance, but it has been known to produce psychoactive effects similar to

Table 4 Definitions of grades of evidence and suggestions for practice

Grade	Definition	Suggestions for practice
A	Our committee recommends this treatment, test, or strategy to improve outcomes. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	Our committee recommends this treatment, test, or strategy to improve outcomes. There is high certainty that the benefit is moderate or there is moderate certainty that the next benefit is moderate to substantial.	Offer or provide this service.
C	Our committee recommends selectively offering or providing this treatment, test, or strategy to improve outcomes to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	Our committee recommends against the intervention. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	Our committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the intervention. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of the Recommendation Statement. If the treatment or service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Table 5 Levels of certainty

Level of certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: <ul style="list-style-type: none"> <li>▶ The number, size, or quality of individual studies.</li> <li>▶ Inconsistency of findings across individual studies.</li> <li>▶ Limited generalizability of findings to routine primary care practice.</li> <li>▶ Lack of coherence in the chain of evidence.</li> </ul> As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: <ul style="list-style-type: none"> <li>▶ The limited number or size of studies.</li> <li>▶ Important flaws in study design or methods.</li> <li>▶ Inconsistency of findings across individual studies.</li> <li>▶ Gaps in the chain of evidence.</li> <li>▶ Findings not generalizable to routine primary care practice.</li> <li>▶ Lack of information on important health outcomes.</li> </ul> More information may allow estimation of effects on health outcomes.

the more well-known  $\Delta 9$ -THC.<sup>79</sup> Until additional studies are performed, we recommend approaching this substance the same as one would manage  $\Delta 9$ -THC. The inconsistency and lack of regulation of the plethora of cannabinoid products being consumed makes perioperative management challenging.

Statement: Cannabinoids are the most commonly used recreational drugs in the USA and other countries, and the use of cannabinoids, both recreational and medicinal, may result in physiologic derangements. They may have interactions with other medications and treatments in the perioperative period. Level of Certainty: Moderate

Recommendation 1: Universal screening for cannabinoids should be performed prior to surgery and should include type of cannabis or cannabinoid product, time of last consumption, route of administration, amount, and frequency of use. Grade A

Recommendation 2: Universal toxicology screening for cannabinoids is not currently indicated based on insufficient available evidence. Grade D

### Question 2: What evidence exists to guide the decision to continue or stop cannabinoids perioperatively and/or postpone elective surgery?

As cannabinoids are increasingly used in the USA and the legal landscape continues to change and expand, anesthesiologists are increasingly being confronted with perioperative cannabinoid use and hence require guidance as to whether or not to continue cannabinoid products perioperatively as well as when to consider postponing elective surgery. The following sections summarize the effects of cannabinoids on the various organ systems with emphasis on the implications for perioperative management and additionally summarize the available guidance related to continuing or stopping cannabinoids perioperatively.

Cannabis use is associated with a dose-dependent impairment of cognitive function and performance. The ability of a patient to provide informed consent is one of the principal concerns when encountering an intoxicated patient perioperatively because of alterations in perception and memory function.<sup>74 80</sup> Depending on the chronicity and quantity of use, a patient may or may not exhibit signs and symptoms of acute intoxication such as anxiety, paranoia, or frank psychosis. It is well known that cognitive and performance skills can be impaired in both recent/new users and chronic/heavy users.<sup>81</sup> As demonstrated

in a systematic review and meta-analysis involving 80 clinical trials,<sup>82</sup> most driving-related cognitive skills recovered within approximately 5 hours (and almost all within 7 hours) of inhaling 20 mg of  $\Delta 9$ -THC. Oral  $\Delta 9$ -THC-induced impairment may take longer to resolve, and regular cannabinoid users experienced less impairment than ‘other’ (mostly occasional) cannabinoid users. Similar studies in perioperative patients are lacking. Still, the current evidence does support the return of some executive function by 5 hours after consumption. These data should be used in conjunction with clinical assessment of cognition and competence.

The cardiovascular effects of cannabinoids are biphasic. When used acutely and in low doses, there is an activation of sympathetic nervous system resulting in tachycardia and hypertension but at escalating doses and especially with chronic usage, bradycardia and hypotension can result from increased parasympathetic tone.<sup>83</sup> In new users, the acute effects following cannabis smoking result in an increase in heart rate and blood pressure initially within the first 60 min from  $\beta$ -adrenergic stimulation and parasympathetic inhibition, followed by norepinephrine-mediated increases in heart rate and blood pressure for up to 120 min following cannabis use.<sup>84</sup> These acute cannabinoid effects can impact perioperative hemodynamics and myocardial oxygen demand and may increase the risk of myocardial infarction (MI).<sup>84 85</sup> While the evidence of increased risk of postoperative MI (OR of 1.88 (95% CI 1.31 to 2.69)) is known to exist in the surgical patient as shown in a recent cohort study,<sup>86</sup> the period of increased risk since last use is not well characterized.

A multicenter case-crossover study of 3882 patients with MI revealed that 124 had smoked cannabis in the year preceding the MI.<sup>87</sup> Of those 124 patients, 37 reported smoking it within 24 hours of MI onset and nine reported smoking within 1 hour of MI symptom onset. In addition to these nine patients, three patients reported smoking cannabis between 60 and 120 min before the onset of symptoms. Case-crossover analysis that controlled for differences between patients showed that within 1 hour after smoking cannabis, the risk of MI onset was elevated 4.8-fold (95% CI 2.9 to 9.5;  $p=0.001$ ) compared with periods of nonuse. In the second hour after smoking cannabis, the relative risk was 1.7 (95% CI 0.6 to 5.1;  $p=0.34$ ), suggesting a rapid decline in the cardiac effects after smoking cannabis.<sup>87</sup> Cannabis smoking has also been found to reduce the anginal threshold by

48% after a single use as compared with 23% after smoking a nicotine cigarette in patients with chronic stable angina.<sup>88</sup>

A nationwide retrospective database study covering the period from 2010 to 2014 revealed that there was a 60% increase in in-hospital mortality among marijuana users managed for acute MI.<sup>89</sup> More recently, a systematic review and case descriptive analysis of cannabis use and acute MI revealed that the onset of acute MI symptoms is within 5 hours in the majority of cases.<sup>90</sup> A systematic review of cannabis-induced cardiovascular effects, which included more than 4 million patients, showed that the most common events were tachycardia and various types of dysrhythmias, including atrial fibrillation, atrial flutter, atrio-ventricular block, and ventricular fibrillation. The researchers concluded that cannabis use is associated with rare but potentially life-threatening instances of cardiac dysrhythmia.<sup>91</sup> Another systematic review, including 3695 individuals with toxicity from the use of synthetic cannabinoids, found that the most common cardiovascular effect was tachycardia in 30%. In addition, death occurred in 0.2%, stroke in 0.1%, and MI in 0.09%.<sup>92</sup> Given the risk of prolonged cardiovascular effects, conservative recommendations suggest avoiding cannabinoids for 72 hours prior to surgery.<sup>93 94</sup> While cannabinoid use does not appear to be a risk factor for coronary artery disease<sup>95-99</sup> it may trigger acute coronary syndromes in those with underlying atherosclerotic heart disease.<sup>90 100-102</sup>

Smoking cannabis has been associated with a dose-dependent impairment of large airway function resulting in airflow obstruction and hyperinflation, but it has seldom been associated with frank emphysema.<sup>103-106</sup> Of critical importance to the anesthesiologist are the effects that justify postponement of surgery. The limited available evidence suggests that the airway inflammation following marijuana smoking is similar to that following tobacco.<sup>107</sup> It is not uncommon to encounter wheezing and productive cough suggestive of chronic bronchitis.<sup>108</sup> Given the available evidence, it would be prudent to consider those who regularly smoke cannabis to be at similar risk for complications to those who smoke tobacco and a heavy/regular cannabis smoker to be at risk for chronic obstructive pulmonary disease (COPD). Another airway concern in cannabis users is the possibility of airway inflammation, rhinopharyngitis, or uvular edema,<sup>109 110</sup> all of which may contribute to airway obstruction in the perioperative period, especially with recent use.<sup>111</sup>

When considering whether to stop cannabinoids perioperatively, several factors come into play including:

- ▶ Medicinal versus recreational use.
- ▶ The dose, frequency and chronicity of use.
- ▶ The THC:CBD ratio of the product(s).
- ▶ The route of administration.

Some synthetic THC<sub>s</sub>, (eg, dronabinol), and synthetic analogs of delta-9-THC (eg, nabilone) as well as cannabis-derived (extracted directly from the plant, for example, CBD (Epidiolex) are FDA approved for chemotherapy-induced nausea/vomiting, HIV/AIDS-associated wasting, and rare forms of epilepsy (Lennox-Gastaut syndrome, Tuberous Sclerosis and Dravet's syndrome), respectively. Abrupt cessation of these cannabinoid-based medications in the perioperative period for these patients is discouraged as such measures may adversely affect their perioperative course; hence, it is probably prudent to continue their use perioperatively until further safety data are available. On the other hand, the consensus panel believes recreational use should be discouraged similar to cigarette smoking.

CBD is generally well tolerated, and even with chronic usage and high doses (up to 1500 mg PO per day), CBD failed to produce any psychoactive, cardiovascular, cognitive, or psychomotor

effects similar to  $\Delta$ 9-THC.<sup>112 113</sup> Pure CBD containing product Epidiolex (100 mg/mL) is approved for certain forms of epilepsy and similar to other antiepileptic medications, should not be abruptly discontinued perioperatively. Safety of perioperatively continuing other FDA approved cannabinoid compounds such as dronabinol (synthetic THC compound), Nabiximol (Sativex 2.7 mg THC and 2.5 mg CBD per spray) and nabilone (Cesamet synthetic cannabinoid mimicking THC) is currently unknown. Similarly, safety data for other formulations containing CBD can be continued perioperatively, safety data are lacking and there is no standardization of THC:CBD ratios in cannabinoid-containing products. In a 2017 study published in *JAMA*, THC was detected in 21% of samples marketed as 'pure CBD' products, some at high concentrations.<sup>114</sup>

Despite the effects of cannabinoids on multiple organ systems, the scientific literature remains unclear as to whether to stop or continue medical cannabinoids preoperatively. A recent consensus-based guideline recommended reducing cannabinoid use 7 days prior to surgery (to less than 1.5 g/day of smoked cannabis, 300 mg/day of CBD oil, 20 mg/day of THC oil) while cautioning not to attempt any tapering strategies within 6 days of elective surgery and not to attempt tapering a day prior to surgery.<sup>115</sup> Contrary to this recommendation, recent reviews of perioperative cannabinoids recommended cessation 72 hours prior to surgery.<sup>84 94</sup> An even more conservative recommendation was recently provided, in which the authors recommended up to 10 days of cessation of oral cannabis consumption.<sup>116</sup> The authors acknowledged the lack of evidence and their recommendation was based entirely on the half-lives of CBD and dronabinol and not on the physiological effects.

Given that cannabis smoking can negatively affect airway resistance, cardiovascular physiology, and cognition, anesthesiologists may consider discouraging cannabis use prior to surgery similar to tobacco smoking, unless its use is medically indicated. Any decision to cancel or postpone an elective surgery/procedure in a cannabis-consuming patient may be further directed by any clinical concerns about underlying cardiorespiratory illnesses or problems with mentation consequent to cannabis use. Given that this is an area of emerging evidence, further research is needed in order to provide evidence-based recommendations about the perioperative management of cannabinoids.

Statement 1: Acute effects of cannabis use can result in altered mental status and impairment of decision-making capacity. Hence, the frequency and the timing of the last dose of cannabis usage are important. Level of Certainty: High

Statement 2: Smoking cannabis can cause increases in heart rate and blood pressure that is prominent within the first 1–2 hours of usage. Level of certainty: High

Statement 3: Smoking cannabis may lead to a higher risk of perioperative acute MI within the first 1–2 hours. Level of certainty: Moderate

Statement 4: Smoking cannabis may have deleterious effects on airway resistance and respiratory adverse events. Level of certainty: Moderate

Statement 5: There is a lack of published data on the perioperative cardiovascular effects following other routes of cannabinoid administration. Level of certainty: Moderate

Recommendation 1: Patients should be counseled on the potential risks of continued perioperative cannabinoids. Grade B

Recommendation 2: We recommend postponing elective surgery in patients who have altered mental status or impairment of decision-making capacity due to acute cannabis intoxication. Grade A



Recommendation 3: We recommend delaying elective surgery for a minimum of 2 hours after cannabis smoking because of increased perioperative risk of acute MI. Grade C

Recommendation 4: With other cannabinoids routes (non-smoking) of administration, consider weighing the risks and benefits before proceeding with elective surgery given the temporal association of cannabis usage and adverse cardiovascular effects. There is a lack of published data to recommend a specific duration. Grade I

### Question 3: For patients on concomitant cannabis and opioid use preoperatively, does existing evidence provide guidance on tapering of cannabinoids prior to surgery?

As the combination of cannabinoids and opioids is becoming more common in perioperative patients, an understanding of the effects on postoperative pain and risk of adverse events is essential. A comparison of data from 2012 to 2017 found that cannabinoid use increased more than 60% while opioid use decreased approximately 30%. The changes were not associated with changes in perioperative complications.<sup>117</sup> Although some evidence suggests that cannabinoid use has improved opioid-related adverse events and reduced overall use,<sup>118–122</sup> more substantial evidence demonstrates that cannabinoids can worsen pain and increase postoperative opioid use.<sup>73 123–126</sup> There is evidence of biphasic effects of THC, with low doses reducing pain and high doses increasing pain, stressing the need for a better understanding of the relationship between THC consumption levels and pain.<sup>127 128</sup>

In a retrospective study of 71 patients undergoing primary unilateral total knee arthroplasty, preoperative exposure to cannabinoids did not affect short-term outcomes.<sup>129</sup> However, in retrospective study involving 21 276 adults treated for traumatic injury, a higher rate of mechanical ventilation was observed.<sup>130</sup> A recent prospective study on perioperative cannabis use compared 79 current cannabis users to 1256 non-cannabis users undergoing elective surgery. A majority of current cannabis users were reportedly using cannabis medicinally, primarily for pain. The results of this study showed higher levels of pain, poorer quality of life, and greater likelihood of using opioids or benzodiazepines in cannabis users compared with non-cannabis users prior to and 3 to 6 months following surgery.<sup>123</sup>

Statement 1: Chronic use of THC may worsen postoperative pain, increase postoperative opioid use and precipitate the development of postoperative hyperalgesia. Level of certainty: Moderate

Statement 2: There is a lack of high-quality evidence describing the risks of concomitant opioids and cannabinoids in the perioperative period and in addition few studies have addressed the benefits and risks of preoperative cannabinoid tapering. We are uncertain of the overall benefit of preoperative cannabinoid tapering. Level of certainty: Low

Recommendation 1: We recommend that the frequent cannabis user be counseled on the potentially negative effects on postoperative pain control. Low-dose, medically supervised use likely has a lower risk of negative effects. Grade A

Recommendation 2: We cannot recommend for or against the routine tapering of cannabis and cannabinoids in the perioperative period. Grade I

### Question 4: What are the specific concerns of chronic cannabinoid use in a parturient presenting for labor or cesarean section?

Cannabinoids are the most common addictive substances used by pregnant women and use in this patient population has been increasing over the last few decades. The 2019 SAMHSA survey

reported 5.4% of all pregnant women using marijuana and 1.7% of all pregnant women using marijuana daily or almost daily in the USA,<sup>131</sup> increasing to over 8% with screening.<sup>132</sup> The cannabinoid system is prevalent throughout the human body, with receptors in maternal, placental and fetal tissues.<sup>133</sup> Cannabinoids affect both maternal and fetal physiology, cross the placenta and have been associated with preterm delivery, lower birth weight, and other adverse outcomes.<sup>134</sup> Thus, the anesthesiologist must be familiar with the physiologic effects and interactions to understand the usage and safety concerns of cannabinoids during pregnancy and the puerperium.

### Placental and fetal effects

Cannabinoids readily cross the placenta.<sup>135</sup> THC crosses the placenta and fetal levels are about 10% of maternal levels and higher with chronic exposure in animal studies.<sup>136</sup> Prenatal exposure to THC has been associated with decreased birth weight,<sup>137 138</sup> decreased pancreatic islet density, and glucose intolerance after birth in rats.<sup>139</sup> The endocannabinoid system is present in the myometrium and placenta, with changes reported in disease states including endometriosis and preeclampsia.<sup>140</sup> CB1 and CB2 receptors are present in the uterus and the placenta. Also present are other cannabinoid system components, including fatty acid amide hydrolase (FAAH), N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD), and endocannabinoid agonists AEA.<sup>141</sup> Indeed, plasma AEA levels may decrease from first to second to third trimester but increase dramatically during labor.<sup>140 141</sup> The endocannabinoid system appears to be involved in placental development and trophoblast proliferation, with CB1 receptor knockout mice having smaller placentas.<sup>140 142</sup> In addition, CB1 receptor levels are higher in the placental tissue of pre-eclamptic women.<sup>143</sup>

Endocannabinoids affect normal fetal brain development, neuron proliferation, differentiation, and neurotransmitter levels.<sup>144 145</sup> Human fetal central nervous system CB1 receptors are present at 14 weeks of gestation, and the number of receptors increases with increasing gestational age.<sup>146 147</sup> Cannabinoids are lipophilic, easily crossing the placenta, resulting in exposure to THC, CBD, or other components of marijuana. Prenatal marijuana exposure has been associated with decreased problem solving, visual-motor coordination, visual analysis, decreased attention span and behavior problems in offspring.<sup>144</sup> Visual evoked potentials have been shown to be delayed at 18 months of age, while subsequent neuroimaging of young adults aged 18–22 show functional MRI scan differences with increased effort required for executive function tasks.<sup>148</sup> Prenatal cannabis exposure has been associated with adolescent vulnerabilities to psychopathology, sleep problems, lower cognition and lower gray matter volume, providing more evidence of long term effects in the offspring.<sup>149 150</sup>

### Maternal effects

The use of recreational marijuana for nausea or vomiting during pregnancy almost doubled to 11% from 2009 to 2016 in one California study.<sup>151</sup> First trimester use of cannabis was associated with symptoms ranging from mild and severe nausea or vomiting during pregnancy.<sup>135</sup> Cannabinoids (cannabis,  $\Delta^9$ -THC, nabilone, levonantradol and nonabine) activate CB1 receptors in the brainstem and enteric nervous system and may act as anti-emetics.<sup>84 152</sup> High levels of cannabis consumption may cause an induced hyperemesis syndrome<sup>74</sup> causing some to seek hot baths as heat activates vanilloid receptor type 1 and releases substance P, mediating nausea. A review found evidence that cannabis helps

with chronic pain in adults and may possess antiemetic properties for chemotherapy-induced nausea and vomiting.<sup>2 153</sup>

Cannabinoid use may be associated with postoperative hypothermia, shivering and increased platelet aggregation.<sup>84</sup> Temperature regulation may be affected by CB1 receptor agonism, especially with chronic, high-quantity use<sup>84</sup> and may be reversed by a CB1-receptor antagonist (eg, rimonabant).<sup>154</sup> CB1 receptor agonism leads to sympathetic activation and parasympathetic inhibition, with a 20%–100% increase in systolic blood pressure, increased cardiac output, and increased norepinephrine plasma levels for up to 2 hours.<sup>155</sup> Parturients consuming high quantities of potent THC formulations may present with fever, tachycardia, and hypertension.<sup>74</sup> CBD may alter temperature regulation by activating the TRPV-1 receptors that detect thermal inputs.<sup>156</sup> Maintaining normothermia during cesarean section is important for enhanced recovery after cesarean, or ERAC, and breast feeding.<sup>157</sup> Neuraxial opioids may decrease the internal set point and be a cause of hypothermia.<sup>158</sup> Interactions between neuraxial opioids and systemic cannabinoids with regards to thermoregulation are unknown. Maternal and neonatal outcomes are optimized when both are warm and bonding/breast feeding are encouraged in the operating room for cesarean delivery.<sup>157</sup> CB1 receptor activation may decrease cerebral blood flow,<sup>159</sup> with ischemia noted in the posterior circulation that can mimic signs of posterior reversible encephalopathy syndrome (PRES) in the postpartum period.<sup>160</sup>

### Pre-eclampsia

Pre-eclampsia spectrum, a hypertensive disorder of pregnancy, occurs in 5%–8% of pregnancies. Cannabinoids may be involved in preeclampsia, as changes in the endocannabinoid system in preeclampsia have been noted, including a high number of CB1 receptors in the placenta, an increase in NAPE-PLD, a decrease of FAAH, and decrease in plasma AEA.<sup>140</sup> Endocannabinoids influence nitric oxide production, which affect regulation of placental blood flow.<sup>161</sup> FAAH blockade, which increases anandamide, led to a decreased response to angiotensin II contraction in normal and pre-eclamptic model mice, while monoacylglycerol lipase blockade, which increases 2-AG, reduced response in pre-eclamptic mice.<sup>162</sup> CB1 receptor blockade had no effect on the angiotensin response in this model. The effect of exogenous cannabinoids on the hypertensive response or interaction with clinical preeclampsia in humans is currently unknown. An increase in blood pressure may be seen following acute cessation of cannabis in chronic, high-quantity users but not occasional users.<sup>163</sup> In one retrospective multivariate analysis adjusted for use of other substances, there was no difference in the overall distribution of hypertensive disorders in women who used marijuana.<sup>164</sup>

### Breast feeding

While the American College of Obstetrics and Gynecologists (ACOG) and the FDA advise against consuming THC, CBD, and marijuana while breast feeding,<sup>144 165</sup> some have suggested that the benefits of breast feeding may outweigh the effects of cannabinoids in breast milk.<sup>166</sup> There are large variations in the concentration of cannabinoids in breast milk, but they may be present for a prolonged period after maternal consumption.<sup>167</sup> Maternal cannabis use in the early postnatal period was positive in 5% of the population surveyed in one study.<sup>138</sup> THC can be found in breast milk for up to 6 days after maternal consumption, although it may be concentrated up to sevenfold compared with maternal plasma in chronic consumption.<sup>168 169</sup> The relative

infant dose, the amount absorbed, has been estimated to be 2.5% (range 0.4%–8.7%) of the maternal dose.<sup>170</sup> One study found the human milk:plasma partition coefficient of 6:1 with a median THC value of 3.2 ng/mL in breast milk. The half-life of THC in breast milk is up to 17 days.<sup>171</sup> Large variations in the concentration of THC in breastmilk have been noted with a peak of up to 420 ng/mL.<sup>170</sup>

### Predelivery anesthetic considerations

Long-term, high-quantity cannabis users may benefit from a predelivery high-risk anesthesia clinic evaluation<sup>172</sup> to assess potential interactions and improve outcomes with development of a multidisciplinary plan. Prenatal marijuana use adversely affects fetal brain development and subsequent behavioral self-regulation, a precursor to later, more serious problems in childhood. Yet, many mothers continue to use cannabis and believe in its safety.<sup>173</sup> Stopping marijuana use before 10 weeks of gestational age prevented these effects and higher maternal choline levels seem to mitigate some of marijuana's adverse effects on the fetus.<sup>174</sup> A majority of pregnant women had poor knowledge about the risks of marijuana use during pregnancy, and 90% were more likely to use marijuana in pregnancy if it were legal.<sup>175</sup>

### Intrapartum anesthetic considerations

A history of occasional or recreational use of marijuana likely does not pose a risk with neuraxial anesthesia for labor analgesia or cesarean delivery. A parturient admitted with acute cannabis intoxication but without long-term, high-quantity use may be susceptible to interactions based on the physiology discussed in other sections of these guidelines. Within a 2-hour window from consumption, norepinephrine levels may be increased with potential for cardiovascular, anesthetic and vasopressor interactions. The potential for acute cannabis intoxication might reduce the amount of opioid medication needed<sup>176</sup> but data are limited to animal studies.

Long-term, high-quantity use may be associated with increased parasympathetic tone, decreased heart rate, and postural hypotension.<sup>84 177</sup> Short-term, high-quantity use may be associated with thermoregulatory changes, hypothermia, and shivering, which may be worsened with vasodilation of regional anesthesia, general anesthesia, or change in temperature set point by neuraxial opioids.<sup>84</sup>

Strong CB1 agonism (or synthetic cannabinoid (eg, 'K2'/'spice')) may lead to or be associated with preeclampsia use may cause or be associated with symptoms resembling preeclampsia, cerebral ischemia, or PRES.<sup>160</sup> Long-term cannabinoid exposure may cause a cross tolerance to opioids and require greater use of opioids.<sup>124 176</sup> Acute intoxication with cannabinoids may augment the analgesia of *mu* and *kappa* opioid agonists, thus potentially reducing the dosage requirement for opioids.<sup>176</sup>

Postoperative analgesic regimens should maximize non-opioid analgesics, use a multi-modal enhanced recovery protocol,<sup>157</sup> and avoid cannabis as an adjunct due to concerns over cannabinoid passage via breastmilk to the neonate.

### Summary of considerations of cannabinoid use in pregnancy and during the peripartum period

Anesthesiologists should be aware of the increasing use of cannabis and cannabinoids preconception, during pregnancy, and in the postpartum period.<sup>151</sup> Cannabis or cannabinoids cannot be recommended during labor, cesarean delivery, or in the immediate postpartum period at this time, and the FDA and ACOG recommend avoiding cannabis/cannabinoids during pregnancy

and breast feeding. The effects of cannabis use during pregnancy may include an increase in the odds of anemia, low birth weight, premature birth, need for neonatal intensive care unit services, and altered brain development.<sup>137 178</sup> THC and other cannabinoids enter human breast milk and may further impact neonatal development. Pregnant patients should be educated about the risks of maternal cannabis use on the fetus/neonate.<sup>175 178 179</sup>

Statement 1: While cannabis use during pregnancy and in the postpartum period has the potential for adverse maternal and fetal physiological complications, there is currently no evidence to suggest that there are any specific implications with neuraxial anesthesia for labor or cesarean section. Level of certainty: Moderate

Recommendation 1: Pregnant patients should be educated and counseled about the risks of maternal cannabis use on the fetus/neonate. Grade A

Recommendation 2: Cannabis use during pregnancy and immediate postpartum period should be discouraged. Grade B

### Question 5: Should the intraoperative doses of anesthetics and analgesics be adjusted in patients who have taken cannabinoids preoperatively?

A key issue for anesthesiologists caring for patients who have short-term or long-term exposure to cannabinoids is to determine what adjustments, if any, are needed with respect to doses of routine perioperative medications. Evidence on this topic is derived from a disparate group of human studies with significant limitations and data from preclinical animal studies. In an animal study of rats administered sevoflurane and various doses of CBD with or without morphine, the addition of CBD did not enhance the minimum alveolar concentration (MAC) of sevoflurane.<sup>180</sup> These results stand in contrast to those of other researchers, such as Müller *et al*,<sup>181</sup> who studied the effects of adding THC to sevoflurane in 38 rats using a blinding protocol and reported that MAC was reduced by 26%. Stoelting *et al*<sup>182</sup> in a 1973 study reported that THC decreased the MAC of halothane in dogs. However, the translation of the study findings to humans was uncertain because of species differences in THC sensitivity. Another animal study from 1973 reported that THC lowered the MAC of cyclopropane, which is a volatile anesthetic no longer used clinically.<sup>183</sup>

Human studies are limited in number and quality. A retrospective analysis of 118 patients who were undergoing tibial fracture repair reported that the MAC requirements of sevoflurane in cannabis users was greater compared with non-cannabis users.<sup>184</sup> Cannabis use was defined as any prior use in the month before surgery. However, there was no difference observed in desflurane and propofol MAC between groups and an accompanying editorial cautioned about making changes to practice based on a study with inconsistent and limited findings.<sup>185</sup> In a retrospective study that involved a random sample of 250 endoscopy patients, 25 were identified as cannabis users.<sup>186</sup> The authors reported that greater midazolam, fentanyl, and propofol doses were administered to individuals in the cannabis group but multiple confounders were identified, including procedure duration and the potential of individual provider differences in administered dosages. In addition, the absolute difference in drug doses between groups was small and of uncertain clinical significance. Finally, in a randomized, single-blinded study, Flisberg *et al*<sup>187</sup> reported that regular cannabis users required greater propofol doses for successful laryngeal mask airway insertion than nonusers (314.0 mg ± 109.3 vs 263.2 ± 69.5 mg,  $p < 0.04$ ). The timing of cannabis use in relation to the time of

anesthesia induction was unclear and requires clarification in future prospective trials.

A final issue relates to the use of intraoperative anesthesia depth monitors, such as the bispectral index (BIS), in patients taking cannabinoids preoperatively. In a double-blind, randomized controlled trial (RCT) 27 patients undergoing elective orthopedic surgery under general anesthesia were allocated to 1 of 4 interventions: (1) high-dose cannabis, (2) low-dose cannabis, (3) active placebo, or (4) placebo.<sup>188</sup> The form of cannabis administered was nabiximols, which is administered as an oral spray and is not available in the USA. In this study, nabiximols was administered 20 min prior to induction of general anesthesia. The authors reported that the average BIS values were higher in the high-dose cannabis group but presented no data to suggest that higher BIS readings indicated ‘lighter’ anesthesia depth. Other human studies have found altered gamma neural oscillations in cannabis users, but it remains unclear how those changes would affect anesthetic management.<sup>189 190</sup>

Finally, in their consensus recommendations on the perioperative management of cannabis, Ladha *et al*<sup>115</sup> suggested giving ‘extra consideration to greater depth of anesthesia during induction and maintenance of anesthesia’ in cannabis users. They also stated that acutely intoxicated cannabis users might have lower anesthetic requirements and recommended the use of intraoperative electroencephalogram (EEG) monitoring. However, there is a lack of evidence about the reliability and clinical utility of processed EEG monitoring in cannabis users.

Statement: In light of the overall weak quality of evidence and absence of RCTs, the effect of preoperative cannabis use needs to be investigated further but the limited evidence suggests that depending on the timing of last cannabis consumption it may have an effect on lowering anesthetic requirements in the acutely intoxicated user and increasing anesthetic requirements in the long-term regular user (not acutely intoxicated). Level of certainty: Low

Recommendation 1: Consideration should be given to adjusting induction and maintenance doses of anesthetic agents based on clinical presentation and timing of the last consumption of cannabis in surgical and procedural patients. Grade C

Recommendation 2: There is insufficient evidence to recommend for or against the use of intraoperative EEG monitoring in patients who have taken cannabinoids. Grade I

### Question 6: Does acute or chronic cannabis exposure require any adjustment of ventilator settings to accommodate for possible V/Q mismatch, smoke inhalation injury, or other lung pathology?

#### Long-term cannabis exposure

Anesthesiologists caring for patients using cannabis-containing products long-term must be aware of alterations in pulmonary function and respiratory physiology that may affect ventilation intraoperatively and postoperatively. While not as well studied as tobacco smoking, cannabis smoking has drawn comparisons to tobacco smoking.<sup>103</sup> For example, cannabis smoke contains many of the same chemical and particulate components found in tobacco smoke that are known to damage lung tissues.<sup>103</sup> Cannabis smoke contains greater levels than tobacco smoke of several toxic substances including acetaldehyde, hydrogen cyanide, and nitrogen oxides.<sup>191 192</sup> Among patients with chronic COPD, initiating use of prescription oral cannabinoids (nabilone, dronabinol) was not associated with increased hospitalization, emergency department or outpatient visits, or

diagnosis of pneumonia, but all-cause mortality was greater among new users of prescription cannabinoids.<sup>193</sup> Alternatively, individuals receiving higher-dose cannabinoids compared with controls experienced increased rates of hospitalization for COPD symptom exacerbation and pneumonia.<sup>193</sup> In a prospective study, 339 subjects were allocated to 1 of 4 groups: (1) cannabis smoking only, (2) tobacco smoking only, (3) combined cannabis and tobacco smoking, and (4) non-smokers. Cannabis smoking was associated with reductions in the forced expiratory volume in 1 s (FEV<sub>1</sub>) to forced vital capacity (FVC) ratio and increased lung capacity. Furthermore, one smoked cannabis cigarette had the respiratory effect of 2.5–5 tobacco cigarettes, and overall pathology was worse when cannabis was combined with tobacco.<sup>103</sup> These findings suggest that smoking cannabis is associated with development of an obstructive respiratory pathology.

Longitudinal and cross-sectional studies have demonstrated that long-term cannabis smoking leads to chronic bronchitis and airflow obstruction involving large airways.<sup>103 194–197</sup> Symptoms including coughing, excessive sputum production, and wheezing have been associated with cannabis use.<sup>103 194 195 198–203</sup> In a population-based study involving 1037 young adults, smoking cannabis at least once per week was also associated with increased incidence of morning cough, sputum production, and wheezing. When these patients discontinued smoking cannabis, symptoms resolved.<sup>201</sup> Cannabis vaping is also associated with increased likelihood of chronic bronchitis symptoms compared with never vaping cannabis, even when adjusting for nicotine vaping, cannabis smoking, tobacco smoking, and sociodemographic factors.<sup>204</sup> These findings are not, however, universal, as several studies have found no or limited associations between cannabis use and pulmonary symptoms.<sup>205 206</sup>

Study of the pulmonary effects of regular cannabis smoking is complicated by the high prevalence of concomitant tobacco use, which is inconsistently controlled for in participant recruitment and statistical analyses. A prospective observational study evaluating the effects of marijuana use on lung function found that while there was no overall association between pulmonary symptoms and cannabis smoking, the subset of patients with a 10-year history of smoking filter-less cannabis cigarettes did report some symptoms.<sup>205</sup> Among young, intermittent smokers, cannabis co-use with intermittent tobacco smoking was more strongly associated with the presence of respiratory symptoms than use of either substance alone.<sup>207</sup> A similar association was found in an observational study of older participants, in whom tobacco use, alone or combined with cannabis, was associated with respiratory symptoms but no significant association was found for cannabis use alone.<sup>208</sup>

A retrospective database analysis of 8932 patients with CUD and an equal number of matched controls found that regular cannabis use was associated with a significantly greater risk of asthma, COPD, and pneumonia diagnoses. Patients who also used tobacco had the greatest prevalence of these diagnoses, but a higher prevalence of all three was associated with tobacco use disorder alone compared with isolated CUD.<sup>209</sup>

Multiple studies have found reduced FEV<sub>1</sub>/FVC among people who smoke cannabis.<sup>194–197 201 210–212</sup> This finding may be due to increases in FVC with preserved or smaller increases in FEV<sub>1</sub> rather than reductions in FEV<sub>1</sub> due to obstruction, as several studies have found an increase in FVC among cannabis smokers.<sup>201 205 208 209 212–215</sup> This also may reflect inadequate control for the effects of tobacco use in some studies.<sup>198</sup> It is notable that several studies that found no significant reduction in FEV<sub>1</sub> did observe greater airway resistance among cannabis smokers compared with non-smokers.<sup>103 199 214</sup> Like tobacco use,

recent cannabis use was associated with reduced exhaled nitric oxide, which may contribute to impaired bronchodilation.<sup>212</sup>

Cannabis smoking has been associated with the formation of lung bullae in relatively young patients in several case series and multiple case reports, but it is unclear if this is a causative association.<sup>216 217</sup> Cannabis smoking has also been associated with pneumothorax,<sup>218</sup> and combining cannabis use with tobacco use may increase this risk.<sup>219</sup> However, in general, cannabis use does not appear to be associated with emphysema.<sup>103 205 213</sup>

### Short-term cannabis exposure

Less is known about the effects of acute cannabis exposure on lung function compared with chronic exposure. The immediate effects of oral or inhaled THC induces bronchodilation both in healthy subjects and those with asthma,<sup>220 221</sup> but aerosolized THC or cannabis smoking may also result in an irritation of the airways and bronchoconstriction in some individuals with reactive airway disease.<sup>222</sup> Evidence of harm is limited to small case series and case reports.<sup>212 223–229</sup> A small clinical trial and several case reports of patients with acute shortness of breath and hemoptysis within hours of cannabis use have been published.<sup>230–233</sup> Alveolar hemorrhage was also reported in another case report.<sup>234</sup> Several cases of cannabis use-related lung injury have also been documented and associated with vaporized cannabis products attributed to additives or contaminants such as vitamin E acetate.<sup>228 235 236</sup> The resulting lung injury has been defined as e-cigarette vaping associated lung injury (EVALI) which results in severe lung pathology such as acute eosinophilic pneumonia, diffuse alveolar hemorrhage, lipid pneumonia, and respiratory-bronchiolitis interstitial lung disease.<sup>228</sup>

Statement 1: There is low-quality evidence that patients taking only oral cannabinoids do not experience significant changes in pulmonary function. Level of certainty: Low

Statement 2: There is conflicting evidence as to whether any ventilatory changes should be made for patients with chronic or acute cannabis exposure via inhalation. Acute cannabis inhalation may result in bronchodilation but may also cause airway irritation and bronchoconstriction in susceptible individuals. Long-term use of inhaled cannabis is likely associated with the development of obstructive lung disease-like patterns such as chronic bronchitis. Level of Certainty: Low

Recommendation 1: Based on the studies reviewed, patients taking only oral cannabis do not need any adjustments in ventilatory settings. Grade C

Recommendation 2: Adjustment of ventilatory settings should be considered since obstructive lung disease-like patterns may be associated with chronic cannabis consumption by inhalation, particularly in patients with comorbid conditions that are associated with an increased risk of pulmonary pathology. Grade C

Recommendation 3: Evidence is insufficient to guide ventilation settings following acute cannabis use via inhalation. Grade I

### Question 7: Do patients taking perioperative cannabinoids require any special postoperative considerations? If so, for how long?

The immediate effects of THC administration in humans results in dose-related tachycardia and increases in cardiac index.<sup>237–239</sup>

In the acute postoperative phase of care, MI, arrhythmias, stroke, cardiac arrest, and cardiomyopathy have been reported.<sup>123 239–244</sup>

A retrospective cohort analysis evaluating perioperative outcomes in major elective surgeries and CUD demonstrated an adjusted OR of postoperative MI of 1.88 (95% CI 1.31 to 2.69,  $p < 0.001$ ) for patients with a reported active CUD compared with those

without.<sup>241</sup> Mittleman *et al* interviewed 3882 patients with acute MI and conducted a case-crossover analysis that controlled for differences among patients, and found that within 1 hour after smoking marijuana, patients' risk of MI onset was elevated 4.8-fold (95% CI 2.9 to 9.5;  $p < 0.001$ ) compared with periods of nonuse.<sup>87</sup> However, in the second hour after smoking, the relative risk was 1.7 (95% CI 0.6 to 5.1;  $p = 0.34$ ), suggesting a rapid decline in the cardiac effects of marijuana. The supply-demand mismatch in oxygen coupled with the increased cardiovascular oxygen demands as a result of hypertension and tachycardia may explain the higher perioperative risk of acute MI among patients with CUD. Cannabis may induce hypothermia which has the potential to aggravate postoperative shivering.<sup>84</sup> Shivering will adversely affect the supply-demand mismatch in oxygen and may further increase the odds of postoperative MI. In another study the authors also demonstrated that active CUD may be associated with higher adjusted odds of suffering a postoperative acute cerebrovascular event.<sup>241</sup>

In a retrospective cohort of 510,007 patients reviewed between 2006 and 2015, CUD was also associated with a significantly higher incidence of acute MI ( $p = 0.001$ ) and perioperative stroke with vascular surgery ( $p = 0.031$ ).<sup>240</sup> Those with CUD had a higher incidence of perioperative MI (3.3% vs 2.1%; OR 1.56; 95% CI 1.09 to 2.24;  $p = 0.016$ ) and perioperative stroke (5.5% vs 3.5%; OR 1.59; 95% CI 1.20 to 2.12;  $p = 0.0013$ ) than patients without CUD. In another large retrospective cohort analysis of patients with CUD undergoing major elective surgeries, the adjusted odds of perioperative MI was 1.88 (95% CI 1.31 to 2.69,  $p < 0.001$ ) times higher for patients with a reported active CUD (89 of 13,603; 0.7%) compared with those without (46 of 13,603; 0.3%) an active CUD (unadjusted OR 2.88; 95% CI 2.34 to 3.55;  $p < 0.001$ ).<sup>241</sup> Owing to limitations in administrative data, it is unclear if this represents a true effect or selection bias; however, these findings do warrant further investigation. Calapai *et al* demonstrated several findings that indicate that CBD can modify the deleterious effects on the blood-brain barrier (BBB) caused by inflammatory cytokines and may play a pivotal role in ameliorating BBB dysfunction consequent to ischemia.<sup>242</sup> In a retrospective evaluation of the Personality and Total Health Through Life study ( $n = 2404$ ), Hemachandra *et al* found a 3.3-fold risk of shock/transient ischemic attack in cannabis users within the past year, but this elevated risk was specific only to participants who used cannabis at least weekly.<sup>243</sup> Patients using perioperative cannabinoids also appear to have a 3.24-fold increased risk of developing hypotension postoperatively (95% CI 1.12 TO 9.36,  $p = 0.03$ ).<sup>244</sup>

### Gastrointestinal system

Cannabis consumption has been associated with poor oral hygiene, caries, and periodontal disease, which may have implications for airway management.<sup>101 102</sup> Cannabis consumption is also linked to delayed gastric emptying, delayed intestinal motility, cyclical vomiting, cannabis hyperemesis syndrome and in surgical patients may also increase the risk of PONV.<sup>78 245 246</sup> The endocannabinoid system is involved in hepatic homeostasis with derangements in this system being implicated in hepatic steatosis, fibrogenesis, and hepatic cirrhosis. Apart from its effect on CB1 and CB2 receptors, cannabis can exert its effect on the gut vanilloid receptors resulting in mesenteric vasodilation.<sup>84</sup> More evidence on the topic is needed especially with special focus on the perioperative patients due to their implications on gastric emptying and subsequent airway management.

### Postoperative analgesia and hyperalgesia

As explained elsewhere in this guideline, there is growing evidence suggesting that long-term, frequent and infrequent marijuana users may experience increased postoperative pain and may require more opioids compared with non-users. In a systematic review and meta-analysis of 4259 patients, Abdallah *et al* demonstrated that patients receiving cannabinoids appeared to have an increased weighted mean difference of pain at 12 hours by 0.83 cm on a 10-cm visual analog scale (VAS). (95% CI 0.04 to 1.63,  $p = 0.04$ ) but no differences in severity of rest pain at 24 hours.<sup>244</sup> In addition, a retrospective pilot study investigating acute pain management in four trauma centers across the USA found that cannabis users reported higher pain scores and consumed larger quantities of opioids for management of acute pain (25%–37% higher) compared with non-cannabis users.<sup>123</sup> In addition, Jamal *et al* reported the effects of recreational cannabis smoking (prevalence 11.9%) on postoperative pain management within the first 24 hours after abdominal surgery. Cannabis users required a higher dose of postoperative morphine, extrapolated to 23% increased dose requirement in a model controlling for age, preoperative morphine use, and other comorbidities, and therefore increased vigilance to pain and opioid use in the postoperative phase may be required.<sup>247</sup>

A recent prospective study of 1335 adults undergoing elective surgery showed that cannabis users have higher pain levels and greater opioid use before and after surgery.<sup>123</sup>

Dose-dependent effects of inhaled marijuana may contribute to hyperalgesia.<sup>247</sup> While the mechanism for hyperalgesia is still unclear, it is postulated that it may be a phenomenon of long-term use and TRPV1 modulation.<sup>176 248</sup> Further discussion about the role of cannabis in pain will be discussed in subsequent questions.

Statement 1: Acute cannabis intoxication and active CUD may be associated with increased risk for acute postoperative MI and cerebrovascular morbidity. Level of certainty: Moderate

Statement 2: A cannabis-using patient may have delayed gastrointestinal motility and may also be at a higher risk for PONV. Level of certainty: Moderate

Statement 3: Cannabis users and patients with CUD may be associated with higher postoperative pain scores and opioids use. Level of certainty: Moderate

Recommendation 1: Based on the currently available evidence, we do not recommend the routine use of additional postoperative monitoring for cardiac or neurological adverse events. However, we do recommend increased vigilance given that cardiac and neurovascular events do frequently occur in the postoperative period. Grade C

Recommendation 2: Based on the currently available evidence, we recommend using multimodal analgesia incorporating regional analgesia if appropriate and using opioids as rescue medication. Patients may need additional follow-up for adequacy of analgesia and the need for adjusting postoperative pain medications accordingly. Grade C

### Question 8: Are there special considerations for concomitant opioid and cannabinoid use and should postoperative opioid prescriptions be adjusted prior to discharge?

Chronic pain is one of the most common indications for medical cannabis prescriptions.<sup>249</sup> However, not all patients who use cannabis for pain relief do so with the guidance of a knowledgeable clinician and therefore may use doses and formulations that lead to greater adverse effects, including alterations in pain and responses to opioids. Furthermore, it may be difficult to ascertain

the quantity of cannabinoid consumed as package labeling may be wildly inaccurate, even when obtained from state-licensed dispensaries.<sup>114</sup>

Multiple surveys of patients with chronic pain have found a significant number of reported reductions in opioid use through the use of cannabis, and case series report similar findings.<sup>250–256</sup> This outcome has not been consistently observed in RCTs and reviews of cannabis for chronic pain.<sup>257–259</sup> A propensity-matched retrospective analysis of a large national database found that non-medical use of cannabis was associated with a significantly greater risk of prescription opioid use disorder, while both medical and non-medical use purposes were associated with an increased risk of prescription opioid *misuse*.<sup>260</sup> However, such findings may depend on what tool is used to define opioid use disorder as some (such as the DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria) overestimate the diagnosis in chronic pain patients.

There are abundant preclinical data demonstrating interactions between the endogenous cannabinoid system and opioid pathways. CB1 and mu-opioid receptors may interact and have been shown to co-localize in the dorsal horn of the spinal cord in rats and share intracellular signaling pathways.<sup>261–263</sup> Cannabinoids may act on opioid receptors and opioid antagonists may block some of the effects of *THC*.<sup>263 264</sup> Local administration of naloxone inhibited the antinociceptive effects of an experimental CB2-receptor agonist in rats, and this drug was found to stimulate beta-endorphin release from cultured human skin cells.<sup>265</sup> CB1 and CB2 knockout mice display reduced antinociceptive responses to spinal and peripheral morphine but not systemic morphine compared with wild-type mice, suggesting that interactions between opioid and cannabinoid receptors may not contribute to supraspinal analgesia.<sup>266</sup> *Intrathecal* *THC* produced antinociception in a rat model of neuropathic pain that was not reversed by naloxone.<sup>267</sup> Several CB2-receptor agonists have been found to have analgesic effects that are additive or synergistic with opioids depending on the drug combinations and pain models studied.<sup>268 269</sup> In rats, systemic *THC* has an additive analgesic effect when combined with morphine, while, a full cannabinoid-receptor agonist showed synergistic effects in a pain model.<sup>270</sup> A meta-analysis of 19 preclinical studies found a synergistic effect between cannabis and opioids.<sup>258</sup>

In patients taking stable doses of opioids for chronic pain, the administration of vaporized cannabis over 5 days resulted in statistically significant reductions in chronic pain without alterations in blood levels of opioids or changes in pulse oximetry values.<sup>271</sup> It has been postulated that cannabinoid-opioid interactions may have a role in treating opioid withdrawal.<sup>272 273</sup> Cannabinoids may ameliorate the symptoms of opioid withdrawal in humans and animals; studies of adjunctive cannabinoid administration during opioid detoxification have not found an increased rate of serious adverse events.<sup>274 275</sup>

A single oral dose of cannabis extract containing 10–15 mg *THC* after surgery produced significant analgesia and significant sedation compared with a 5 mg dose suggesting a dose-dependent effect although there was no placebo group for comparison.<sup>237</sup> Retrospective analyses have found the addition of dronabinol to the postoperative pain regimen was associated with improved pain control, significantly reduced opioid consumption, independent of patients' preadmission cannabis use and consequently significantly shorter length of stay.<sup>124 276</sup> However, when authors compared opioid consumption between groups per same inpatient days, there was no difference in opioid consumption. Unfortunately, these studies did not examine the frequency of adverse events between the groups.

A single dose of the cannabinoid levonantradol produced significant but not dose-dependent analgesia after surgery compared with placebo but was associated with frequent but primarily mild side effects.<sup>277</sup> In other randomized placebo-controlled trials, oral *THC*, dronabinol, nabilone, and novel experimental cannabinoid-receptor agonists given perioperatively did not appear to reduce postoperative pain or opioid use compared with placebo, and perioperative high-dose nabilone was associated with higher pain scores at rest and with movement compared with placebo.<sup>128 278–282</sup> There is little evidence to support the use of cannabinoids for acute pain.<sup>283</sup> A 2020 meta-analysis of cannabis for the treatment of acute postoperative pain based on eight RCTs and four observational studies found no difference in rest pain at 1, 6 or 24 hours after surgery or cumulative opioid consumption at 2 or 24 hours postoperatively compared with controls.<sup>284</sup> Rather, patients receiving cannabinoids reported significantly greater pain scores compared with controls in three studies that evaluated pain at 12 hours after surgery. Notably, patients who received cannabinoids had 3.24 times greater odds of developing postoperative hypotension compared with controls (95% CI 1.12 to 9.36;  $p=0.03$ ).<sup>284</sup>

Few clinical or experimental studies of cannabis and opioid coadministration in healthy participants have reported adverse effects on vital signs. In one study involving healthy volunteers, the co-administration of dronabinol 20 mg with an opioid failed to produce analgesia for any pain modality and antagonized morphine analgesia for pressure pain.<sup>285</sup> Dronabinol alone significantly increased heart rate but changes in oxygen saturation were only observed when *THC* and morphine were combined. An intravenous dose of *THC* after oxymorphone increased sedation and further decreased ventilation and  $\text{CO}_2$ -ventilatory response without significantly changing respiratory rate.<sup>286</sup> The combination of oxymorphone and *THC* increased cardiac index and heart rate while decreasing total peripheral resistance, but blunted the cardiovascular response to increasing  $\text{CO}_2$ .<sup>286</sup> In a study specifically designed to assess safety, a bolus of fentanyl 1  $\mu\text{g}/\text{kg}$  following by either 400 or 800 mg of oral CBD resulted in no respiratory depression or cardiovascular complications.<sup>58</sup> Among patients undergoing endoscopy, those who reported daily cannabis use required more fentanyl for procedural sedation than patients who did not use cannabis, but no significant group differences in postprocedure recovery time or frequency of cardiopulmonary events were reported.<sup>287</sup> Multiple observational studies reported a positive association between preoperative cannabis use and postoperative pain and opioid use. A retrospective cohort study of outcomes after total knee arthroplasty, which excluded patients with a history of opioid use, found no difference in postoperative inpatient opioid administration between cannabis users and non-users.<sup>288</sup> Among trauma patients, a history of marijuana use was associated with higher opioid use and pain scores during hospitalization.<sup>124</sup> A survey study of musculoskeletal trauma patients reported that patients using cannabis during recovery reported greater levels of pain relief and reduced opioid consumption.<sup>289</sup> However, among patients who reported marijuana use during recovery from a musculoskeletal injury, there was an increase in total prescribed opioid dose and duration of opioid use compared with patients who had never used marijuana, even among patients who specifically reported that marijuana decreased their opioid use.<sup>125</sup> In adolescent trauma patients, a history of marijuana use was positively associated with duration of opioid use after injury.<sup>290</sup> Interestingly, a history of marijuana use was associated with significantly higher postoperative opioid use yet a trend toward lower pain scores after bariatric surgery.<sup>126</sup>

The assessment of cannabis use on postoperative pain and opioid use is complicated by frequent comorbid preoperative opioid use. Several retrospective studies of patients undergoing elective surgery reported that patients using cannabis preoperatively were significantly more likely to also use opioids and benzodiazepines before surgery compared with patients who did not use cannabis.<sup>73 117 123 129</sup> A retrospective cohort study of early postoperative pain after major orthopedic surgery in patients who reported a history of cannabis or cannabinoid use found that patients using preoperative cannabis were not more likely to use opioids compared matched controls.<sup>73</sup> The patients using cannabis had significantly greater pain scores at rest and with movement, and higher incidence of sleep disruption compared with propensity-matched control patients, with a non-significant trend toward greater opioid use among patients who used cannabis.<sup>73</sup> In contrast, Jamal *et al*<sup>291</sup> found significantly higher postoperative opioid use among cannabis users than non-users, but this finding lost significance ( $p=0.06$ ) once additional variables including preoperative opioid use were included in the statistical model.

Statement 1: Cannabinoid studies in patients taking opioids for chronic pain suggest that there may be a therapeutic benefit of low-dose THC on pain and opioid use, but the opioid-sparing effect is not apparent in the setting of acute pain. Level of certainty: Low

Statement 2: None of the studies reviewed identified any increase in significant adverse events (moderate to severe respiratory depression or nausea/vomiting) with the co-administration of THC and an opioid in experimental studies with healthy volunteers, and few studies reported on these outcomes in the clinical setting. Level of certainty: Low

Statement 3: There is evidence of increased pain and opioid requirements postoperatively among patients who use cannabis. Level of certainty: Low

Recommendation 1: Opioids may be administered when indicated for the management of perioperative pain in patients who use cannabis with increased vigilance. Grade C

Recommendation 2: There is insufficient evidence to recommend for or against adjusting postoperative opioid prescriptions in surgical patients who consume cannabinoids. Grade I

### Question 9: How do cannabis withdrawal symptoms present in the postoperative period and is there evidence for specific treatment?

Cannabis withdrawal symptoms (CWS) can occur in the postoperative period.<sup>292</sup> A thorough preoperative cannabis use history aimed at understanding the quantity of cannabis routinely consumed may be difficult to obtain but is important for assessing the risk of withdrawal. Human and animal studies have suggested there is minimal risk of developing CWS with products containing CBD only.<sup>293 294</sup>

The DSM-5 criteria for the diagnosis of CWS includes the abrupt cessation of prolonged or heavy cannabis use accompanied by three or more symptoms including irritability or anger, anxiety, insomnia, decreased appetite, restlessness, altered mood and a physical symptom causing significant discomfort (ie, abdominal pain, tremors, sweating, fever, chills, or headache).<sup>295</sup> Symptoms of CWS can occur 24 to 72 hours after cannabis cessation, peak in the first week, and can last up to 2 weeks.<sup>296</sup> 'Heavy cannabis use' is not defined in the diagnostic criteria of the DSM-5.<sup>295</sup> The magnitude of cannabis withdrawal can be related to the quantity of cannabis consumed and is often seen following cessation of prolonged high-quantity cannabis use.<sup>296</sup> A Canadian panel of experts suggested in a consensus document that there should be a high index of suspicion for cannabis withdrawal

postoperatively in patients who consume greater than 1.5 g/day of inhaled cannabis or 20 mg/day THC-dominant cannabis oil.<sup>292</sup> In addition, patients consuming a cannabis product with an unknown phytocannabinoid content more than 2–3 times per day are at risk for cannabis withdrawal.

Cannabis users who are at risk for withdrawal (see above) should be monitored for cannabis withdrawal postoperatively. The Cannabis Withdrawal Scale<sup>297</sup> can be used to monitor severity of the withdrawal symptoms. Withdrawal for a hospitalized patient can manifest as disrupted sleep, inadequate pain control, changes in opioid use, agitation, restlessness, and even early discontinuation of treatment.

Animal models suggest the cerebellum may mediate cannabis withdrawal.<sup>298</sup> Another postulated mechanism is that regular cannabis use is associated with a down-regulation and desensitization of cortical and subcortical CB1 receptors, which begins to reverse after 24–48 hours of abstinence before returning to normal in approximately 4 weeks.<sup>299</sup> Several pharmacological treatments for CWS exist including cannabinoid agonists,<sup>300</sup> gabapentin,<sup>301</sup> and N-acetylcysteine.<sup>302</sup> A phase 2a pilot study examined the safety and efficacy of gabapentin for the treatment of cannabis dependence. A 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted in 50 treatment-seeking outpatients for CUD. Gabapentin 1200 mg significantly decreased withdrawal symptoms as measured by the Marijuana Withdrawal Checklist compared with placebo.<sup>301</sup> The FAAH inhibitor, PF-7845, reduced CWS and cannabis use in a double-blind, placebo-controlled, parallel group phase 2a trial of 48 men with CUD.<sup>303</sup> A larger replication trial is currently ongoing. At the time of this document, replacement therapy with a cannabinoid agonist has the most supportive evidence as a treatment to minimize CWS.<sup>304</sup> The most common cannabinoid agonists available in the USA are dronabinol, a synthetic form of THC, and nabilone, a synthetic THC derivative. Dronabinol significantly reduced CWS at a dose of 20 mg twice daily but failed to show efficacy in reducing CUD.<sup>300</sup> Nabilone attenuated cannabis withdrawal and relapse in an experimental medicine study.<sup>305</sup> The panel acknowledges that dronabinol and nabilone are not FDA-approved for this indication in the USA. Both are approved by the FDA for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.<sup>306</sup>

Statement: CWS may present in the postoperative period. Highest risk patients are those consuming high quantities or unknown amounts of THC containing products. The risk is considered to be less with individuals consuming CBD dominant (>10:1 CBD to THC ratio) products. Level of certainty: Moderate

Recommendation 1: Patients using cannabis should be counseled regarding the risk of CWS. Postoperatively, patients that consume cannabis routinely should be monitored for CWS using a validated and reliable scale. Grade C

Recommendation 2: The expert panel came to the consensus that initiating a cannabinoid agonist such as dronabinol at a low dose is the best choice to treat severe CWS postoperatively. Grade C

### CONCLUSION

The medical, social, and political landscape of cannabis is fluid, changing on an almost daily basis. Cannabinoid use in the perioperative setting has significant potential negative medical implications. We hope these guidelines will help both clinicians and researchers in their pursuit of optimal patient care. In accordance with the National Academy of Medicine's standards for

developing clinical practice guidelines the ASRA Pain Medicine task force will continue monitoring newly released relevant publications following the publication of this guideline and may revise the entire document or specific sections if new evidence warrants updated recommendations.

#### Author affiliations

<sup>1</sup>Dept of Anesthesiology & Perioperative Care, UC Irvine Health, Orange, California, USA

<sup>2</sup>Anesthesiology and Perioperative Medicine, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, USA

<sup>3</sup>Anesthesia, University of Iowa Healthcare, Iowa City, Iowa, USA

<sup>4</sup>Anesthesiology and Pain Medicine, Univ Toronto, Toronto, Ontario, Canada

<sup>5</sup>Anesthesiology, Cedars-Sinai Medical Center, Los Angeles, California, USA

<sup>6</sup>Anesthesiology, University of Colorado Health, Aurora, Colorado, USA

<sup>7</sup>Anesthesiology and Perioperative Care, University of California Irvine, Irvine, California, USA

<sup>8</sup>National Pain Advocacy Center, Golden, Colorado, USA

<sup>9</sup>AABP Integrative Pain Care, Melville, New York, USA

<sup>10</sup>Anesthesiology, Maimonides Medical Center, Brooklyn, New York, USA

<sup>11</sup>Anesthesiology, Mayo Clinic, Rochester, Minnesota, USA

<sup>12</sup>Anesthesiology, Division of Pain Medicine, University of California San Diego, La Jolla, California, USA

<sup>13</sup>Center for Pain Medicine, Western Reserve Hospital, Cuyahoga Falls, Ohio, USA

**Correction notice** This article has been corrected since it published Online First. The title and heading for question 6 has been updated

**Twitter** Shalini Shah @ShaliniShahMD, Eric S Schwenk @ESchwenkMD, Rakesh V Sondekoppam @rakesh6282, Hance Clarke @drhaclarke, Gary Schwartz @garyschwartzmd and Samer Narouze @NarouzeMD

**Acknowledgements** Copyediting and formatting performed by Bridget Colvin, PhD, and Emma Hitt Nichols, PhD, on behalf of Nascent Medical, LLC. The authors wish to thank Ms. Angela Stengel for assisting with coordination of this project.

**Contributors** All authors contributed to the researching, drafting, and final writing and approval of this manuscript. SS is the guarantor for this manuscript and accepts full responsibility for its content.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** SS discloses consultant honorarium from Masimo, Allergan and SPR Therapeutics. HC is supported in part by a Merit Award from the Department of Anesthesiology and Pain Medicine at the University of Toronto (Toronto, Canada). The remaining authors declare no competing interests.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data such as group vote tallies and comments on each Delphi round are available upon request.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

#### ORCID iDs

Shalini Shah <http://orcid.org/0000-0001-5200-225X>

Eric S Schwenk <http://orcid.org/0000-0003-3464-4149>

Rakesh V Sondekoppam <http://orcid.org/0000-0003-1132-9066>

Hance Clarke <http://orcid.org/0000-0003-4975-3823>

W Michael Hooten <http://orcid.org/0000-0001-5645-6355>

Eugene R Viscusi <http://orcid.org/0000-0003-0260-4396>

Samer Narouze <http://orcid.org/0000-0003-1849-1402>

#### REFERENCES

- Centers for Disease Control and Prevention. Process for updating the opioid prescribing guideline. Available: <https://www.cdc.gov/opioids/guideline-update/index.html> [Accessed 23 Jun 2022].
- National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington (DC) National Academies Press (US); 2017.
- Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2017 national survey on drug use and health (HHS publication No. SMA 18-5068, NSDUH series H-53). Rockville, MD Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2018. <https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFRR2017/NSDUHFRR2017.pdf> <https://www.samhsa.gov/marijuana>
- State Medical Marijuana Laws. National conference of state legislatures (NCSL). Available: <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx#3> [Accessed 25 Apr 2020].
- Narouze S, Hakim SM, Kohan L, et al. Medical cannabis attitudes and beliefs among pain physicians. *Reg Anesth Pain Med* 2020;45:917–9.
- Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. *J Am Chem Soc* 1964;86:1646–7.
- Vučković S, Srebro D, Vujović KS, et al. Cannabinoids and pain: new insights from old molecules. *Front Pharmacol* 2018;9:1259.
- Mehmedic Z, Chandra S, Slade D, et al. Potency trends of Δ9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci* 2010;55:1209–17.
- Howlett AC, Barth F, Bonner TI, et al. International Union of pharmacology. XXVII. classification of cannabinoid receptors. *Pharmacol Rev* 2002;54:161–202.
- Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and Delta9-tetrahydrocannabinol. *Br J Pharmacol* 2008;153:199–215.
- Pertwee RG. Pharmacological actions of cannabinoids. *Handb Exp Pharmacol* 2005;168:1–51.
- Rice ASC, Farquhar-Smith WP, Nagy I. Endocannabinoids and pain: spinal and peripheral analgesia in inflammation and neuropathy. *Prostaglandins Leukot Essent Fatty Acids* 2002;66:243–56.
- Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 2006;58:389–462.
- Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: an overview. *Int J Obes* 2006;30 Suppl 1:S13–18.
- Pistis M, Ferraro L, Pira L, et al. Delta(9)-tetrahydrocannabinol decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex: an in vivo microdialysis study. *Brain Res* 2002;948:155–8.
- Gardner EL. Endocannabinoid signaling system and brain reward: emphasis on dopamine. *Pharmacol Biochem Behav* 2005;81:263–84.
- Pisanu A, Acquas E, Fenu S, et al. Modulation of Delta(9)-THC-induced increase of cortical and hippocampal acetylcholine release by micro opioid and D(1) dopamine receptors. *Neuropharmacology* 2006;50:661–70.
- Justinova Z, Goldberg SR, Heishman SJ, et al. Self-Administration of cannabinoids by experimental animals and human marijuana smokers. *Pharmacol Biochem Behav* 2005;81:285–99.
- Ryberg E, Larsson N, Sjögren S, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* 2007;152:1092–101.
- Amin MR, Ali DW. Pharmacology of Medical Cannabis. In: Bukiya AN, ed. *Recent advances in cannabinoid physiology and pathology*. Springer, 2019: 151–65. <https://link.springer.com/book/>
- Basbaum AI, Bautista DM, Scherrer G, et al. Cellular and molecular mechanisms of pain. *Cell* 2009;139:267–84.
- Russell C, Rueda S, Room R, et al. Routes of administration for cannabis use - basic prevalence and related health outcomes: A scoping review and synthesis. *Int J Drug Policy* 2018;52:87–96.
- Varlet V, Concha-Lozano N, Berthet A, et al. Drug vaping applied to cannabis: Is "Cannavaping" a therapeutic alternative to marijuana? *Sci Rep* 2016;6:25599.
- Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, delta9-tetrahydrocannabinol, cannabidiol and cannabinol. *Handb Exp Pharmacol* 2005;168:657–90.
- Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. II. models for the prediction of time of marijuana exposure from plasma concentrations of delta 9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (THCCOOH). *J Anal Toxicol* 1992;16:283–90.
- Lindgren JE, Ohlsson A, Agurell S, et al. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology* 1981;74:208–12.
- Chiang CW, Barnett G. Marijuana effect and delta-9-tetrahydrocannabinol plasma level. *Clin Pharmacol Ther* 1984;36:234–8.
- Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003;42:327–60.
- Abrams DI, Vizoso HP, Shade SB, et al. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther* 2007;82:572–8.



- 30 Ohlsson A, Lindgren JE, Wahlén A, *et al.* Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users. *Biomed Spectrom* 1982;9:6–10.
- 31 Harvey DJ, Samara E, Mechoulam R. Comparative metabolism of cannabidiol in dog, rat and man. *Pharmacol Biochem Behav* 1991;40:523–32.
- 32 Grotenhermen F. Harm reduction associated with inhalation and oral administration of cannabis and THC. *Journal of Cannabis Therapeutics* 2001;1:133–52.
- 33 Zgair A, Wong JC, Lee JB, *et al.* Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. *Am J Transl Res* 2016;8:3448–59.
- 34 Widman M, Agurell S, Ehrnebo M, *et al.* Binding of (+)- and (minus)-delta-1-tetrahydrocannabinols and (minus)-7-hydroxy-delta-1-tetrahydrocannabinol to blood cells and plasma proteins in man. *J Pharm Pharmacol* 1974;26:914–6.
- 35 Wall ME, Sadler BM, Brine D, *et al.* Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther* 1983;34:352–63.
- 36 Barnett G, Chiang CW, Perez-Reyes M, *et al.* Kinetic study of smoking marijuana. *J Pharmacokinetic Biopharm* 1982;10:495–506.
- 37 Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. *J Pharmacol Exp Ther* 1980;215:35–44.
- 38 Bebee B, Taylor DM, Bourke E, *et al.* The CANBACK trial: a randomised, controlled clinical trial of oral cannabidiol for people presenting to the emergency department with acute low back pain. *Med J Aust* 2021;214:370–5.
- 39 Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006;66:234–46.
- 40 Bergamaschi MM, Queiroz RHC, Zuardi AW, *et al.* Safety and side effects of cannabidiol, a cannabis sativa constituent. *Curr Drug Saf* 2011;6:237–49.
- 41 Laprairie RB, Bagher AM, Kelly MEM, *et al.* Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *Br J Pharmacol* 2015;172:4790–805.
- 42 McPartland JM, Duncan M, Di Marzo V, *et al.* Are cannabidiol and  $\Delta(9)$ -tetrahydrocannabinol negative modulators of the endocannabinoid system? A systematic review. *Br J Pharmacol* 2015;172:737–53.
- 43 Tham M, Yilmaz O, Alaverdashvili M, *et al.* Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. *Br J Pharmacol* 2019;176:1455–69.
- 44 Ryberg E, Larsson N, Sjögren S, *et al.* The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* 2007;152:1092–101.
- 45 Kathmann M, Flau K, Redmer A, *et al.* Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn Schmiedebergs Arch Pharmacol* 2006;372:354–61.
- 46 Lewke FM, Piomelli D, Pahlisch F, *et al.* Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012;2:e94.
- 47 Millar SA, Stone NL, Yates AS, *et al.* A systematic review on the pharmacokinetics of cannabidiol in humans. *Front Pharmacol* 2018;9:1365.
- 48 Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers* 2007;4:1770–804.
- 49 Agurell S, Hallidin M, Lindgren JE, *et al.* Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* 1986;38:21–43.
- 50 Consroe P, Kennedy K, Schram K. Assay of plasma cannabidiol by capillary gas chromatography/ion trap mass spectroscopy following high-dose repeated daily oral administration in humans. *Pharmacol Biochem Behav* 1991;40:517–22.
- 51 Ujváry I, Hanuš L. Human metabolites of cannabidiol: a review on their formation, biological activity, and relevance in therapy. *Cannabis Cannabinoid Res* 2016;1:90–101.
- 52 MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med* 2018;49:12–19.
- 53 Yamaori S, Ebisawa J, Okushima Y, *et al.* Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety. *Life Sci* 2011;88:730–6.
- 54 Yamaori S, Koeda K, Kushihara M, *et al.* Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. *Drug Metab Pharmacokinetic* 2012;27:294–300.
- 55 Bouquié R, Deslandes G, Mazaré H, *et al.* Cannabis and anticancer drugs: societal usage and expected pharmacological interactions - a review. *Fundam Clin Pharmacol* 2018;32:462–84.
- 56 Zendulka O, Dovrtělová G, Nosková K, *et al.* Cannabinoids and cytochrome P450 interactions. *Curr Drug Metab* 2016;17:206–26.
- 57 Epidiolex. Prescribing information. Jazz Pharmaceuticals, 2022. Available: [https://www.epidiox.com/sites/default/files/pdfs/0222/EPX-03645-0222-EPIDIOLEX\\_\(cannabidiol\)\\_USPI.pdf](https://www.epidiox.com/sites/default/files/pdfs/0222/EPX-03645-0222-EPIDIOLEX_(cannabidiol)_USPI.pdf) [Accessed 23 Jun 2022].
- 58 Manini AF, Yiannoulos G, Bergamaschi MM, *et al.* Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *J Addict Med* 2015;9:204–10.
- 59 Vierke C, Marxen B, Boettcher M, *et al.* Buprenorphine-cannabis interaction in patients undergoing opioid maintenance therapy. *Eur Arch Psychiatry Clin Neurosci* 2021;271:847–56.
- 60 Damkier P, Lassen D, Christensen MMH, *et al.* Interaction between warfarin and cannabis. *Basic Clin Pharmacol Toxicol* 2019;124:28–31.
- 61 Grayson L, Vines B, Nichol K, *et al.* An interaction between warfarin and cannabidiol, a case report. *Epilepsy Behav Case Rep* 2018;9:10–11.
- 62 Greger J, Bates V, Mechtler L, *et al.* A review of cannabis and interactions with anticoagulant and antiplatelet agents. *J Clin Pharmacol* 2020;60:432–8.
- 63 Narouze S, Strand N, Roychoudhury P. Cannabinoids-based medicine pharmacology, drug interactions, and perioperative management of surgical patients. *Adv Anesth* 2020;38:167–88.
- 64 Lucas CJ, Galetti P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol* 2018;84:2477–82.
- 65 Antoniou T, Bodkin J, Ho JM-W. Drug interactions with cannabinoids. *CMAJ* 2020;192:E206.
- 66 Foster BC, Abramovici H, Harris CS. Cannabis and cannabinoids: kinetics and interactions. *Am J Med* 2019;132:1266–70.
- 67 Brown J, Winterstein A. Potential adverse drug events and Drug–Drug interactions with medical and consumer cannabidiol (CBD) use. *J Clin Med* 2019;8:989.
- 68 U.S. Preventive Services Task Force. Grade definitions. Available: <https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions> [Accessed 23 Jun 2022].
- 69 Cohen SP, Bhaskar A, Bhatia A, *et al.* Consensus practice guidelines on interventions for lumbar facet joint pain from a Multispecialty, International Working group. *Reg Anesth Pain Med* 2020;45:424–67.
- 70 Cohen SP, Bhatia A, Buvanendran A, *et al.* Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of regional anesthesia and pain medicine, the American Academy of pain medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018;43:1–546.
- 71 American Society of Anesthesiologists. Basic standards for Preanesthesia care. Available: <https://www.asahq.org/standards-and-guidelines/basic-standards-for-preanesthesia-care> [Accessed 05 Feb 2022].
- 72 Patnode CD, Perdue LA, Rushkin M. Screening for unhealthy drug use in primary care in adolescents and adults, including pregnant persons: updated systematic review for the U.S. preventive services Task force. Rockville (MD) Agency for Healthcare Research and Quality (US); 2020.
- 73 Liu CW, Bhatia A, Buzon-Tan A, *et al.* Weeding out the problem: the impact of preoperative cannabinoid use on pain in the perioperative period. *Anesth Analg* 2019;129:874–81.
- 74 Alexander JC, Joshi GP. A review of the anesthetic implications of marijuana use. *Proc* 2019;32:364–71.
- 75 Adamson SJ, Kay-Lambkin FJ, Baker AL, *et al.* An improved brief measure of cannabis misuse: the cannabis use disorders identification Test-Revised (CUDIT-R). *Drug Alcohol Depend* 2010;110:137–43.
- 76 Abramovici H, Health Canada. Information for health care professionals: cannabis (marijuana, marijuana) and the cannabinoids, 2018. Available: <https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids-eng.pdf> [Accessed 23 Jun 2022].
- 77 Montoya Z, Conroy M, Vanden Heuvel BD, *et al.* Cannabis contaminants limit pharmacological use of cannabidiol. *Front Pharmacol* 2020;11:571832.
- 78 Suhre W, O'Reilly-Shah V, Van Cleve W. Cannabis use is associated with a small increase in the risk of postoperative nausea and vomiting: a retrospective machine-learning causal analysis. *BMC Anesthesiol* 2020;20:115.
- 79 US Centers for Disease Control and Prevention. Increases in availability of cannabis products containing delta-8 THC and reported cases of adverse events. contract No.: CDCHAN-00451. Available: <https://stacks.cdc.gov/view/cdc/109759> [Accessed 26 Jun 2022].
- 80 Martel ML, Klein LR, Miner JR, *et al.* A brief assessment of capacity to consent instrument in acutely intoxicated emergency department patients. *Am J Emerg Med* 2018;36:18–23.
- 81 Dellalazzo L, Potvin S, Giguère S, *et al.* Evidence on the acute and residual neurocognitive effects of cannabis use in adolescents and adults: a systematic meta-review of meta-analyses. *Addiction* 2022;117:1857–70.
- 82 McCartney D, Arkell TR, Irwin C, *et al.* Determining the magnitude and duration of acute  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC)-induced driving and cognitive impairment: A systematic and meta-analytic review. *Neurosci Biobehav Rev* 2021;126:175–93.
- 83 Andonian DO, Seaman SR, Josephson EB. Profound hypotension and bradycardia in the setting of synthetic cannabinoid intoxication - A case series. *Am J Emerg Med* 2017;35:940.e5–940.e6.
- 84 Echeverría-Villalobos M, Todeschini AB, Stoicea N, *et al.* Perioperative care of cannabis users: a comprehensive review of pharmacological and anesthetic considerations. *J Clin Anesth* 2019;57:41–9.
- 85 Lucas CJ, Galetti P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol* 2018;84:2477–82.
- 86 Goel A, McGuinness B, Jivraj NK. Cannabis use disorder and perioperative outcomes in major elective surgeries: a retrospective cohort analysis. *Anesthesiology* 2020;625–35.
- 87 Mittleman MA, Lewis RA, Maclure M, *et al.* Triggering myocardial infarction by marijuana. *Circulation* 2001;103:2805–9.

- 88 Aronow WS, Cassidy J. Effect of marijuana and placebo-marijuana smoking on angina pectoris. *N Engl J Med* 1974;291:65–7.
- 89 Patel RS, Katta SR, Patel R, et al. Cannabis use disorder in young adults with acute myocardial infarction: trend inpatient study from 2010 to 2014 in the United States. *Cureus* 2018;10:e3241.
- 90 Patel RS, Kamil SH, Bachu R, et al. Marijuana use and acute myocardial infarction: a systematic review of published cases in the literature. *Trends Cardiovasc Med* 2020;30:298–307.
- 91 Richards JR, Blohm E, Toles KA, et al. The association of cannabis use and cardiac dysrhythmias: a systematic review. *Clin Toxicol* 2020;58:861–9.
- 92 Courts J, Maskill V, Gray A, et al. Signs and symptoms associated with synthetic cannabinoid toxicity: systematic review. *Australas Psychiatry* 2016;24:598–601.
- 93 Dickerson SJ. Cannabis and its effect on anesthesia. *AANA J* 1980;48:526–8.
- 94 Huson HB, Granados TM, Rasko Y. Surgical considerations of marijuana use in elective procedures. *Heliyon* 2018;4:e00779.
- 95 Alshaarawy O, Sidney S, Auer R, et al. Cannabis use and markers of systemic inflammation: the coronary artery risk development in young adults study. *Am J Med* 2019;132:1327–34.
- 96 Jakob J, von Wyl R, Stalder O, et al. Cumulative marijuana use and carotid intima-media thickness at middle age: the CARDIA study. *Am J Med* 2021;134:777–87.
- 97 Auer R, Sidney S, Goff D, et al. Lifetime marijuana use and subclinical atherosclerosis: the coronary artery risk development in young adults (CARDIA) study. *Addiction* 2018;113:845–56.
- 98 Rodondi N, Pletcher MJ, Liu K. Coronary artery risk development in young adults (cardia) study. marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *Am J Cardiol* 2006;98:478–84.
- 99 Reis JP, Auer R, Bancks MP, et al. Cumulative lifetime marijuana use and incident cardiovascular disease in middle age: the coronary artery risk development in young adults (CARDIA) study. *Am J Public Health* 2017;107:601–6.
- 100 Chami T, Kim CH. Cannabis abuse and elevated risk of myocardial infarction in the young: a population-based study. *Mayo Clin Proc* 2019;94:1647–9.
- 101 Underner M, Maes I, Urban T, et al. [Effects of smoking on periodontal disease]. *Rev Mal Respir* 2009;26:1057–73.
- 102 Liu C, Qi X, Yang D, et al. The effects of cannabis use on oral health. *Oral Dis* 2020;26:1366–74.
- 103 Aldington S, Williams M, Nowitz M, et al. Effects of cannabis on pulmonary structure, function and symptoms. *Thorax* 2007;62:1058–63.
- 104 Hancox RJ, Gray AR, Zhang X, et al. Differential effects of cannabis and tobacco on lung function in mid-adult life. *Am J Respir Crit Care Med* 2022;205:1179–85.
- 105 Vakharia RM, Mannino A, Salem HS, et al. The association between cannabis use disorder and the outcome following primary total hip arthroplasty: analysis of a nationwide administrative claims database. *Bone Joint J* 2021;103-B:111–5.
- 106 Abdallah SJ, Smith BM, Ware MA, et al. Effect of vaporized cannabis on exertional breathlessness and exercise endurance in advanced chronic obstructive pulmonary disease. A randomized controlled trial. *Ann Am Thorac Soc* 2018;15:1146–58.
- 107 Roth MD, Arora A, Barsky SH, et al. Airway inflammation in young marijuana and tobacco smokers. *Am J Respir Crit Care Med* 1998;157:928–37.
- 108 Moore BA, Augustson EM, Moser RP, et al. Respiratory effects of marijuana and tobacco use in a U.S. sample. *J Gen Intern Med* 2005;20:33–7.
- 109 Sloan M. Uvulitis from smoking marijuana. *Pediatric Notes* 1985;9:56.
- 110 Tennant FS, Prendergast TJ. Medical manifestations associated with hashish. *JAMA* 1971;216:1965–9.
- 111 Pertwee RG. Neuropharmacology and therapeutic potential of cannabinoids. *Addict Biol* 2000;5:37–46.
- 112 World Health Organization & WHO Expert Committee on Drug Dependence. WHO expert Committee on drug dependence: fortieth report. license: CC BY-NC-SA 3.0 IGO, 2018. Available: <https://apps.who.int/iris/handle/10665/279948> [Accessed 22 Aug 2022].
- 113 Iffland K, Grotenhermen F. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. *Cannabis Cannabinoid Res* 2017;2:139–54.
- 114 Bonn-Miller MO, Loflin MJE, Thomas BF, et al. Labeling accuracy of cannabidiol extracts sold online. *JAMA* 2017;318:1708–9.
- 115 Ladha KS, McLaren-Blades A, Goel A, et al. Perioperative pain and addiction interdisciplinary network (pain): consensus recommendations for perioperative management of cannabis and cannabinoid-based medicine users by a modified Delphi process. *Br J Anaesth* 2021;126:304–18.
- 116 Stewart C, Fong Y. Perioperative cannabis as a potential solution for reducing opioid and benzodiazepine dependence. *JAMA Surg* 2021;156:181–90.
- 117 Denduluri SK, Woolson ST, Indelli PF, et al. Cannabinoid and opioid use among total joint arthroplasty patients: a 6-year, single-institution study. *Orthopedics* 2021;44:e101–6.
- 118 Wendelboe AM, Mathew R, Chongsuwan T, et al. Is there less opioid abuse in states where marijuana has been decriminalized, either for medicinal or recreational use? A Clin-IQ. *J Patient Cent Res Rev* 2019;6:267–73.
- 119 Lake S, Walsh Z, Kerr T, et al. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: a longitudinal analysis. *PLoS Med* 2019;16:e1002967.
- 120 Livingston MD, Barnett TE, Delcher C, et al. Recreational cannabis legalization and opioid-related deaths in Colorado, 2000–2015. *Am J Public Health* 2017;107:1827–9.
- 121 Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ* 2018;58:29–42.
- 122 Schneider-Smith E, Salottolo K, Swartwood C, et al. Matched pilot study examining cannabis-based dronabinol for acute pain following traumatic injury. *Trauma Surg Acute Care Open* 2020;5:e000391.
- 123 McAfee J, Boehnke KF, Moser SM, et al. Perioperative cannabis use: a longitudinal study of associated clinical characteristics and surgical outcomes. *Reg Anesth Pain Med* 2021;46:137–44.
- 124 Salottolo K, Peck L, Tanner li A, et al. The grass is not always greener: a multi-institutional pilot study of marijuana use and acute pain management following traumatic injury. *Patient Saf Surg* 2018;12:16.
- 125 Bhashyam AR, Heng M, Harris MB, et al. Self-Reported marijuana use is associated with increased use of prescription opioids following traumatic musculoskeletal injury. *J Bone Joint Surg Am* 2018;100:2095–102.
- 126 Bauer FL, Donahoo WT, Hollis HW, et al. Marijuana's influence on pain scores, initial weight loss, and other bariatric surgical outcomes. *Perm J* 2018;22:18–002.
- 127 Wallace MS, Marcotte TD, Atkinson JH, et al. A secondary analysis from a randomized trial on the effect of plasma tetrahydrocannabinol levels on pain reduction in painful diabetic peripheral neuropathy. *J Pain* 2020;21:1175–86.
- 128 Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. *Can J Anaesth* 2006;53:769–75.
- 129 Jennings JM, Williams MA, Levy DL, et al. Has self-reported marijuana use changed in patients undergoing total joint arthroplasty after the legalization of marijuana? *Clin Orthop Relat Res* 2019;477:95–100.
- 130 Banks K, Biswas S, Wong M, et al. Cannabis use is associated with increased mechanical ventilation and polysubstance use in trauma patients. *Am Surg* 2019;85:226–9.
- 131 Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2019 national survey on drug use and health, 2020. Available: <https://www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRDFWHTML/2019NSDUHFFR1PDF/W090120.pdf> [Accessed 05 Feb 2022].
- 132 Young-Wolff KC, Ray GT, Alexeff SE, et al. Rates of prenatal cannabis use among pregnant women before and during the COVID-19 pandemic. *JAMA* 2021;326:1745–7.
- 133 Kozakiewicz ML, Grotegut CA, Howlett AC. Endocannabinoid system in pregnancy maintenance and labor: a mini-review. *Front Endocrinol* 2021;12:699951.
- 134 Michalski CA, Hung RJ, Seeto RA, et al. Association between maternal cannabis use and birth outcomes: an observational study. *BMC Pregnancy Childbirth* 2020;20:771.
- 135 Singh S, Filion KB, Abenhaim HA, et al. Prevalence and outcomes of prenatal recreational cannabis use in high-income countries: a scoping review. *BJOG* 2020;127:8–16.
- 136 Hutchings DE, Martin BR, Gamagaris Z, et al. Plasma concentrations of delta-9-tetrahydrocannabinol in dams and fetuses following acute or multiple prenatal dosing in rats. *Life Sci* 1989;44:697–701.
- 137 Gunn JKL, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ Open* 2016;6:e009986.
- 138 Crume TL, Juhl AL, Brooks-Russell A, et al. Cannabis use during the perinatal period in a state with legalized recreational and medical marijuana: the association between maternal characteristics, breastfeeding patterns, and neonatal outcomes. *J Pediatr* 2018;197:90–6.
- 139 Nashed MG, Hardy DB, Lavolette SR. Prenatal cannabinoid exposure: emerging evidence of physiological and neuropsychiatric abnormalities. *Front Psychiatry* 2020;11:624275.
- 140 Maia J, Fonseca BM, Teixeira N, et al. The fundamental role of the endocannabinoid system in endometrium and placenta: implications in pathophysiological aspects of uterine and pregnancy disorders. *Hum Reprod Update* 2020;26:586–602.
- 141 Habayeb OMH, Taylor AH, Evans MD, et al. Plasma levels of the endocannabinoid anandamide in women—a potential role in pregnancy maintenance and labor? *J Clin Endocrinol Metab* 2004;89:5482–7.
- 142 Sun X, Xie H, Yang J, et al. Endocannabinoid signaling directs differentiation of trophoblast cell lineages and placentalization. *Proc Natl Acad Sci U S A* 2010;107:16887–92.
- 143 Fügedi G, Molnár M, Rigó J, et al. Increased placental expression of cannabinoid receptor 1 in preeclampsia: an observational study. *BMC Pregnancy Childbirth* 2014;14:395.
- 144 Committee opinion no. 722: marijuana use during pregnancy and lactation. *Obstet Gynecol* 2017;130:e205–9.
- 145 Campolongo P, Trezza V, Ratano P, et al. Developmental consequences of perinatal cannabis exposure: behavioral and neuroendocrine effects in adult rodents. *Psychopharmacology* 2011;214:5–15.

- 146 Mato S, Del Olmo E, Pazos A. Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. *Eur J Neurosci* 2003;17:1747–54.
- 147 Biegón A, Kerman IA. Autoradiographic study of pre- and postnatal distribution of cannabinoid receptors in human brain. *Neuroimage* 2001;14:1463–8.
- 148 Morie KP, Crowley MJ, Mayes LC, et al. Prenatal drug exposure from infancy through emerging adulthood: results from neuroimaging. *Drug Alcohol Depend* 2019;198:39–53.
- 149 Paul SE, Hatoum AS, Fine JD, et al. Associations between prenatal cannabis exposure and childhood outcomes: results from the ABCD study. *JAMA Psychiatry* 2021;78:64–76.
- 150 Baranger DAA, Paul SE, Colbert SMC, et al. Association of mental health burden with prenatal cannabis exposure from childhood to early adolescence: longitudinal findings from the adolescent brain cognitive development (ABCD) study. *JAMA Pediatr* 2022. doi:10.1001/jamapediatrics.2022.3191. [Epub ahead of print: 12 Sep 2022].
- 151 Young-Wolff KC, Sarovar V, Tucker L-Y, et al. Trends in marijuana use among pregnant women with and without nausea and vomiting in pregnancy, 2009–2016. *Drug Alcohol Depend* 2019;196:66–70.
- 152 Sorensen CJ, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment—a systematic review. *J Med Toxicol* 2017;13:71–87.
- 153 Clarke H, Roychoudhury P, Ladha KS, et al. Daring discourse - yes: practical considerations for cannabis use in the perioperative setting. *Reg Anesth Pain Med* 2020;45:524–7.
- 154 Pryce G, Baker D. Antidote to cannabinoid intoxication: the CB<sub>1</sub> receptor inverse agonist, AM25<sub>1</sub>, reverses hypothermic effects of the CB<sub>1</sub> receptor agonist, CB-13, in mice. *Br J Pharmacol* 2017;174:3790–4.
- 155 Gash A, Karliner JS, Janowsky D, et al. Effects of smoking marijuana on left ventricular performance and plasma norepinephrine: studies in normal men. *Ann Intern Med* 1978;89:448–52.
- 156 Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci U S A* 2006;103:7895–900.
- 157 Bollag L, Lim G, Sultan P, et al. Society for obstetric anesthesia and perinatology: consensus statement and recommendations for enhanced recovery after cesarean. *Anesth Analg* 2021;132:1362–77.
- 158 Sessler DI. Perioperative thermoregulation and heat balance. *Lancet* 2016;387:2655–64.
- 159 Benyó Z, Ruisanchez Éva, Leszl-Ishiguro M, et al. Endocannabinoids in cerebrovascular regulation. *Am J Physiol Heart Circ Physiol* 2016;310:H785–801.
- 160 Parajuli P, Regmi MR, Lara-Garcia OE, et al. Man vs. man-made marijuana: a case of drug-induced posterior reversible encephalopathy syndrome (PRES) due to K2, a synthetic cannabinoid (SCB). *J Community Hosp Intern Med Perspect* 2020;10:361–4.
- 161 Abán CE, Accialini PL, Etcheverry T, et al. Crosstalk between nitric oxide and endocannabinoid signaling pathways in normal and pathological placentation. *Front Physiol* 2018;9:1699.
- 162 Pulgar VM, Yamaleyeva LM, Varagic J, et al. Increased angiotensin II contraction of the uterine artery at early gestation in a transgenic model of hypertensive pregnancy is reduced by inhibition of endocannabinoid hydrolysis. *Hypertension* 2014;64:619–25.
- 163 Malinowska B, Toczek M, Pędzińska-Betiuk A, et al. Cannabinoids in arterial, pulmonary and portal hypertension - mechanisms of action and potential therapeutic significance. *Br J Pharmacol* 2019;176:1395–411.
- 164 Greiner KS, Lo JO, Speranza RJ, et al. Marijuana use and pregnancy outcomes among women with hypertension in pregnancy. *J Matern Fetal Neonatal Med* 2022;35:2286–93.
- 165 U.S. Food and Drug Administration. What you should know about using cannabis, including CBD, when pregnant or breastfeeding, 2009. Available: <https://www.fda.gov/consumers/consumer-updates/what-you-should-know-about-using-cannabis-including-cbd-when-pregnant-or-breastfeeding> [Accessed 05 Feb 2022].
- 166 Mourh J, Rowe H. Marijuana and breastfeeding: applicability of the current literature to clinical practice. *Breastfeed Med* 2017;12:582–96.
- 167 Bertrand KA, Hanan NJ, Honerkamp-Smith G, et al. Marijuana use by breastfeeding mothers and cannabinoid concentrations in breast milk. *Pediatrics* 2018;142:e20181076.
- 168 Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med* 1982;307:819–20.
- 169 Navarrete F, García-Gutiérrez MS, Gasparian A, et al. Cannabis use in pregnant and breastfeeding women: behavioral and neurobiological consequences. *Front Psychiatry* 2020;11:586447.
- 170 Baker T, Datta P, Rewers-Felkins K, et al. Transfer of inhaled cannabis into human breast milk. *Obstet Gynecol* 2018;131:783–8.
- 171 Wymore EM, Palmer C, Wang GS, et al. Persistence of Δ-9-tetrahydrocannabinol in human breast milk. *JAMA Pediatr* 2021;175:632–4.
- 172 Butwick AJ, Tiouririne M. Evaluation of high-risk obstetric patients: a survey of US academic centers. *J Clin Anesth* 2016;33:460–8.
- 173 Jarlenski M, Koma JW, Zank J, et al. Trends in perception of risk of regular marijuana use among US pregnant and nonpregnant reproductive-aged women. *Am J Obstet Gynecol* 2017;217:705–7.
- 174 Hoffman MC, Hunter SK, D'Alessandro A, et al. Interaction of maternal choline levels and prenatal marijuana's effects on the offspring. *Psychol Med* 2020;50:1716–26.
- 175 Ng JH, Rice KK, Ananth CV, et al. Attitudes about marijuana use, potential risks, and legalization: a single-center survey of pregnant women. *J Matern Fetal Neonatal Med* 2022;35:4635–43.
- 176 Narouze S. Antinociception mechanisms of action of cannabinoid-based medicine: an overview for anesthesiologists and pain physicians. *Reg Anesth Pain Med* 2021;46:240–50.
- 177 Ghuran A, Nolan J. Recreational drug misuse: issues for the cardiologist. *Heart* 2000;83:627–33.
- 178 Substance Abuse and Mental Health Services Administration. Know the risk of marijuana, 2021. Available: <https://www.samhsa.gov/marijuana> [Accessed 05 Feb 2022].
- 179 American College of Obstetrics and Gynecologists. Marijuana and pregnancy. Poster 2018 <https://www.acog.org/store/products/patient-education/poster/marijuana-and-pregnancy-poster>
- 180 Orden C, Santos M, Ceprian M, et al. The effect of cannabidiol on sevoflurane minimum alveolar concentration reduction produced by morphine in rats. *Vet Anaesth Analg* 2021;48:74–81.
- 181 Müller J, Plöchl W, Reiter B, et al. The effect of oral Δ-9-tetrahydrocannabinol on the minimal alveolar concentration of sevoflurane: a randomised, controlled, observer-blinded experimental study. *Eur J Anaesthesiol* 2021;38:58–63.
- 182 Stoelting RK, Martz RC, Gartner J, et al. Effects of delta-9-tetrahydrocannabinol on halothane MAC in dogs. *Anesthesiology* 1973;38:521–4.
- 183 Vitez TS, Way WL, Miller RD, et al. Effects of delta-9-tetrahydrocannabinol on cyclopropane MAC in the rat. *Anesthesiology* 1973;38:525–7.
- 184 Holmen IC, Beach JP, Kaizer AM, et al. The association between preoperative cannabis use and intraoperative inhaled anesthetic consumption: a retrospective study. *J Clin Anesth* 2020;67:109980.
- 185 Karim HMR, Bhakta P, O'Brien B. Observed links between cannabis consumption and volatile anesthetic requirements warrant skepticism. *J Clin Anesth* 2021;68:110085.
- 186 Twardowski MA, Link MM, Twardowski NM. Effects of cannabis use on sedation requirements for endoscopic procedures. *J Am Osteopath Assoc* 2019.7556/jaoa.2019.052. [Epub ahead of print: 15 Apr 2019].
- 187 Flisberg P, Paech MJ, Shah T, et al. Induction dose of propofol in patients using cannabis. *Eur J Anaesthesiol* 2009;26:192–5.
- 188 Ibera C, Shalom B, Saifi F, et al. [Effects of cannabis extract premedication on anesthetic depth]. *Harefuah* 2018;157:162–6.
- 189 Nottage JF, Stone J, Murray RM, et al. Delta-9-tetrahydrocannabinol, neural oscillations above 20 Hz and induced acute psychosis. *Psychopharmacology* 2015;232:519–28.
- 190 Skosnik PD, D'Souza DC, Steinmetz AB, et al. The effect of chronic cannabinoids on broadband EEG neural oscillations in humans. *Neuropsychopharmacology* 2012;37:2184–93.
- 191 Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol* 2008;21:494–502.
- 192 Van Hoozen BE, Cross CE. Marijuana. respiratory tract effects. *Clin Rev Allergy Immunol* 1997;15:243–69.
- 193 Vozoris NT, Pequeno P, Li P, et al. Morbidity and mortality associated with prescription cannabinoid drug use in COPD. *Thorax* 2021;76:29–36.
- 194 Bloom JW, Kaltenborn WT, Paoletti P, et al. Respiratory effects of non-tobacco cigarettes. *Br Med J* 1987;295:1516–8.
- 195 Sherrill DL, Krzyzanowski M, Bloom JW, et al. Respiratory effects of non-tobacco cigarettes: a longitudinal study in general population. *Int J Epidemiol* 1991;20:132–7.
- 196 Taylor DR, Fergusson DM, Milne BJ, et al. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction* 2002;97:1055–61.
- 197 Tashkin DP. Effects of marijuana smoking on the lung. *Ann Am Thorac Soc* 2013;10:239–47.
- 198 Tashkin DP. Marijuana and lung disease. *Chest* 2018;154:653–63.
- 199 Tashkin DP, Coulson AH, Clark VA, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *Am Rev Respir Dis* 1987;135:209–16.
- 200 Macleod J, Robertson R, Copeland L, et al. Cannabis, tobacco smoking, and lung function: a cross-sectional observational study in a general practice population. *Br J Gen Pract* 2015;65:e89–95.
- 201 Hancox RJ, Shin HH, Gray AR, et al. Effects of quitting cannabis on respiratory symptoms. *Eur Respir J* 2015;46:80–7.
- 202 Tashkin DP, Simmons MS, Tseng C-H. Impact of changes in regular use of marijuana and/or tobacco on chronic bronchitis. *COPD* 2012;9:367–74.
- 203 Ribeiro L, Ind PW. Marijuana and the lung: hysteria or cause for concern? *Breathe* 2018;14:196–205.

- 204 Braymiller JL, Barrington-Trimis JL, Leventhal AM, et al. Assessment of nicotine and cannabis vaping and respiratory symptoms in young adults. *JAMA Netw Open* 2020;3:e2030189.
- 205 Morris MA, Jacobson SR, Kinney GL, et al. Marijuana use associations with pulmonary symptoms and function in tobacco smokers enrolled in the subpopulations and intermediate outcome measures in COPD study (SPIROMICS). *Chronic Obstr Pulm Dis* 2018;5:46–56.
- 206 Tan WC, Lo C, Jong A, et al. Marijuana and chronic obstructive lung disease: a population-based study. *CMAJ* 2009;180:814–20.
- 207 Correa JB, Myers MG, Tully LK, et al. Co-Occurring use of cannabis and tobacco and the presence of acute respiratory symptoms among young adult light and intermittent smokers. *Subst Use Misuse* 2020;55:2129–37.
- 208 Tan WC, Bourbeau J, Aaron SD, et al. The effects of marijuana smoking on lung function in older people. *Eur Respir J* 2019;54:1900826.
- 209 Winhusen T, Theobald J, Kaelber DC, et al. Regular cannabis use, with and without tobacco co-use, is associated with respiratory disease. *Drug Alcohol Depend* 2019;204:107557.
- 210 Kempker JA, Honig EG, Martin GS. The effects of marijuana exposure on expiratory airflow. A study of adults who participated in the U.S. National health and nutrition examination study. *Ann Am Thorac Soc* 2015;12:135–41.
- 211 Taylor DR, Poulton R, Moffitt TE, et al. The respiratory effects of cannabis dependence in young adults. *Addiction* 2000;95:1669–77.
- 212 Papatheodorou SI, Buettner H, Rice MB, et al. Recent marijuana use and associations with exhaled nitric oxide and pulmonary function in adults in the United States. *Chest* 2016;149:1428–35.
- 213 Wenger DS, Triplett M, Shahrir S, et al. Associations of marijuana with markers of chronic lung disease in people living with HIV. *HIV Med* 2021;22:92–101.
- 214 Hancox RJ, Poulton R, Ely M, et al. Effects of cannabis on lung function: a population-based cohort study. *Eur Respir J* 2010;35:42–7.
- 215 Pletcher MJ, Vittinghoff E, Kalkan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA* 2012;307:173–81.
- 216 Hii SW, Tam JDC, Thompson BR, et al. Bullous lung disease due to marijuana. *Respirology* 2008;13:122–7.
- 217 Fiorelli A, Accardo M, Vicidomini G, et al. Does cannabis smoking predispose to lung bulla formation? *Asian Cardiovasc Thorac Ann* 2014;22:65–71.
- 218 Feldman AL, Sullivan JT, Passero MA, et al. Pneumothorax in polysubstance-abusing marijuana and tobacco smokers: three cases. *J Subst Abuse* 1993;5:183–6.
- 219 Stefani A, Aramini B, Baldi C, et al. Secondary spontaneous pneumothorax and bullous lung disease in cannabis and tobacco smokers: a case-control study. *PLoS One* 2020;15:e0230419.
- 220 Gong H, Tashkin DP, Simmons MS, et al. Acute and subacute bronchial effects of oral cannabinoids. *Clin Pharmacol Ther* 1984;35:26–32.
- 221 Tashkin DP, Shapiro BJ, Frank IM. Acute effects of smoked marijuana and oral delta-9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. *Am Rev Respir Dis* 1974;109:420–8.
- 222 Tashkin DP, Reiss S, Shapiro BJ, et al. Bronchial effects of aerosolized delta 9-tetrahydrocannabinol in healthy and asthmatic subjects. *Am Rev Respir Dis* 1977;115:57–65.
- 223 Ali M, Khan K, Buch M. A case series of vaping-induced lung injury in a community hospital setting. *Case Rep Pulmonol* 2020;9631916.
- 224 Alqahtani A, Ammari Z, Ramahi A, et al. Cannabis smoking-induced diffuse alveolar hemorrhage. *Cureus* 2019;11:e5089.
- 225 Bucchino L, Monzani A, Fracon S, et al. Cannabis-related diffuse alveolar hemorrhage in a 16-year-old patient: a case report. *Front Pediatr* 2019;7:468.
- 226 Farris SG, Metrik J. Acute effects of cannabis on breath-holding duration. *Exp Clin Psychopharmacol* 2016;24:305–12.
- 227 Qarajeh R, Kitchin J. The Vaping-Induced acute respiratory distress syndrome. *Am J Med* 2020;133:e147–8.
- 228 Galo J, Celli D, Gross D, et al. A presentation of e-cigarette vaping associated lung injury (EVALI) caused by THC-Containing electronic smoking device. *Respir Med Case Rep* 2020;31:101154.
- 229 Mughal MS, Dalmacion DLV, Mirza HM, et al. E-cigarette or vaping product use associated lung injury, (EVALI) - A diagnosis of exclusion. *Respir Med Case Rep* 2020;31:101174.
- 230 Tashkin DP, Shapiro BJ, Frank IM. Acute pulmonary physiologic effects of smoked marijuana and oral (Delta)9 -tetrahydrocannabinol in healthy young men. *N Engl J Med* 1973;289:336–41.
- 231 Yarlagadda K, Singh P, Shrimanker I, et al. Pot smokers puffing away lung health. *Heart Lung* 2019;48:462–4.
- 232 Hashmi HRT, Duncalf R, Khaja M. A case report of cannabis induced hemoptysis. *Medicine* 2016;95:e3232.
- 233 Caviedes I, Labarca G, Silva CF, et al. Marijuana use, respiratory symptoms, and pulmonary function. *Ann Intern Med* 2019;170:142.
- 234 Shafi MI, Liaquat S, Auckley D. Up in smoke: an unusual case of diffuse alveolar hemorrhage from marijuana. *Respir Med Case Rep* 2018;25:22–4.
- 235 McGraw MD, Houser GH, Galambos C, et al. Marijuana medusa: the many pulmonary faces of marijuana inhalation in adolescent males. *Pediatr Pulmonol* 2018;53:1619–26.
- 236 Traboulsi H, Cherian M, Abou Rjeili M, et al. Inhalation toxicology of vaping products and implications for pulmonary health. *Int J Mol Sci* 2020;21:3495.
- 237 Malit LA, Johnstone RE, Bourke DI, et al. Intravenous delta9-tetrahydrocannabinol: effects of ventilatory control and cardiovascular dynamics. *Anesthesiology* 1975;42:666–73.
- 238 Holdcroft A, Maze M, Doré C, et al. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology* 2006;104:1040–6.
- 239 Gregg JM, Campbell RL, Levin KJ, et al. Cardiovascular effects of cannabinol during oral surgery. *Anesth Analg* 1976;55:203–13.
- 240 McGuinness B, Goel A, Elias F, et al. Cannabis use disorder and perioperative outcomes in vascular surgery. *J Vasc Surg* 2021;73:1376–87.
- 241 Goel A, McGuinness B, Jivraj NK, et al. Cannabis use disorder and perioperative outcomes in major elective surgeries: a retrospective cohort analysis. *Anesthesiology* 2020;132:625–35.
- 242 Calapai F, Cardia L, Sorbara EE, et al. Cannabinoids, blood-brain barrier, and brain disposition. *Pharmaceutics* 2020;12:265.
- 243 Hemachandra D, McKetin R, Cherbuin N, et al. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. *Aust N Z J Public Health* 2016;40:226–30.
- 244 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.
- 245 Bhurwal A, Bartel MJ, Ivanovic S, et al. Mo1557 - Cyclical Vomiting Syndrome: National Trends and Impact on Healthcare Utilization from 2008-2014. *Gastroenterology* 2018;154:S-751–751.
- 246 Bakshi C, Barrett AM. Impact of recreational and medicinal marijuana on surgical patients: a review. *Am J Surg* 2019;217:783–6.
- 247 Wallace M, Schulteis G, Atkinson JH, et al. Dose-Dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology* 2007;107:785–96.
- 248 Hill KP, Palastro MD, Johnson B, et al. Cannabis and pain: a clinical review. *Cannabis Cannabinoid Res* 2017;2:96–104.
- 249 Oregon Health Authority, Public Health Division. The Oregon medical marijuana program, 2016. Available: <https://www.oregon.gov/oha/PH/DISEASES/CONDITIONS/CHRONICDISEASE/MEDICALMARIJUANA/PROGRAM/Documents/OMMP-Statistic-Snapshot-10-2016.pdf> [Accessed 06 Feb 2022].
- 250 Aviram J, Pud D, Gershoni T, et al. Medical cannabis treatment for chronic pain: outcomes and prediction of response. *Eur J Pain* 2021;25:359–74.
- 251 Boehnke KF, Scott JR, Litinas E, et al. Pills to pot: observational analyses of cannabis substitution among medical cannabis users with chronic pain. *J Pain* 2019;20:830–41.
- 252 Haroutounian S, Ratz Y, Ginosar Y, et al. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. *Clin J Pain* 2016;32:1036–43.
- 253 Meng H, Page MG, Ajrawat P, et al. Patient-Reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients. *Can J Anaesth* 2021;68:633–44.
- 254 Piper BJ, DeKeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. *J Psychopharmacol* 2017;31:569–75.
- 255 Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. *Cannabis Cannabinoid Res* 2017;2:160–6.
- 256 Schröder NHB, Duipmans JC, Molenbuur B, et al. Combined tetrahydrocannabinol and cannabidiol to treat pain in epidermolysis bullosa: a report of three cases. *Br J Dermatol* 2019;180:922–4.
- 257 Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage* 2018;55:179–88.
- 258 Nielsen S, Sabioni P, Trigo JM, et al. Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. *Neuropsychopharmacology* 2017;42:1752–65.
- 259 Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain* 2012;13:438–49.
- 260 Liang D, Wallace MS, Shi Y. Medical and non-medical cannabis use and risk of prescription opioid use disorder: findings from propensity score matching. *Drug Alcohol Rev* 2019;38:597–605.
- 261 Rios C, Gomes I, Devi LA. mu opioid and CB1 cannabinoid receptor interactions: reciprocal inhibition of receptor signaling and neurogenesis. *Br J Pharmacol* 2006;148:387–95.
- 262 Salio C, Fischer J, Franzoni MF, et al. CB1-Cannabinoid and mu-opioid receptor co-localization on postsynaptic target in the rat dorsal horn. *Neuroreport* 2001;12:3689–92.
- 263 Tapley P, Kellett S. Cannabis-Based medicines and the perioperative physician. *Perioper Med* 2019;8:19.

- 264 Manzanares J, Corchero J, Romero J, *et al.* Pharmacological and biochemical interactions between opioids and cannabinoids. *Trends Pharmacol Sci* 1999;20:287–94.
- 265 Ibrahim MM, Porreca F, Lai J, *et al.* CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. *Proc Natl Acad Sci U S A* 2005;102:3093–8.
- 266 Desroches J, Bouchard J-F, Gendron L, *et al.* Involvement of cannabinoid receptors in peripheral and spinal morphine analgesia. *Neuroscience* 2014;261:23–42.
- 267 Mao J, Price DD, Lu J, *et al.* Two distinctive antinociceptive systems in rats with pathological pain. *Neurosci Lett* 2000;280:13–16.
- 268 Kazantzis NP, Casey SL, Seow PW, *et al.* Opioid and cannabinoid synergy in a mouse neuropathic pain model. *Br J Pharmacol* 2016;173:2521–31.
- 269 Stachtari CC, Thomareis ON, Tsaousi GG, *et al.* Interaction of a cannabinoid-2 agonist with tramadol on nociceptive thresholds and immune responses in a rat model of incisional pain. *Am J Ther* 2016;23:e1484–92.
- 270 Maguire DR, France CP. Antinociceptive effects of mixtures of mu opioid receptor agonists and cannabinoid receptor agonists in rats: impact of drug and fixed-dose ratio. *Eur J Pharmacol* 2018;819:217–24.
- 271 Abrams DI, Couey P, Shade SB, *et al.* Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther* 2011;90:844–51.
- 272 Meng H, Hanlon JG, Katznelson R, *et al.* The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: a case report. *Can J Anaesth* 2016;63:307–10.
- 273 Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience* 2013;248:637–54.
- 274 Bisaga A, Sullivan MA, Glass A, *et al.* The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. *Drug Alcohol Depend* 2015;154:38–45.
- 275 Wiese B, Wilson-Poe AR. Emerging evidence for cannabis' role in opioid use disorder. *Cannabis Cannabinoid Res* 2018;3:179–89.
- 276 Hickernell TR, Lakra A, Berg A, *et al.* Should cannabinoids be added to multimodal pain regimens after total hip and knee arthroplasty? *J Arthroplasty* 2018;33:3637–41.
- 277 Jain AK, Ryan JR, McMahon FG, *et al.* Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 1981;21:3205–6.
- 278 Buggy DJ, Toogood L, Maric S, *et al.* Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain* 2003;106:169–72.
- 279 Kalliomäki J, Segerdahl M, Webster L, *et al.* Evaluation of the analgesic efficacy of AZD1940, a novel cannabinoid agonist, on post-operative pain after lower third molar surgical removal. *Scand J Pain* 2013;4:17–22.
- 280 Levin DN, Dulberg Z, Chan AW. A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. Une étude reventio contrôlée pour évaluer l'efficacité du nabilone pour la revention des nausées et vomissements postopératoires aigus lors de chirurgie non urgente. *Can J Anaesth* 2017;64:385–95.
- 281 Ostenfeld T, Price J, Albanese M, *et al.* A randomized, controlled study to investigate the analgesic efficacy of single doses of the cannabinoid receptor-2 agonist GW842166, ibuprofen or placebo in patients with acute pain following third molar tooth extraction. *Clin J Pain* 2011;27:668–76.
- 282 Seeling W, Kneer L, Büchele B, *et al.* [Delta(9)-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain]. *Anaesthesist* 2006;55:391–400.
- 283 Stevens AJ, Higgins MD. A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain. *Acta Anaesthesiol Scand* 2017;61:268–80.
- 284 Gazendam A, Nucci N, Gouveia K, *et al.* Cannabinoids in the management of acute pain: a systematic review and meta-analysis. *Cannabis Cannabinoid Res* 2020;5:290–7.
- 285 Naef M, Curatolo M, Petersen-Felix S, *et al.* The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain* 2003;105:79–88.
- 286 Johnstone RE, Lief PL, Kulp RA, *et al.* Combination of delta9-tetrahydrocannabinol with oxymorphone or pentobarbital: effects on ventilatory control and cardiovascular dynamics. *Anesthesiology* 1975;42:674–84.
- 287 Lee HS, Nagra N, La Selva D, *et al.* Nurse-administered propofol continuous infusion sedation for gastrointestinal endoscopy in patients who are difficult to sedate. *Clin Gastroenterol Hepatol* 2021;19:180–8.
- 288 Jennings JM, Angerame MR, Eschen CL, *et al.* Cannabis use does not affect outcomes after total knee arthroplasty. *J Arthroplasty* 2019;34:1667–9.
- 289 Heng M, McTague MF, Lucas RC, *et al.* Patient perceptions of the use of medical marijuana in the treatment of pain after musculoskeletal trauma: a survey of patients at 2 trauma centers in Massachusetts. *J Orthop Trauma* 2018;32:e25–30.
- 290 Whiteside LK, Russo J, Wang J, *et al.* Predictors of sustained prescription opioid use after admission for trauma in adolescents. *J Adolesc Health* 2016;58:92–7.
- 291 Jamal N, Korman J, Musing M, *et al.* Effects of pre-operative recreational smoked cannabis use on opioid consumption following inflammatory bowel disease surgery: a historical cohort study. *Eur J Anaesthesiol* 2019;36:705–6.
- 292 Ladha KS, Manoo V, Virji A-F, *et al.* The impact of perioperative cannabis use: a narrative scoping review. *Cannabis Cannabinoid Res* 2019;4:219–30.
- 293 Taylor L, Crockett J, Tayo B, *et al.* Abrupt withdrawal of cannabidiol (CBD): a randomized trial. *Epilepsy Behav* 2020;104:106938.
- 294 Viudez-Martinez A, Garcia-Gutiérrez MS, Medrano-Relinque J, *et al.* Cannabidiol does not display drug abuse potential in mice behavior. *Acta Pharmacol Sin* 2019;40:358–64.
- 295 American Psychiatric Association. Substance-related and addictive disorders. In: *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington D.C, 2013: 481–540.
- 296 Hesse M, Thylstrup B. Time-Course of the DSM-5 cannabis withdrawal symptoms in poly-substance abusers. *BMC Psychiatry* 2013;13:258.
- 297 Allsop DJ, Copeland J, Lintzeris N, *et al.* Nabilone as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry* 2014;71:281–91.
- 298 Tzavara ET, Valjent E, Firmo C, *et al.* Cannabinoid withdrawal is dependent upon PKA activation in the cerebellum. *Eur J Neurosci* 2000;12:1038–46.
- 299 Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil* 2017;8:9–37.
- 300 Levin FR, Mariani JJ, Brooks DJ, *et al.* Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend* 2011;116:142–50.
- 301 Mason BJ, Crean R, Goodell V, *et al.* A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. *Neuropsychopharmacology* 2012;37:1689–98.
- 302 Gray KM, Carpenter MJ, Baker NL, *et al.* A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry* 2012;169:805–12.
- 303 D'Souza DC, Cortes-Briones J, Creatura G, *et al.* Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. *Lancet Psychiatry* 2019;6:35–45.
- 304 Danovitch I, Gorelick DA. State of the art treatments for cannabis dependence. *Psychiatr Clin North Am* 2012;35:309–26.
- 305 Haney M, Cooper ZD, Bedi G, *et al.* Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. *Neuropsychopharmacology* 2013;38:1557–65.
- 306 U.S. Food and Drug Administration. CesametTM (nabilone) capsules. Available: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2006/018677s011lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf) [Accessed 06 Feb 2022].
- 307 FDA. FDA regulation of cannabis and cannabis-derived products: questions and answers. Available: <https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers> [Accessed 29 Apr 2021].
- 308 Arboleda MF, Prosk E. Cannabis Terminology. In: Narouze SN, ed. *Cannabinoids and pain*. Springer, 2021: 31–6.