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A review of the anesthetic implications of marijuana use

John C. Alexander, MD, MBA and Girish P. Joshi, MD, MBBS

Department of Anesthesiology and Pain Management, The University of Texas Southwestern Medical Center, Dallas, Texas

ABSTRACT

Marijuana, derived from plants of the genus *Cannabis*, is the most commonly used illicit drug in the United States. Marijuana is illegal at the federal level and remains a Drug Enforcement Agency Schedule 1 substance. Nevertheless, most states have passed less stringent legislation related to its use, ranging from decriminalization of possession to allowing medical or even recreational use, and some county and municipal law enforcement agencies have refrained from prosecuting personal possession and/or use even when statute would require such action. Therefore, as use of marijuana becomes more common in the larger population, more patients who are chronic and/or heavy users of marijuana present for surgical procedures, raising the question of best practices to care for these patients in the perioperative period. This review summarizes the known physiologic effects of marijuana in humans, discusses potential implications of marijuana use that the anesthesiologist should consider at each phase of the perioperative period, and outlines recommendations for future study.

KEYWORDS Anesthesiology; cannabinoid; cannabis; marijuana; perioperative

Marijuana is derived from female plants of the genus *Cannabis*, of which three species contain cannabinoid compounds for which the plant is known (*indica*, *sativa*, *ruderalis*).[1] Common names for the psychoactive products created from the *Cannabis* genus go by a variety of names, including marijuana, hashish, ganja, bud, hemp, weed, or, simply, cannabis. Marijuana use, for both medicinal and recreational purposes, dates back thousands of years.[2] Cannabis products had variable degrees of legality in the USA until the Controlled Substance Act of 1970 relegated all cannabis products to Schedule I classification reserved for compounds without any accepted medical use and a high potential for abuse.[3] Other Schedule I drugs include heroin, lysergic acid diethylamide, and "ecstasy."[4] This scheduling effectively ended the ability of US-based researchers to study the effects of cannabis products. Multiple states in the USA have passed legislation allowing both medical and recreational use of cannabis products *(Figure 1)*.[5] Cannabis products remain the most commonly used illicit drug in the USA, with an estimated 22 million Americans over the age of 12 using cannabis products per year.[6] With the widespread and growing availability of cannabis products in the larger population, it is expected that increasing numbers of patients with a history of chronic marijuana use will present for anesthesia. We review the current evidence evaluating the influence of marijuana use on perioperative care. We also attempt to outline important gaps in our knowledge as targets for future research.

CHEMICAL COMPOUNDS IN CANNABIS

Cannabinoids can generally be grouped into three categories: endocannabinoids, synthetic cannabinoids, and phytocannabinoids. Endocannabinoids include any endogenous cannabinoid receptor (CB1 or CB2) ligands and various eicosanoid compounds, most notably ananamide and 2-arachidonoylglycerol.[7] Synthetic cannabinoids are laboratory derived and may be Food and Drug Administration (FDA)-approved pharmacologic agents, such as nabilone,[8] or drugs of abuse, like K2 or Spice.[9,10] Phytocannabinoids are the plant-derived cannabinoid receptor ligands. Modern chemical methods have derived hundreds of organic compounds from various strains of the plant, including over 100 cannabinoid compounds.[11] The most potent psychoactive product is delta-9-tetrahydrocannabinol, or THC,[12,13] which is present mostly in the flowering buds (hence the colloquial name) of the plant and to a lesser degree in the leaves, stems, and seeds.[14] Another common cannabinoid is cannabidiol

Corresponding author: John C. Alexander, MD, MBA, Department of Anesthesiology and Pain Management, The University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9068 (e-mail: John.Alexander@UTSouthwestern.edu)

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Table 1. Physiological effects of marijuana

	Acute effects	Chronic effects
Cardiovascular	Tachycardia Vasodilation Orthostasis	Atheromatous disease
Pulmonary	Bronchodilation Hyperreactivity Airway edema	Chronic bronchitis Emphysema
Central nervous system	Anxiolysis Anxiety Paranoia/psychosis Euphoria Dizziness Headache Memory dysfunction Analgesia	Similar to acute effects but tolerance develops, requiring higher doses for similar effects
Gastrointestinal	Antinausea Increased appetite Abdominal pain	Hyperemesis
Endocrine	None	Gynecomastia Anovulation Galactorrhea

(CBD), though it lacks the psychoactive effects seen with THC.[10,12]

Cultivation efforts have sought to maximize the THC content of cannabis, because it is responsible for the desired recreational effects. These efforts have resulted in significantly more potent strains in regards to THC concentration than when cannabis products were outlawed in 1970.[15] The average marijuana cigarette prior to the 1980s contained 1% to 3% THC compared to 6% to 20% THC in the 1990s,[15,16] and some currently available strains have achieved up to 33% THC.[17] In addition to modern cultivation efforts, more sophisticated extraction techniques have resulted in widespread availability of even higher potency products, such as butane hash oil (BHO) extracts, with THC concentrations as high as 90%.[18]

PHARMACOLOGY

The pharmacokinetics of cannabinoids are difficult to predict because the THC concentration in any one delivered dose depends on several variables, including the THC concentration of the cannabis products, the route of delivery, and the metabolism and elimination of the cannabinoids.

For example, two marijuana cigarettes from a high-potency strain may deliver different total doses of THC depending on the relative proportion of buds, leaves, stems, and seeds in the cigarette because the THC concentration is variable in each portion of the plant. Similarly, dose delivery is highly dependent on the user's smoking style.[19] Cannabinoids are rapidly distributed within the vessel-rich group, so effects are apparent within seconds to minutes of inhalation but may be delayed up to 1 to 2 hours with oral ingestion.[12,14] Conceptually, BHO extracts and oral preparations may have more consistent THC concentrations, because they are extracted from the *Cannabis* plant matter, but lack of testing and regulation makes such conclusions mere speculation. Cannabinoids are also highly lipid soluble, so significant redistribution and accumulation occur once ingested. Metabolism of THC occurs via the liver, leading to multiple psychoactive and nonpsychoactive metabolites. Elimination of metabolites occurs via urine, bile, and feces. The plasma half-life ranges from 20 to 30 hours,[19] but the tissue half-life may be as long as 30 days depending on frequency and chronicity of use due to fat accumulation.[20] As such, one cannot predict the degree of intoxication based on laboratory studies.[21]

Cannabinoids act primarily via adenylyl cyclase G-protein–coupled receptors. CB1 receptors are widely distributed in the central and peripheral nervous systems, especially the hippocampus, cortex, olfactory areas, basal ganglia, cerebellum, and dorsal horn of the spinal cord, but less so in the brainstem. This distribution may account for cannabinoid effects on nociception, anxiolysis, memory, cognition, emotion, and movement with a relative sparing of respiratory depression.[22] The CB2 receptors are distributed primarily in peripheral lymphoid and hematopoietic cells, suggesting an immunomodulatory function, though our understanding of the effects of cannabinoids at these receptors remains incomplete.[22] It is clear, however, that each of the hundreds of cannabinoids has variable effects. For example, whereas THC is an agonist at CB1 and CB2 receptors, CBD may act as an antagonist or inverse agonist at both CB1 and CB2

receptors. Yet CBD also has agonist actions at the serotonin 5-HT1A and transient receptor potential cation channel subfamily V member 1 receptors and may decrease the reuptake of endocannabinoids, thus augmenting their effect.[23]

PHYSIOLOGY

Our understanding about the physiologic changes with administration of cannabinoids in humans is incomplete for several reasons. First, there are many cannabinoids present in *Cannabis* products, and each has variable effects. Next, the relegation of cannabis to Schedule 1 status has hampered the ability of scientists to pursue research on *Cannabis* products within the USA. In addition, the only federally approved source of cannabis for research purposes comes from a single location, the University of Mississippi's National Center for Natural Products Research.[24] There have been widely documented concerns about the quality of the cannabis plants produced at this facility, because the maximum THC potency of the strains produced is approximately 13% to 14%[25,26] compared to commercially available strains with potency as high as 33%[17] and even higher potency extraction formulations like BHO. Thus, the cannabis available for research does not accurately reflect what is used in the population. Finally, there are substantial interspecies differences in the physiologic changes with THC administration, which limits the ability to extrapolate the results from animal studies to humans. For example, THC has been shown to reliably cause tachycardia and postural hypotension in humans regardless of the route of administration[27] but causes bradycardia in anesthetized dogs[28,29] and cats[30] as well as bradycardia and hypertension in rats.[31] THC administration also results in bronchodilation in humans[27,32] but causes a vagally mediated increase in lung resistance in dogs[29] and marked respiratory depression in cats.[30]

The physiologic effects of marijuana are summarized in *Table 1*. The most widely known effects involve the central nervous system, including euphoria, sedation, relaxation, and altered spatial and/or temporal perception. In addition, deficits in reward processing, such as apathy and amotivation, are commonly cited adverse effects. Though these are anecdotally considered to occur in both acute and chronic cannabis users, a recent study showed that these behaviors occurred transiently in acute users, whereas chronic users did not display decreased effort-related behaviors.[33]

ACUTE EFFECTS

One of the most consistent acute effects of cannabis administration in humans is tachycardia.[28] One study showed that cannabis-naive tobacco smokers with stable angina developed angina symptoms with exercise significantly faster after smoking cannabis.[34] Another study noted a fivefold increased risk of myocardial infarction (MI) in the first hour following cannabis smoking compared to a 24-fold increased risk of MI in the hour following cocaine ingestion. About 40% of these patients used marijuana at least weekly and over two-thirds used marijuana at least monthly.[35] The elevated risk of MI in cannabis use is thought to be due to a combination of tachycardia and peripheral vasodilation resulting in compensatory orthostatic hypotension and an increase in cardiac output, oxygen demand, and cardiac work.[36] The risk of MI rapidly decreases after 1 hour of use,[35] and these physiologic effects may be blunted in chronic cannabis users.[37]

Laboratory studies consistently show bronchodilation and decreased airway resistance with either inhaled or ingested THC.[27,32] Despite this underlying bronchodilation, though, cannabis smoking can result in similar airway hyperreactivity as seen with tobacco smoking.[38] In fact, some authors have expressed concern that cannabis may be more irritating to airways given that it burns at a higher temperature than tobacco. These authors presented one case of severe uvular edema following general anesthesia in a patient who had recently smoked cannabis that improved following dexamethasone administration. They advocate cancellation of elective surgery in patients with recent marijuana inhalation given the remote, but potentially severe, risk of airway compromise in this clinical scenario.[39]

Though some users report improvement in anxiety with cannabis use, there are many reports of worsened anxiety leading to paranoia or frank psychosis with cannabis use.[20] A meta-analysis showed that the risk of a psychotic episode increased with cannabis use and that more frequent use resulted in a greater risk of psychosis.[40] The advent of organic extraction techniques has allowed rapid ingestion of extremely high doses of THC.[18] This has resulted in several case reports of acute psychosis.[41–43] In two of these cases,[42,43] the patients also presented with fever as well as severe tachycardia and hypertension. In one case, the patient required tracheal intubation, and subsequent testing of "dabs" recovered from the patient's home showed a THC concentration of approximately 20%,[43] though other studies document concentrations as high as 90% THC with BHO.[18] Given such potential adverse effects, some have advocated that concurrent mood/anxiety disorder or personal/family history of psychosis or schizophrenia should be a contraindication for medical cannabis use.[44]

Cannabinoid hyperemesis syndrome is another adverse effect of cannabis characterized by recurrent episodes of severe nausea, vomiting, and abdominal pain. Patients with this syndrome may also present with dehydration and electrolyte abnormalities. The underlying pathophysiology of the syndrome is unclear.[45] In addition, there have been several recent case reports of severe bleeding in conjunction with use of non-FDA-approved synthetic cannabinoids (e.g., K2 or Spice) for recreational purposes, leading to nationwide health alerts.[9] These patients presented with unexplained, persistent bleeding in the setting of greatly elevated prothrombin time and international normalized ratio. Bleeding persisted despite administration of intravenous vitamin K and fresh frozen plasma. The mechanism of action is thought to be due to a potential synthetic cannabinoid–warfarin interaction, though

Table 2. Cannabis withdrawal syndrome

Variable	Description
Signs and symptoms	Irritability/anger Anxiety/depressed mood Insomnia Altered dreams Anorexia Abdominal cramping Headaches Tremors Fevers/chills
Onset	<1 day for high-dose, chronic users
Duration	Up to several weeks
Treatment	Symptomatic therapy, synthetic THC

THC indicates delta-9-tetrahydrocannabinol.

there was no known exposure to anticoagulants or rodenticide agents in these cases.

Given the psychomotor effects of cannabis, it is perhaps not surprising that cannabis use is often implicated in motor vehicle accidents. Studies have shown a dose-dependent effect of acute cannabis administration on increased reaction time and "weaving" during both live and simulated traffic conditions that is augmented by co-administration with ethanol.[46] This may lead to more frequent presentation to anesthesiologists for emergent surgical procedures related to traffic accidents. Another common reason for increased health care utilization among cannabis users is unintentional overdose of oral preparations, especially in children,[47] and burn injuries from combustion of butane in making cannabis extract products.[48] Other common, but less severe, acute effects include dry mouth, headache, dizziness, memory dysfunction, abdominal pain, and increased appetite.

CHRONIC EFFECTS

Chronic effects may include cough, bronchitis, and emphysema similar to those seen in chronic tobacco smokers,[20,38] which is thought to be due to higher particulate matter in marijuana smoke and a tendency for marijuana smokers to inhale a greater volume of smoke and hold it longer when compared to tobacco smokers.[49] Due to the relatively high amount of carbon monoxide in marijuana cigarettes compared to tobacco cigarettes, chronic marijuana smokers may be at higher risk for development of atheromatous disease.[16] In addition, cannabinoids decrease androgen and prolactin concentration; thus, in chronic users, it may result in suppression of gonadal function leading to impaired sperm morphology/function and gynecomastia in males and anovulation and galactorrhea in females.[50] Tolerance develops within weeks of regular use due to downregulation of both CB1 receptors and endocannabinoid levels.[51]

WITHDRAWAL SYNDROME

Table 2 summarizes some key points related to cannabis withdrawal syndrome. Withdrawal symptoms can develop within a day of cessation for high-dose chronic cannabis users and may take weeks to fully resolve.[52] Furthermore, though cannabis use is more frequent in males, females tend to develop dependence more rapidly with prolonged use and have more severe withdrawal symptoms. Symptoms of cannabis withdrawal include irritability, anger, aggression, anxiety, nervousness, insomnia, disturbed dreams, restlessness, depressed mood, anorexia, weight loss, abdominal cramping, tremors, sweating, fevers, chills, and headache.[51] No specific treatment guidelines exist, though administration of benzodiazepines and synthetic THC, which is used for chemotherapy-induced nausea, has been recommended to improve withdrawal symptoms.[53]

PREOPERATIVE CONSIDERATIONS

Preoperative patients with a known or suspected history of marijuana use should be asked about the duration, frequency, and route of use. In addition, it is necessary to ask about the most recent intake. Care should be taken to reassure patients that information on illicit use of cannabis products is only being used to help guide safe perioperative care. It is key to assess for signs and symptoms of acute intoxication, because the most concerning anesthetic implications are related to acute intoxication.

If patients exhibit central nervous symptoms of acute cannabis intoxication, care should be taken to assess for symptoms of escalating anxiety, paranoia, or psychosis, because these may result in a more violent emergence from anesthesia. In addition, episodes of cannabis-induced psychosis, especially after use of higher potency THC formulations, can co-present with fever, tachycardia, and hypertension. These symptoms could be mistaken for other conditions with similar symptom clusters like malignant hyperthermia, serotonin syndrome, neuroleptic malignant syndrome, 3,4-methylenedioxymethamphetamine overdose, or thyrotoxicosis. In addition, cannabis withdrawal has a presentation similar to that of other withdrawal disorders, so careful and directed history taking may help identify at-risk patients. Unfortunately, current quantitative testing methods do not provide effective clinical guidance to refute or corroborate patient reports on timing of use due to nonlinear relationships between plasma or urine cannabinoid levels and degree of intoxication.[21] Thus, history and physical examination are more important than toxicology screens.

In cannabis users with a history of angina, anesthesiologists should inquire about angina-free functional capacity both before and after cannabis use. It may be prudent to consider delaying elective surgery for an hour after use, especially in patients at high risk of coronary artery disease, because the elevated risk of MI resolves an hour after cannabis use.[35] A delay of anesthetic induction may also be appropriate until resolution of tachycardia and/or postural hypotension in acutely intoxicated patients. Another

preoperative consideration is the risk of airway hyperreactivity in cannabis smokers. It would be prudent to follow a preoperative evaluation for chronic marijuana smokers similar to that used for chronic tobacco smokers. There is controversy surrounding the appropriateness of obtaining informed consent in the intoxicated patient, because both memory and perception are impaired.[54] It is reasonable to assume that a patient with acute cannabis intoxication may have similar deficits and may also be unable to provide informed consent. Similar procedures should be pursued for all intoxicated patients regardless of means of intoxication.

In summary, in addition to the standard preoperative evaluation, anesthesiologists should assess for signs and symptoms of acute cannabis intoxication and inquire about patterns of cannabis use. Further evaluation should focus on assessment of cardiovascular, pulmonary, and psychologic systems to mitigate the risk of poor perioperative outcomes. Issues of informed consent can be addressed, and one can begin preoperative planning for potential postoperative withdrawal symptoms. We do not recommend specific baseline laboratory studies in this population. Drug screening will provide qualitative data on the use of cannabis products over the past 30 days. Other testing should proceed based on clinical judgment and established guidelines and protocols.

INTRAOPERATIVE CONSIDERATIONS

Both acute and chronic administration of crude extracts of cannabis plants has been shown to decrease the required induction dose of thiopental in rabbits without a commensurate prolongation of anesthetic duration.[55] A study in mice with pure extracts of THC, CBD, and cannabinol showed that both THC and CBD displayed additive prolongation of anesthetic duration, whereas cannabinol-containing extracts blunted this prolongation. This led to the conclusion that cannabinol may antagonize or have a negative effect on the sedative-hypnotics, thus prolonging effects of THC and CBD.[56] Other studies in mice and rats showed cannabinoid-induced analgesic tolerance to morphine[57] but not to mescaline or lysergic acid diethylamide.[58] Similar studies in humans have not been published. Of note, the effects of cannabis on anesthesia care have been more thoroughly studied in animal models, and extrapolation to humans should be done with caution due to interspecies differences in cannabis physiology.

A human study of the propofol induction dose required to achieve a bispectral index (BIS) <60 in self-reported cannabis users showed that they required significantly higher induction doses of propofol when compared to self-reported cannabis nonusers.[59] Another small study showed that administration of Sativex, a synthetic THC and CBD analogue in a 1:1 ratio, resulted in an increase in BIS even when controlling for minimum alveolar concentration of volatile anesthetics.[60] It was unclear whether this represented a shallower depth of anesthesia or cannabinoid-induced increase in electroencephalogram (EEG) activity. In addition, most users utilize high-THC, minimal-CBD strains of cannabis, whereas this study utilized strains with an equal THC:CBD ratio, and it is unclear whether the CBD in this study would have a differential effect compared with THC alone. Though chronic cannabis users develop tolerance to the neurocognitive effects of the drug, it is unclear whether cross-tolerance exists between cannabis and anesthetic agents. One human study showed a lack of cross-tolerance of such effects with alcohol in heavy cannabis users.[61]

Thus, experimental and anecdotal data support the view that cannabis users require higher induction doses of propofol. Less is known about the maintenance phase of anesthesia. Each cannabinoid has differential effects on the body, and there are simply insufficient studies to draw firm conclusions on their individual or summated effects on anesthetic maintenance. Cannabinoid-induced elevations in EEG activity may render BIS a less reliable marker of anesthetic depth of anesthesia in this population. Further studies are needed to determine whether BIS is an effective guide in monitoring depth of anesthesia for this population. Anecdotal data would suggest that, as with induction doses, higher doses of volatile agents are required to achieve adequate maintenance.

There are no specific data regarding intraoperative analgesic use in cannabis users, but recent studies have shown that cannabis users report higher pain scores, have worse sleep, and require more rescue analgesics in the immediate postoperative phase of care.[62–64] It is possible that this population may require greater analgesic use in the intraoperative phase, but there are no data to support or refute this view. Nevertheless, the use of a multimodal perioperative analgesic approach utilizing acetaminophen and a nonsteroidal anti-inflammatory drug or a cyclooxygenase-2-specific inhibitor combined with a local or regional analgesia technique, if possible, would be beneficial.[65,66]

POSTOPERATIVE CONSIDERATIONS

In the postoperative phase of care, anesthesiologists should remain vigilant to presenting symptoms or potential cannabis-related adverse effects, particularly withdrawal symptoms. Though administration of pharmacologic synthetic THC analogues has been shown to be of use in mitigating symptoms of cannabis withdrawal syndrome,[53] none of these analogues have FDA indications for such purposes. As such, the potential risks and benefits of off-label use to treat cannabis withdrawal syndrome in the perioperative period should be considered prior to proceeding.

Of particular interest in this phase of care is the relationship between cannabis and analgesia. Cannabinoids have been used for certain chronic pain conditions,[67,68] but evidence is lacking on the use of cannabis for acute pain.[44] Despite this, there is a perception among perioperative patients that cannabis may be helpful in decreasing postoperative pain.[69] Recent trials have actually shown higher pain scores and greater analgesic use in the postoperative period among cannabis users.[62–64] Thus, though evidence seems to support the analgesic effects of cannabis in chronic pain

conditions, it is possible that cannabis users may have augmented pain perception in the acute postoperative period.

CONCLUSIONS

Table 3 summarizes some anesthetic considerations for marijuana users. Anesthesiologists should query patients on the use of cannabis products during the preoperative evaluation, particularly if evidence of acute intoxication or withdrawal is present. Specific attention should be paid to the most recent use as well as the overall duration and frequency of use. In addition, anesthesiologists should inquire about the type of cannabis product used and the route of ingestion. These questions will help gauge the potential for acute intoxication, tolerance, or withdrawal. Clinical history and examination with pointed questions will be more important than quantitative factors such as toxicology screens, given the limitations of current toxicology screening methods for cannabis products due to the unique pharmacokinetics of cannabis metabolism and elimination. As use of highly potent cannabis products grows more common, patients may more commonly present with an altered sensorium that precludes the ability to query about cannabis use. Thus, when the anesthesiologist is called to care for patients with such a constellation of symptoms, a high index of suspicion and consideration of acute cannabis intoxication in the differential diagnosis may guide care of these patients.

Cannabis use seems to require increased induction doses of propofol, but the effect of cannabis on maintenance and emergence from general anesthesia has not been widely studied in humans. Cannabinoid-induced elevations in EEG activity may render BIS a less reliable guide of anesthetic depth of anesthesia in this population. In the postoperative period, when cannabis dependence is suspected, it may be prudent to provide supplementation with pharmacologic THC analogues to mitigate symptoms of withdrawal. Additionally, cannabis users appear to have worse pain after surgery and require higher doses of rescue analgesics. A preoperative multimodal analgesic plan is recommended, including consideration for incorporating regional anesthesia in the preoperative phase.

Finally, given the lack of formal studies regarding the anesthetic implications of cannabis products and the inability to pursue such studies, it is imperative that our specialty pursue other means of determining these implications. Though the silence in the literature of case reports for cannabis-related morbidity or mortality is deafening, the adage that

Table 3. Anesthetic considerations in patients consuming marijuana

Period	Considerations
Preoperative	Elevated risk of myocardial infarction within 1 hour after use Airway hyperreactivity Anxiety/paranoia Psychosis Need to assess for other drugs
Intraoperative	Tolerance to induction agents Elevated bispectral index Unknown cross-tolerance to other anesthetic agents Elevated risk of myocardial infarction within 1 hour after use Airway hyperreactivity
Postoperative	Unknown cross-tolerance to analgesics Possible heightened pain perception Withdrawal

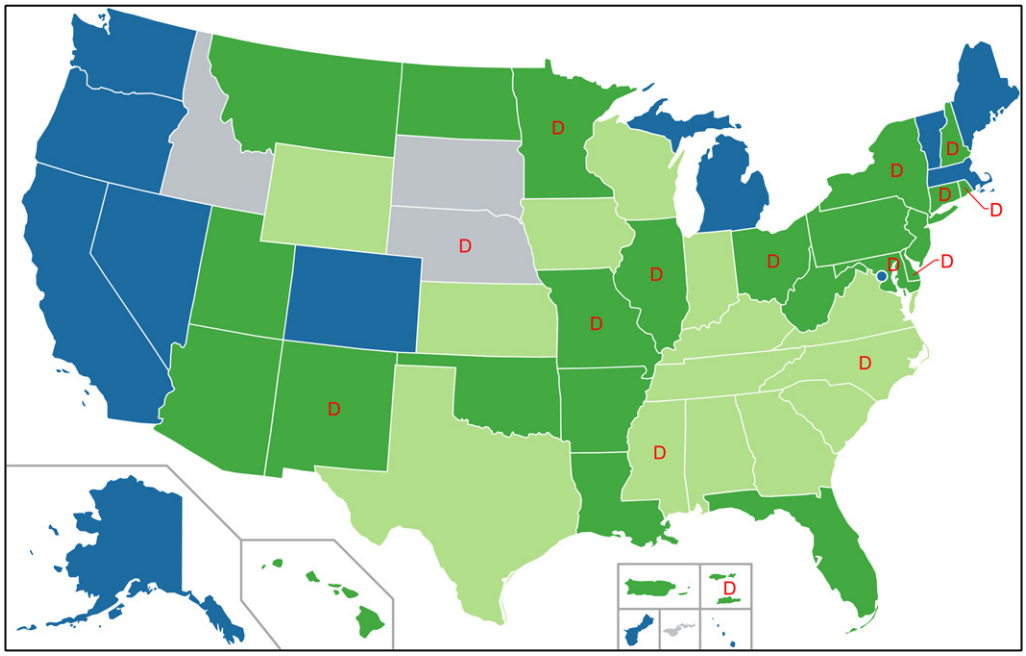

Figure 1. US state marijuana laws in 2019. Data from Lokal_Profil, Wikimedia; Creative Commons Attribution-Share Alike 2.5 Generic license.

"absence of evidence does not mean evidence of absence" comes to mind. If cannabis is removed from the Drug Enforcement Agency Schedule I list, well-designed prospective clinical trials should be pursued to better evaluate the implications of cannabis use throughout the perioperative period, especially in the maintenance phase, because there is less data on this phase of care. Until that time, anesthesiologists should make every effort to document and publish case reports or series of suspected cannabis-related perioperative morbidity and mortality to help create best practices for the care of this large and growing patient population, which will only continue to grow as states continue to enact less restrictive laws governing cannabis use.

ORCID

John C. Alexander http://orcid.org/0000-0001-9797-6322

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