NARRATIVE REVIEW ARTICLE

CME

Cannabis and Cannabinoids in the Perioperative Period

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Cannabis use is increasingly common, and with a growing number of jurisdictions implementing legalization frameworks, it is likely that providers will encounter more patients who use cannabis. Therefore, it is important for providers to understand the implications of cannabis use and practical considerations for the perioperative period. Cannabis affects multiple organ systems and may influence intraoperative anesthesia, as well as postoperative pain management. The effects of cannabis and key anesthetic considerations are reviewed here. (Anesth Analg 2024;138:16–30)

GLOSSARY

2-AG = 2-arachidonoylglycerol; **ADP** = adenosine diphosphate; **AEA; anandamide** = N-arachidonoylethanolamine; **BIS** = bispectral index; **BP** = blood pressure; **CABG** = coronary artery bypass graft; **CB1-R** = cannabinoid-1 receptor; **CB2-R** = cannabinoid-2 receptor; **CBD** = cannabidiol; **CBF** = cerebral blood flow; **CHS** = cannabinoid hyperemesis syndrome; **CNS** = central nervous system; **CO** = cardiac output; **COPD** = chronic obstructive pulmonary disease; **CUD** = cannabis use disorder; **CVA** = cerebrovascular accident; **CWS** = cannabis withdrawal syndrome; **CYP3A4** = cytochrome P450 3A4; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **EEG** = electroencephalogram; **FRC** = functional residual capacity; **FVC** = forced vital capacity; **GABA** = gamma amino butyric acid; **GI** = gastrointestinal; **GPCR** = G protein-coupled receptor; **HR** = heart rate; **ICD** = International Classification of Diseases; **ICD-11** = International Classification of Diseases, 11th revision; **ICD-9,** = International Classification of Diseases, 9th revision; **INR** = international normalized ratio; **MAC** = monitored anesthesia care; **MI** = myocardial infarction; **NMDA** = ***N***-methyl-D-aspartate; **NPS** = new psychoactive substances; **RV** = residual volume; **THC** = delta-9-tretrahydrocannabinol; **TIA** = transient ischemic attack; **TLC** = total lung capacity; **TRPV1** = transient receptor potential cation channel subfamily V member 1

Cannabis has been used for centuries for both recreational and medical purposes, such as pain, anorexia, spasticity, and cancer.[1] With widespread use, it is increasingly relevant and important for perioperative physicians to be familiar with the implications of caring for patients with either acute or long-term consumption of cannabis. In this article, we approach the topic systematically and review the pharmacology and physiologic effects of cannabis, as well as anesthetic considerations for patients using cannabis, to aid clinicians in managing patients in the perioperative period.

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Accepted for publication March 30, 2022.

Funding: Research reported in this publication was supported by the Hospital for Special Surgery Department of Anesthesiology, Critical Care and Pain Management Research and Education Fund and the C.V. Starr Foundation Grant.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000006070

METHODS

A literature search was performed using PubMed, Google Scholar, Embase, and Cochrane Library databases from inception through 2021 to identify reports discussing cannabis, cannabinoids, physiology, pharmacology, and perioperative considerations. The following keywords were utilized: "cannabis," "marijuana," "cannabinoids," "prevalence," "physiology," "pharmacology," "perioperative," "intraoperative," "sedation," "drug interaction," "postoperative," "pain," "complications," and "outcomes." Reports published in English and the following types of articles were included: case reports, clinical trials, editorials, narrative reviews, meta-analyses, and systematic reviews. Conference abstracts were excluded.

RESULTS

A total of 140 articles were identified and used in this narrative review. Fifty-three review articles, 74 clinical studies, 7 editorials, 4 book chapters, and 2 case reports were included.

Terms and Definitions

First, "cannabis" and other associated terms need to be clearly defined (Table 1). Cannabinoids are chemical compounds found in cannabis or produced by the human body, and these compounds are grouped into

Table 1. Terms and Definitions

Term	Definition
Cannabinoids	Refers to chemical compounds found in cannabis or produced by the human body
Endocannabinoid	Ligand to endogenous cannabinoid receptors (CB1-R or CB2-R); examples are AEA and 2-AG
Synthetic cannabinoid	New psychoactive substances derived from laboratory; includes pharmacologic agents and drugs of abuse; examples are dronabinol and nabilone
Phytocannabinoid	Compounds found in or derived from cannabis plants; examples are THC and CBD
Flavonoids and terpenes	Nonphytocannabionid chemicals found in cannabis that exert synergistic effects may enhance bioactivities of phytocannabinoids
Cannabis	Refers to plant material or its extracts

Abbreviations: 2-AG, 2-arachidonolyglyerol; AEA, anandamide; CB1-R, cannabinoid-1 receptor; CB2-R, cannabinoid-2 receptor; CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol.

categories of endocannabinoids, synthetic cannabinoids, and phytocannabinoids.[2,3] Endocannabinoid refers to any ligand to endogenous cannabinoid receptors (cannabinoid-1 receptor [CB1-R] or cannabinoid-2 receptor [CB2-R]).[2,4] For example, N-arachidonoylethanolamine (AEA; anandamide) and 2-arachidonoylglycerol (2-AG) are endocannabinoids synthesized from cell membrane phospholipids in response to different stimuli, such as pain, stress, or inflammation.[5–8] Synthetic cannabinoids, such as dronabinol and nabilone, are a group of new psychoactive substances (NPS) that are derived from the laboratory and include pharmacologic agents and drugs of abuse[2,9,10] (note: these products are not labeled for use under discussion). These compounds are agonists of cannabinoid receptors and have varying effects.[10] Phytocannabinoid describes a compound found in or derived from cannabis plants.[11–13] Over 100 cannabinoid compounds have been identified in various strains of plants including delta-9-tretrahydrocannabinol (or THC), which is the most potent psychoactive chemical, as well cannabidiol (CBD), which is nonintoxicating.[12,14] Flavonoids and terpenes are nonphytocannabinoid chemicals found in cannabis that exert synergistic effects that may enhance bioactivities of phytocannabinoids commonly referred to as "the entourage effect."[15] Cannabis refers to the plant material or its extracts.

Mechanism of Action

Cannabinoids are lipophilic and act via G protein-coupled receptors resulting in inhibition of the adenyl cyclase pathway and depressed neuronal excitability.[2,16] CB1-R is distributed through the central and peripheral nervous systems, while CB2-R is found primarily in lymphoid and hematopoietic cells.[6,16] Cannabinoids exert most of their effects by acting through these receptors functioning as agonists or antagonists.[2] For example, THC is a partial agonist at both CB1-R and CB2-R.[9] CBD, on the other hand, is a noncompetitive antagonist at CB1-R at high concentrations and inverse agonist at CB2-R.[9] Cannabinoids have additional effects within the nervous system and interact with many other targets, including transient receptor potential cation channel subfamily V member 1 (TRPV1), opioid, *N*-methyl-D-aspartate (NMDA), and gamma amino butyric acid (GABA) receptors.[16]

Heterogeneity of Cannabis and Implications for the Perioperative Patient

Though THC and CBD are the most well-known and studied phytocannabinoids, there are >100 other chemicals that have been identified in the plant.[17] The vast number of cannabis cultivars currently available in legal state markets reflect significant heterogeneity in the concentrations of THC, CBD, and other lesser-studied plant compounds.[18] The potency of cannabis, determined by its THC concentration, has significantly increased over time.[19] Moreover, the type of cannabis preparation affects potency. For example, a flower may have up to 24% THC, while a concentrate can range from 70% to 90% THC.[20] Nonpharmaceutical grade CBD preparations are ubiquitous and increasingly being used to manage a variety of medical conditions.[21] Unfortunately, products sold in an unregulated market may be labeled inaccurately,[22] and not all states require quality control of products to test and label samples for cannabinoid content.[23] Consequently, while patients presenting for surgery or medical treatment may report that they are using cannabis, providers have scant information on what their patients are taking. While the literature summarized in this article provides an overview of the physiologic effects of cannabis and its extracts that are relevant during the perioperative period, the types of cannabis preparations, routes, and duration of use vary across studies. Additional research facilitated by federal and state agencies is needed to address issues associated with increasing potency, variety of products, and use habits.

Prevalence of Cannabis and Cannabinoid Use in General Population and Perioperative Settings

The true prevalence of cannabis use in perioperative settings is unknown due to potential underreporting and differences in definitions of use, as previously discussed. However, cannabis use is increasingly common, and with a growing number of jurisdictions implementing legalization frameworks, it is likely that providers will encounter more patients who use cannabis.[24] Therefore, it is important for providers to understand the implications of cannabis use and practical considerations for the perioperative period.

In the United States, cannabis is consumed by >15% of the population, and it is among the most utilized recreational substances behind only alcohol and tobacco.[25,26] Among individuals with drug use

disorder, cannabis is the most common substance used with an estimated 22 to 25 million Americans ages ≥12 years reporting cannabis use.[2,27,28] Over the past decade, there has been increasing use among adolescents and young adults, and 11% of Americans ages ≥18 years report using cannabis in the past month.[29,30]

Regarding global trends, cannabis is among the most commonly used psychoactive substances, and it is the most common illicit drug in the world, with nearly 200 million users worldwide.[31,32] In the Canadian population, where cannabis was federally legalized, the self-reported prevalence of cannabis use increased from 5.6% in 1985 to 12.3% in 2015.[33,34] Even in countries in which cannabis remains illegal, the use is still fairly prevalent. In England and Wales, for example, recreational use is prohibited, yet there are an estimated 2.1 million people who use cannabis.[29,35]

In terms of the population using cannabis, the age of onset typically occurs in late adolescence with mean age of 15 to 16 years.[36] Earlier age of onset is associated with increased risks of substance use disorder, and studies have found associations of cannabis use with mental health disorders, including mood, anxiety, and personality disorders.[36] Patients with cannabis use disorder (CUD) are also more likely to have alcohol and other drug use disorders.[36] In the past, more men than women have been found to use cannabis; however, more recently, the rates of cannabis use between genders have become similar.[36]

The types and frequency of cannabis use are explored more closely by Goodman et al[30] by comparing the prevalence and forms of cannabis in legal versus illegal recreational cannabis markets in the United States and Canada. Prevalence of cannabis use in the past 12 months was found to be significantly higher in legal states within the United States than in Canada or illegal US states—34.4% of respondents in legal states reported use within the past 12 months compared to 23.8% in illegal states and 27.6% in Canada.[30] Regarding cannabinoid use reported in populations specific to the perioperative setting, there are few studies that provide insight. In an anonymous survey administered to 501 patients in the preoperative registration area at Mount Sinai Hospital in New York, approximately 27% of respondents reported a history of cannabis use.[37] Among patients seeking consultation for spine surgery, approximately 25.2% reported CBD use for spine-related pain.[38] Finally, data from 195 patients who underwent primary knee or hip replacement identified 16.4% of patients having tried CBD/THC products in the perioperative period.[39]

Regarding classification of use, cannabis use can be further classified as "cannabis dependence" and "CUD" depending on the source. Cannabis use is considered problematic when it continues despite negative consequences on social functioning and physical or mental health.[36] The most recent Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) now recognizes a single CUD category because the symptoms of cannabis abuse and dependence fall on a single severity dimension.[36] DSM-5 diagnostic criteria include symptoms in 3 broad domains: impaired control, increasing priority resulting in social and physical risk, and physiologic dependence.[36] By contrast, the 11th revision of the International Classification of Diseases (ICD-11) classifies cannabis use into categories of "hazardous," "harmful," and "dependence," which allow room for clinical judgment and cultural variation.[36] "Hazardous" use, per ICD-11, has the potential to cause harm, while "harmful" is similar to the previous Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosis of "cannabis abuse." Like the DSM-5 criteria, the diagnosis of dependence in ICD-11 uses similar criteria in the domains of impaired control, increasing priority, and physiologic dependence.[36]

Anesthetic Considerations in Patients With a History of Cannabis Physiology

Cannabis affects multiple organ systems, and physiologic effects are quite varied and heterogenous because many factors are involved, including cannabis composition (ie, THC content), route, and chronicity of use. Furthermore, cannabis interacts with multiple receptors, and the predominant effect depends on the cannabinoids that are present. Exact mechanisms that mediate each effect are also not well defined. Therefore, the physiologic effects reported with cannabis are not consistent across studies. One approach is to consider physiologic effects as either acute or chronic because cannabis administration can manifest differently with short- versus long-term use. It is also important to distinguish the recency of use as it might lead to different anesthetic considerations. The physiologic effects of inhaled cannabis are summarized in the Figure and Table 2.

Cardiovascular

Cardiovascular responses to cannabinoids are mediated primarily through CB1-R and the autonomic nervous system.[3,31,40] In naive users at lower doses, the initial response to inhaled cannabis or intravenous THC is tachycardia, with 20% to 100% increase in heart rate (HR), as well as increased systolic and diastolic blood pressures that can last several hours.[3,31,41–43] This is followed by a parasympathetic response characterized by bradycardia and hypotension.[40–43] Other cardiovascular responses seen shortly after use are increased cardiac output and possible premature ventricular contractions.[3,42,44] At high cannabinoid doses, parasympathetic response may predominate with bradycardia and postural hypotension.[3,31,45]

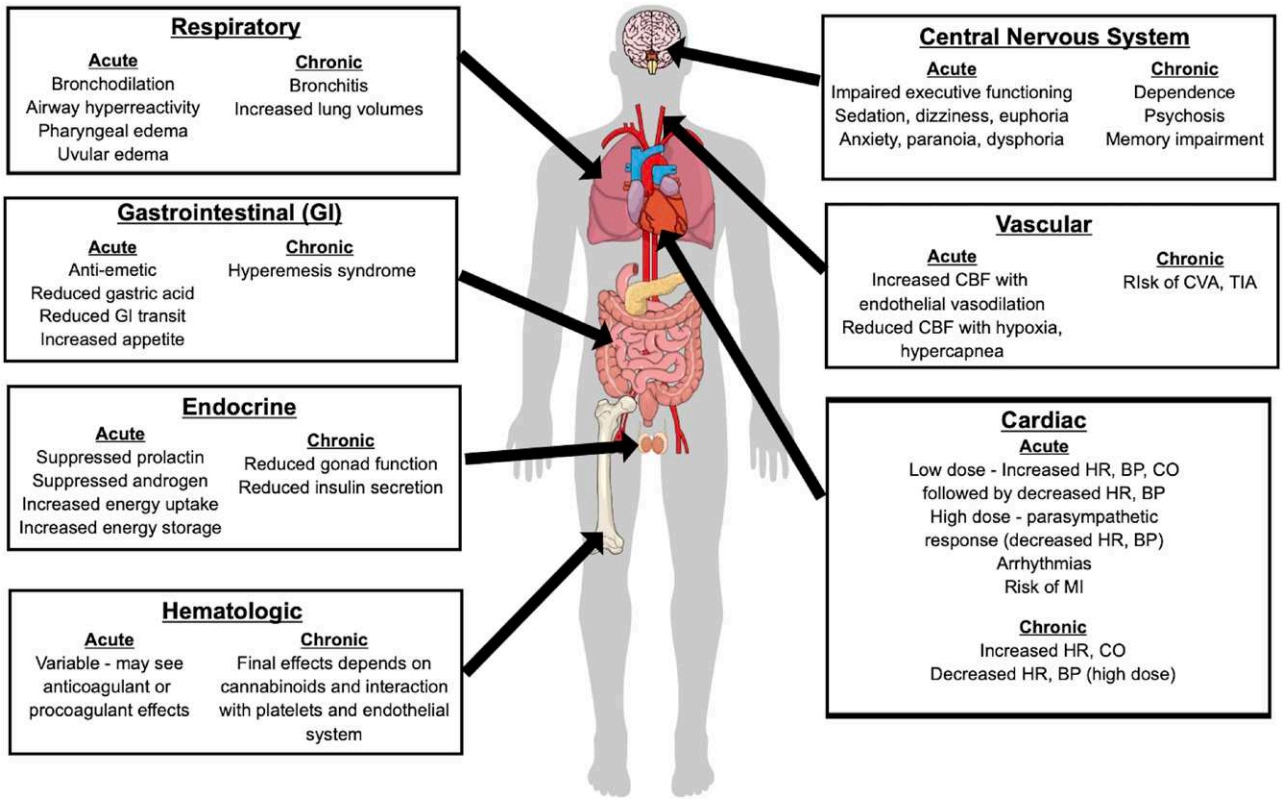

Figure. Physiologic effects of inhaled cannabis. Cannabis affects multiple organ systems with either acute or chronic use. Key manifestations of inhaled cannabis are depicted here. BP indicates blood pressure; CBF, cerebral blood flow; GI, gastrointestinal; CO, cardiac output; CVA, cerebrovascular accident; HR, heart rate; MI, myocardial infarction; TIA, transient ischemic attack.

With long-term use, there can be a similar response of increased HR and cardiac output with heavy daily cannabis consumption.[44] On the other hand, in those with chronic use, administration of high doses of THC can result in decreased HR and tolerance to orthostatic hypotension.[40]

In terms of other cardiovascular effects, arrhythmias may be observed with acute cannabis use including risks of atrial fibrillation, ventricular tachycardia, and supraventricular tachycardia.[3,31] Other arrhythmias associated with cannabis use are atrial flutter, second-degree atrioventricular block, and ventricular fibrillation.[46,47] Cannabis use also results in increased myocardial oxygen demand and higher levels of carboxyhemoglobin.[3,48] Possibly related to these cardiovascular effects, cannabis use may be associated with 4 to 8 times increased risk of myocardial infarction (MI) within 60 minutes after use.[31,49] Other proposed explanations for MI risk are coronary spasm, angiopathy, and prothrombotic effects.[31]

Vascular

The endocannabinoid system plays a role in regulating cerebral blood flow with variable effects depending on neuronal activity.[3,50] CB1 receptor agonists induce endothelial vasodilators that can increase cerebral blood flow.[51,52] On the other hand, conditions of hypoxia or hypercapnia may reduce cerebral blood flow due to changes in neuron metabolic rate and electrical activity.[50] Increased incidence of ischemic stroke and transient ischemic attack (TIA) have been identified in cannabis users, which may be related to cerebral vasospasm and atherosclerosis.[3,53]

Respiratory

There are acute, short-term effects of smoked cannabis, as well as chronic, long-term effects. After smoking cannabis, bronchodilation may occur with fairly rapid onset and can last 1 to 2 hours.[54–56] The mechanism is not well understood, though it seems related to THC content and likely mediated through CB1-R rather than via beta-adrenergic stimulation, cholinergic blockade, or prostaglandins.[54,55] There is also some evidence of airway hyperreactivity with either acute or chronic cannabis use likely due to local irritation from smoke or CB1-R activation rather than autonomically mediated.[3,57] Experimental models demonstrate that the bidirectional effects on the airway depends on the underlying tone, and this might be mediated through peripheral cannabinoid receptors that increase or reduce bronchial smooth muscle tone.[57] A case report also discusses uvular edema after recent cannabis inhalation before general anesthesia, though the mechanism is unknown.[58]

Table 2. Physiologic Effects of Inhaled Cannabis

System	Acute	Chronic
Cardiovascular	Naive users at low dose → Increased HR, increased systolic and diastolic blood pressures, followed by parasympathetic response (bradycardia and hypotension); acute use may result in increased CO	Increased HR and CO with heavy daily cannabis use
	Naive users at high dose → parasympathetic response may predominate with bradycardia and postural hypotension	High-dose THC can also result in decreased HR and tolerance to orthostatic hypotension
	Various arrhythmias associated with acute use (atrial fibrillation/flutter and ventricular tachycardia/fibrillation)	
	Increased risk of myocardial infarction	
Vascular	Variable effects depending on neuronal activity	Increased incidence of CVA and TIA related to cerebral vasospasm and atherosclerosis
	Endothelial vasodilation can increase CBF	
	Hypoxia or hypercapnia may reduce CBF	
Respiratory	Bronchodilation related to THC-mediated effects	Chronic bronchitis (coughing, increased sputum, and wheezing)
	Airway hyperreactivity related to local irritation by cannabis smoke	Increases in lung volumes
	Case report of pharyngeal, uvular edema	
Hematological	Variable effects	Final effect on hemostasis depends on particular cannabinoids involved and interaction with platelets, endothelial system
	Anticoagulant effects → increased clotting times (animal models) and decreased platelet function (human studies)	
	Procoagulant effects → increased platelet aggregation and arterial wall inflammation	
Gastrointestinal	Antiemetic effects	CHS → abdominal pain, nausea, and vomiting
	Reduced gastric acid secretion/emptying	
	Reduced GI transit, colonic emptying	
	Increased appetite	
CNS	Impaired executive functioning (decision-making, reasoning, and problem-solving)	Dependence
	Sedation, dizziness, euphoria, and disorientation	Psychosis
	Anxiety paranoia and dysphoria	Lasting impairments in memory and attention
Endocrine	Suppressed secretion of prolactin, growth hormone, and androgen	Decreased gonadal function (males → impaired sperm function and gynecomastia; females → anovulation and galactorrhea)
	Appetite stimulation	Reduced insulin secretion and glucose intolerance
	Increased energy intake and storage → adipogenesis, growth/maturation of adipocytes, and increased glucose uptake	
Thermoregulation	Hypothermia	

Abbreviations: CBF, cerebral blood flow; CHS, cannabinoid hyperemesis syndrome; CNS, central nervous system; CO, cardiac output; CVA, cerebrovascular accident; GI, gastrointestinal; HR, heart rate; THC, tetrahydrocannabinol; TIA, transient ischemic attack.

With persistent use, habitual cannabis smokers are more likely to experience symptoms of chronic bronchitis, including cough, sputum, and wheezing.[54,59] These respiratory symptoms appear to improve within several months after cessation of smoking similar to that seen in tobacco smokers.[54] It is unclear whether combined use of cannabis and tobacco necessarily increases the incidence of chronic respiratory symptoms compared with cannabis smoking alone.[54,60,61]

Studies of long-term effects of cannabis on lung function are limited largely due to legal issues and confounding effects of tobacco. Several studies have explored effects on lung function in habitual cannabis smokers,[54,60,62,63] and findings demonstrate increases in lung volumes, including forced vital capacity (FVC), total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV).[54,63] There are mixed results on FEV1 in cannabis smokers. Some studies show little or no difference in FEV1 in cannabis smokers compared with nonsmokers,[63,64] and reduced FEV1/FVC ratio is possibly due to increased FVC.[54,64] There are other studies that demonstrate reduced FEV1 consistent with airflow obstruction.[64] Based on the current literature, it is not definitive whether chronic-inhaled cannabis causes chronic obstructive pulmonary disease (COPD) and is an area of ongoing investigation.[54]

Hematological

There is evidence for both procoagulant and anticoagulant effects of cannabinoids.[65,66] In vitro studies in rat models show increased clotting times,[67] and human studies have demonstrated decreased platelet function and coagulopathy.[67–70] There are also reports of coagulopathies associated with synthetic cannabinoids due to their effects on vitamin K–dependent clotting factors.[71,72] On the other hand, multiple reports indicate that cannabinoids can cause increased platelet aggregation and thrombosis possibly due to adenosine diphosphate (ADP)-induced platelet activation, arterial wall inflammation, and oxidative stress.[65,66,73] The final effect on hemostasis with cannabis use likely depends on the particular cannabinoids and receptors involved, as well as their interaction with platelets and the endothelial system.[68] Cannabis use and

interaction of drugs metabolized by cytochrome P450 3A4 (CYP3A4), such as warfarin, will be discussed further below.

Gastrointestinal

CB1 and CB2 receptors are present throughout the gastrointestinal (GI) tract and are present in the enteric nervous system,[74] and various GI effects are mediated through these receptors, as well as those present centrally.[75] For example, cannabinoids influence the sensation of nausea through central mechanisms.[75] Cannabis has demonstrated antiemetic effects,[76] and CB1 and CB2 agonists can also block emesis.[77] However, cannabinoid hyperemesis syndrome (CHS) can also occur with chronic cannabis use, resulting in abdominal pain, nausea, and vomiting.[75,78] The mechanism of CHS is poorly understood, though it may be related to toxins in cannabis, and standard antiemetics appear to be ineffective for treating CHS.[79] Cannabinoids have other well-described effects on GI activity, including reduced gastric acid secretion and emptying, as well as slowing GI transit and colonic emptying.[31,75,80–82] Finally, cannabinoids can increase appetite,[80,81] and the endocannabinoid system may play a role in mediating gut inflammation potentially reducing conditions such as colitis.[75,80,83]

Central Nervous System

CB1 receptors in cortical areas and midbrain regions influence functions such as cognition and motor control.[84,85] The acute effects of cannabis and THC on executive functioning are well known and include impairment of decision-making, reasoning, problem-solving, and planning.[84,86–88] Acute administration also results in effects of sedation, dizziness, euphoria, and disorientation, and these effects may be compounded by coadministration of other central nervous system (CNS) depressants.[9,89,90] While cannabis may induce euphoria and calm in habitual users, in some naive users, THC may actually cause anxiety, paranoia, and dysphoria due to distorted sensorium and increased sensory reception.[31,91]

There are CB1 receptors present throughout the spinal cord and nociceptive sensory neurons of the dorsal root ganglion, and cannabis may mediate pain perception and provide analgesic effects.[92] Cannabinoids also act simultaneously on pain targets within the peripheral nervous system, and they interact with G protein-coupled receptors (GPCRs) in addition to cannabinoid receptors.[93] These GPCRs include opioid and serotonin (5-HT) receptors that modulate pain.[93] The efficacy of cannabinoids has been described in chronic pain conditions, such as multiple sclerosis, cancer, rheumatic pain, and neuropathic pain.[94,95] The role of cannabis in treating acute pain, however, is not well elucidated, and evidence does not support the efficacy of cannabis for acute postoperative pain management.[96]

There is some evidence that neuropsychologic impairment from cannabis may be more pronounced in adolescents due to ongoing brain development and plasticity.[97–99] Cannabis use may also lead to persistent use and dependence, and there is some evidence of risk of psychosis associated with cannabis.[100] Chronic users of cannabis have also demonstrated lasting impairments in memory and attention that may worsen with increasing use.[84,101–103]

Endocrine

Cannabinoids have various effects on hormone secretion and metabolism.[104–106] Through actions in the pituitary and reproductive organs, cannabinoids suppress the secretion of hormones, such as prolactin, growth hormone, and androgen.[2,105] With continued cannabis use, this may lead to decreased gonadal function and impaired sperm function and gynecomastia in men.[107] In women, hormonal effects may result in anovulation and galactorrhea.[108]

In terms of metabolism, cannabinoids are known to have an orexigenic, or appetite stimulating, effect that is mediated through brain centers involved in feeding behaviors such as the nucleus acumbens.[104,109,110] Cannabinoids also affect various organs to promote energy intake and storage.[104] In adipose tissue, activation of CB1 receptors promotes energy storage by stimulating adipogenesis and the growth and maturation of adipocytes.[111] CB1 activation also increases glucose uptake in adipocytes to increase energy storage,[112] while decreasing glucose uptake and oxygen consumption in skeletal muscle.[113] In the pancreas, endocannabinoid action results in reduced insulin secretion and glucose intolerance.[114,115]

Thermoregulation

Though inconclusive, there is some evidence that cannabis may affect thermoregulation.[3,116,117] Specifically, hypothermia has been seen in some patients with perioperative cannabis use.[3] The mechanism may involve CB1 receptor activation, and CB1 receptor blockade with an antagonist, rimonabant, seems to reverse these effects.[117] One study found higher incidence of postoperative shivering in cannabis users, though these results were not statistically significant.[116]

Perioperative Considerations

Perioperative considerations are summarized in Table 3. Physicians should consider routinely screening and identifying patients who use cannabis given its prevalence of use in 15% to 34.4% of the population.[25,26,30] After identifying those with known cannabis

Table 3. Perioperative Considerations

Phase of care	Considerations
Preoperative	Screen and identify patients with cannabis use
	Obtain details that may influence perioperative management → chronicity, frequency, type, and recency of cannabis administration
	Distinguish recreational versus medical use
	Determine appropriateness of continuing versus tapering use
	Consider postponing elective surgery if concerns with acute intoxication
Intraoperative	Possible increase in propofol induction dose requirements
	Evidence of increased sedation requirements
	Potential airway hyperreactivity with acute administration
Postoperative	Cannabis users may have difficulty with postoperative pain
	Potential for higher pain scores and increased opioid requirements
	Consider strategies such as multimodal analgesia and regional techniques to improve analgesia and limit opioid consumption

use, the preoperative discussion provides an opportunity to obtain details that may influence perioperative management. For example, as reviewed previously, physiologic effects may vary depending on the chronicity and recency of cannabis use.[2,3,31] Therefore, it is helpful to know whether the patient has used cannabis long term, the frequency of use, and timing of last administration.

Furthermore, there are different considerations between cannabis products used recreationally versus medically. Because of the wide range of cannabinoid products used recreationally, it is necessary to clarify details if possible, including the type of product, route of administration, amount of THC and/or CBD, and potency. Effects vary depending on these factors, and acute administration can lead to varying symptoms of acute intoxication, including anxiety, dysphoria, paranoia, and even psychosis that results in fever and tachycardia.[2,31,89,91] Given these issues, physicians might consider delaying elective surgery for patients demonstrating symptoms of acute intoxication given potential risks of airway reactivity and cardiac complications in addition to unexpected delayed awakening, emergency agitation and delirium, and hypotension.[31,118] On the other hand, patients using cannabinoid products regularly for medical purposes may present differently. Patients may use cannabinoid products for various conditions, such as pain, depression, appetite stimulant, and nausea.[119] In these patients, an argument can be made that discontinuing use may pose some risk due to withdrawal symptoms,[34,120] and it may be more appropriate to continue use or substitute through the perioperative period.[118,121]

Currently, there are no published guidelines on preoperative testing for patients with acute or chronic cannabis use who present for elective surgery. Based on the literature, additional testing simply due to the history of cannabis use is not recommended. Each patient should be considered individually based on their history and physical examination, and testing ordered when appropriate but not solely due to the use of cannabis.

Intraoperative

Induction. There are limited studies on the effects of cannabis use on induction requirements. Flisberg et al[122] found that in men 18 to 50 years of age, there was no difference in propofol dose required to achieve bispectral index (BIS) value of <60 in those who used cannabis more than once per week compared with men who were not cannabis users. However, they did identify a significantly higher dose of propofol needed to insert laryngeal mask airway in the group of patients who were regular cannabis users.[122] Similarly, Zhang et al[24] found that propofol induction doses were increased in cannabis users, though this did not reach statistical significance. On the other hand, animal studies show varying results.[123] In rats, pretreatment with low doses of CBD resulted in shorter induction times and quicker recovery using isoflurane compared with high doses of CBD.[123] While these results are not translatable to humans, they seem to suggest that there is dose-dependent variability in how CBD influences induction and recovery from anesthesia. Also, this only reflects the effect of CBD, whereas THC is often the active component in cannabis products. The effect of cannabis use on induction requirements is, therefore, not well established, though there is some suggestion that higher doses of propofol may be necessary.

Effects on Sedation and Monitored Anesthesia Care Requirement and Intraoperative Analgesia. Various studies have investigated the influence of cannabis on anesthetic requirements for sedation and maintenance of anesthesia, though these are mostly limited to animal studies and human studies involving small sample sizes or case reports. Cannabis has cross-tolerance with substances including alcohol, barbiturates, and opioids.[124] Consistent with this, Brand et al[125] found an increased propofol requirement necessary for sedating rodents that were administered THC. In humans, there is also evidence of increased sedation requirements related to cannabis as studies have demonstrated higher doses of propofol used to achieve similar levels of sedation in cannabis

users.[126,127] Similarly, a retrospective study identified increased doses of midazolam needed for conscious sedation in patients using cannabis.[128]

In 1 small randomized controlled trial, Ibera et al[129] explored the relationship of cannabis and depth of anesthesia using the cannabis-extract nabiximol and BIS monitoring. While controlling for monitored anesthesia care (MAC), the average BIS values were higher during steady-state anesthesia in patients who received high-dose cannabis.[129] However, they concluded that the higher BIS values may have been due to electroencephalogram (EEG) changes induced by cannabis rather than reflecting the depth of anesthesia; therefore, the use of BIS may not be accurate in patients with acute high-dose cannabis administration. Apart from this, there are multiple case reports that describe tolerance to anesthetic drugs and increased anesthetic requirement in patients who consumed cannabis just before surgery.[130,131]

Although there is some suggestion that anesthetic requirements may be increased with acute administration of cannabis, these findings are limited to studies with small sample sizes, anecdotal and observational reports, and animal research.[132] More research is needed to understand the true significance of influence of cannabis on sedation and the maintenance of anesthesia.

Effects on Respiratory System. As discussed previously, cannabis use can affect the respiratory system, and clinicians should keep these effects in mind during intraoperative management. Related to irritation from cannabis smoke, airway hyperreactivity may occur and result in increased airway pressures. Postoperative airway edema has been reported in a case report by an unknown mechanism, and this can lead to stridor and impaired air exchange after extubation. Cannabis smoking long term is not definitively associated with airway obstruction; however, concurrent tobacco smoking is common and can cause airway obstruction requiring adjustments in mechanical ventilation such as increased expiratory time to allow adequate air exchange. Finally, symptoms of chronic bronchitis such as coughing and increased secretions are seen with chronic cannabis use, and patients require proper suctioning and adequate analgesia to clear secretions during and after anesthesia.

Potential Drug-Drug Interactions. Cannabis may interact with medications administered perioperatively and influence their effects (Table 4). For instance, there is evidence that ketamine induces the release of endogenous cannabinoids, and psychomotor effects of ketamine are possibly potentiated with cannabinoid administration.[133,134] Gabapentin acts via voltage-dependent Ca^{2+} channels, and CB receptor activation results in inhibition of voltage-dependent Ca^{2+} channels.[6,135] Synergistic effects of gabapentin and THC have been demonstrated where combined gabapentin and THC improved neuropathic pain, and high-dose gabapentin amplified THC-like effects.[135,136] Though not demonstrated in humans, possible synergistic analgesic effects between synthetic THC and dexmedetomidine have been demonstrated in an animal model.[137] Finally, CB1-Rs are located at the neuromuscular junction, and there is evidence of increased acetylcholine release and postsynaptic action potentials,[6,138] though the clinical significance of neuromuscular blockers and whether blockade is shortened in cannabis users is not well studied.

In addition to drug interactions, cannabis also affects drug metabolism enzymes and thereby alters the pharmacokinetics of various medications. Most notably, CBD inhibits CYP3A4, and the concomitant administration of CBD with certain drugs has shown consequences of altered drug levels.[9] For example, the combined use of CBD with clobazam, a benzodiazepine, in patients treated for epilepsy led to elevated levels of clobazam necessitating dose reductions of medication.[9,139] Warfarin, which is metabolized by CYP3A4, has also shown a possible interaction with cannabinoids as evidenced by a report of a patient with heavy cannabis use while taking warfarin resulting in supratherapeutic international normalized ratio (INR) and significant bleeding complications.[3,9] The inhibition of CYP3A4 has further been implicated in the metabolism of other medications including

Table 4. Potential Drug-Drug Interactions

Drug	Potential effects
Ketamine	Induces release of endogenous cannabinoids; psychomotor effects may be potentiated with cannabinoids
Gabapentin	CB receptor activation results in inhibition of voltage-gated Ca^{2+} channels, resulting in synergistic effects between gabapentin and THC
Dexmedetomidine	Synergistic analgesic effects between synthetic THC and dexmedetomidine seen in animal models
Nondepolarizing neuromuscular blocking agents	Increased acetylcholine release with CB1-R activation suggesting possible shortened blockade with cannabis use
Cannabidiol	Inhibits CYP3A4 and alters drug levels of drugs metabolized by CYP3A4 (eg, benzodiazepines, warfarin, and certain opioids), increasing risk for side effects and possible toxicity

Abbreviations: CB, cannabinoid; CB1-R, cannabinoid-1 receptor; CYP3A4, cytochrome P450 3A4; THC, delta-9-tretrahydrocannabinol.

oxycodone, benzodiazepines, haloperidol, topiramate, and zinosamide.[9,139] Drugs that are used during induction of anesthesia and common local anesthetics are also substrates for cytochrome P450 enzymes including midazolam, bupivacaine, ropivacaine, fentanyl, and ondansetron.[9,140] The availability and clearance of these medications are, therefore, affected by the activity of cytochrome P450 enzymes.

Finally, just as cannabis can influence drug metabolism, medications that affect cytochrome enzymes may similarly alter cannabinoid levels. For instance, rifampicin induces CYP3A4 and significantly reduces peak plasma concentrations of CBD, and ketoconazole inhibits CYP3A4, resulting in higher CBD plasma concentrations.[141]

Postoperative Considerations (Pain Levels and Opioid Consumption). Studies have demonstrated worse postoperative pain scores in patients who are habitual cannabis users, and there is evidence for increased opioid consumption in this population, as well.[34,142,143] Liu et al[34] explored the outcomes of patients undergoing major orthopedic surgery and compared pain and opioid use in nonusers with those consuming cannabinoids preoperatively for medical and recreational purposes. Patients on preoperative cannabinoids were found to have higher pain scores at rest and with movement in the early postoperative period, and these patients also reported higher incidence of sleep disruption.[34] Cannabinoid users who underwent hip and knee replacement also had higher opioid consumption in the early postoperative period compared with patients who were not on cannabinoids previously.[34] Similarly, other authors have found an increased need for opioids for pain control in habitual cannabis users. In patients undergoing bowel surgery, those who used cannabis before surgery were found to have increased opioid use in the first 24 hours postoperatively compared with patients who were not using cannabis.[142] In a separate study, 500 patients with musculoskeletal injuries including soft tissue, upper, and lower extremity trauma were self-identified as (1) never user, (2) prior user, or (3) user during recovery, and prescription opioid use was assessed among these groups.[143] Patients who reported cannabis use during recovery had higher total prescribed opioids and duration of use compared with patients who reported never using cannabis.[143] Whether cannabis users have more difficulty with pain control and require more opioids is not definitive, however. Multiple factors may be involved including the type of surgery and concurrent use of other substances or medications.

Two separate meta-analyses failed to demonstrate a significant clinical benefit with the use of cannabinoids for treating acute pain.[96,144] A randomized controlled trial investigating the use of THC after abdominal hysterectomy with the primary outcome of pain intensity also found no benefit of THC.[145] A separate study found that the addition of dronabinol to multimodal pain regimen after total joint arthroplasty reduced length of stay but not daily opioid consumption.[146] In patients who do not use cannabis, the initiation of cannabinoids for treating acute postoperative pain is not supported by current literature. Of note, an important limitation of current studies is that they do not necessarily reflect clinical situations—for example, many studies use formulations or investigational compounds that are not reflective of more typical patient circumstances.

In summary, though not definitive, there are data to support the possibility of worse pain control and potential for increased opioid consumption in patients who use cannabis regularly.[34,142,143] Therefore, in this population, it may be prudent to consider utilizing strategies such as multimodal analgesia and regional anesthesia techniques that can improve analgesia while limiting opioid consumption until more research is conducted.[147]

Potential Postoperative Complications in Patients With a History of Cannabis Use. As discussed previously, there are many physiologic effects that can occur with cannabis use including those involving respiratory and cardiovascular systems. The clinical significance of these effects in terms of postoperative complications and outcomes is presented in case reports and explored in various studies. Summary of potential postoperative complications is presented in Table 5.

Chiu et al[25] used a retrospective cohort analysis to investigate the association of cannabis use and adverse events after elective spine surgery. Patients were identified based on coded diagnosis suggestive of cannabis disorder, which included "cannabis dependence" and "cannabis abuse" International Classification of Diseases, Ninth Revision (ICD-9) codes, and these patients were compared with controls. The cannabis use cohort was found to have an increased hospital length of stay, higher rates of respiratory complications, thromboembolic events, sepsis, and neurologic complications such as postoperative stroke.[25] The rates of acute kidney injury and MI were not significantly different between the cannabis cohort and controls.[25]

In another study, patients undergoing major elective surgeries including coronary artery bypass graft (CABG), cesarean section, colectomy, and total hip and knee revision surgery, were analyzed to investigate the association of cannabis use with postoperative complications.[27] Similar to the study by Chiu et al, patients were identified with active CUD based

Table 5. Potential Postoperative Complications[a]

System	Outcomes
Renal	Acute kidney injury
Neurologic and psychologic	Stroke, cannabis withdrawal syndrome, fatigue, sleep disturbance, anxiety, depression
Pulmonary	Respiratory failure
Cardiovascular	Thromboembolic events, myocardial infarction, arrhythmia
Other	Increased hospital length of stay, sepsis, low bone mineral density, fracture risk, hospital readmission

[a]Based on certain retrospective analyses.

on ICD-9 codes for cannabis dependence and cannabis abuse. Compared to controls, patients with active CUD were not found to have significantly higher risk of respiratory failure, kidney injury, thromboembolism, sepsis, or mortality.[27] However, patients with CUD were more likely to suffer postoperative MI.[27] The adjusted odds of stroke was also higher in those with cannabis use, though this did not reach statistical significance.[27] Similar findings were reported in patients undergoing vascular surgery, and CUD was associated with an increased incidence of perioperative MI and stroke.[27,28]

A recent retrospective analysis investigating perioperative outcomes identified cannabis use through self-reporting and included patients undergoing a wide range of procedures such as orthopedic, thoracic, plastic, general, and obstetrics and gynecology.[24] This study identified a higher incidence of new-onset arrhythmia in cannabis users compared with controls, though this did not reach statistical significance.[24] The incidence of postoperative nausea was lower in patients reporting cannabis use.[24] There was no difference, however, in the composite outcome of respiratory or cardiac arrest, ICU admission, stroke, MI, or mortality.[24]

Apart from other potential postoperative complications, patients need to be monitored for cannabis withdrawal syndrome (CWS) in the postoperative period, which is a validated clinical entity included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD).[3] Patients who suffer withdrawal may experience irritability, anger, aggression, nervousness, anxiety, sleep difficulty, decreased appetite, restlessness, and depressed mood.[3] Physical symptoms of withdrawal also occur, such as abdominal pain, shaking, tremors, sweating, fever, chills, and headache.[3] Abrupt cessation of THC can result in withdrawal in the early postoperative period, and physicians might consider continuing cannabis products for patients who have used these long term for medical purposes.[118] Current therapies for CWS are investigational, though there is some low-level evidence that gabapentin and THC-analogs may reduce symptoms.[148]

Patients face several constraints in terms of continuing cannabinoid use postoperatively. Patients cannot smoke cannabis indoors, and hospitals do not permit patients to go outside to smoke. Therefore, patients cannot practically continue inhaled cannabis while hospitalized. At the same time, many hospitals do not have THC-analogs in their formularies, so the options for continuing cannabinoid are limited. Nonformulary use is unlikely to be permitted, as well, given the unknown content of such substances. Due to such constraints, patients who are unable to continue cannabinoid use postoperatively may be at risk for withdrawal.

In counseling patients, clinicians should discuss the potential risks associated with cannabis use before surgery. These potential risks include, as discussed above, complications of the respiratory, cardiovascular, neurologic, and renal systems, as well as infection and increased hospital length of stay. The evidence is not definitive, and certain patients and procedures may carry greater risks than others. By presenting this information, clinicians can help inform patients and address concerns related to these issues. Patients may want to know about their options for continuing cannabinoid use postoperatively, which can also be discussed during preoperative counseling.

Potential Longer-term Complications. There are few studies investigating longer-term complications after surgery associated with cannabis use. One recent prospective study explored outcomes by following patients after undergoing various types of surgeries, including hysterectomy, total joint arthroplasty, thoracic, hand, ankle, abdominal, breast, and inguinal hernia surgery.[149] Patients were surveyed at baseline and at 3- and 6-month time points postoperatively to collect data on pain, functioning, mood and opioid use, and relevant surgical outcomes.[149]

Compared with nonusers, on the day of surgery, patients using cannabis were more likely to report worse pain, greater functional impairment, fatigue, sleep disturbance, and anxiety and depression.[149] Similarly, at 3-month and 6-month follow-ups, patients who used cannabis preoperatively reported worse clinical characteristics in pain scores, functional impairment, fatigue, and anxiety and depression relative to patients who were nonusers.[149] Postoperatively, a higher proportion of patients also reported opioid use at 3-month and 6-month follow-ups compared with nonusers.[149]

In terms of surgical outcomes, by the 6-month time point, cannabis users and nonusers were found to

have similar improvements in surgical site pain and perceived treatment efficacy, suggesting that preoperative cannabis use did not necessarily impede recovery.[149] Conversely, other studies have demonstrated that cannabis use may negatively affect factors involved in healing and longer-term outcomes. For instance, heavy cannabis use in patients has been associated with low bone mineral density, increased fracture risk, and increased time to union after surgery.[150] The direct impact of cannabinoids on these outcomes is unclear, however. There are confounding factors, and a higher proportion of patients reporting cannabis use preoperatively have also reported use of tobacco, benzodiazepines, and opioids, which could be implicated in influencing recovery after surgery.[149]

In patients undergoing joint arthroplasty, one study found that cannabis use was associated with decreased mortality.[151] Another study identified cannabis use to increase the risk of requiring revision surgery after total knee arthroplasty.[152] In total hip arthroplasty patients, cannabis use was associated with longer length of stay, increased implant-related complications, and higher average 90-day costs.[153] Finally, individuals with cannabis use were found to be more likely to develop thromboembolic events and have higher readmission rates after total knee arthroplasty.[154]

FUTURE RESEARCH

Much of the current literature, unfortunately, is limited, and we rely largely on observational studies because there is little laboratory or human research characterizing long-term effects of cannabis. Much of the data may also not necessarily accurately reflect the true potency and composition of products used by patients. Future research is necessary to better understand the consequences of cannabis use in patients undergoing surgery. This will help guide perioperative physicians in caring for patients with acute and/or chronic cannabis use. Questions that remain include how cannabis affects anesthetic requirement, and which medications are most impacted by cannabis use, especially in populations with coexisting diseases such as cirrhosis or chronic kidney disease that may impact metabolism and excretion. The topic of postoperative pain and whether cannabis use preoperatively is beneficial or harmful to patient outcomes also need to be further elucidated. Perioperative complications including cardiovascular and respiratory risks in various patient populations also require better understanding—for example, which patients are most prone to developing complications and which other factors are involved.

One of the limitations with the current body of evidence is that cannabis is often treated as a monolithic substance and consumption as binary, whereas, in reality, there is significant variability in the constitution and consumption of cannabis and cannabinoid products. The heterogeneity of findings is reflected by this. As the body of literature grows, hopefully the true effect and impact of specific substances, doses, and routes of administration will become clearer. Eventually, evidence-based guidelines may offer a way to help physicians make important decisions including when to postpone or delay surgery, whether to maintain or taper cannabis user before surgery, which medications to adjust, and how to optimize pain control for patients.

SUMMARY

Cannabis use is increasingly common—a trend that is likely to continue with greater legalization across the United States. There are key considerations for clinicians to keep in mind as they encounter and care for patients using cannabis. Effects of cannabis are influenced by chronicity and recency of use, composition (eg, THC content), route, and frequency. The preoperative period is an important opportunity to gather details related to use. Physicians may consider delaying elective surgery in patients displaying acute intoxication (anxiety, dysphoria, paranoia, and psychosis). Intraoperatively, patients with recent cannabis ingestion potentially have increased anesthetic requirements. Cannabis interacts with various drugs and could enhance or depress their effects, as well as metabolism of certain drugs. In the postoperative period, habitual cannabis users may have worse pain control and increased opioid consumption. Multimodal and regional anesthesia techniques are, therefore, helpful for postoperative analgesia. Habitual cannabis users face other potential challenges postoperatively, including complications related to cardiovascular, respiratory, neurologic, and renal systems, as well as risks of cannabis withdrawal. Longer-term complications include worse pain, functional impairment, mood disturbance, and hospital readmission. Clinicians should discuss potential risks before surgery to inform patients and address relevant concerns and devise appropriate postoperative care and follow-up.

DISCLOSURES

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