Cannabis, e-cigarettes and anesthesia

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Purpose of review
Both cannabis and e-cigarette use are increasing, particularly among adolescents. The use of cannabis products may impact patients' physiology under anesthesia. Understanding the effects of cannabis and vaping are critical to the provision of safe and effective anesthetic care.

Recent findings
E-cigarettes have recently been implicated in a severe presentation of acute lung injury, often in association with vaporization of the cannabinoid, THC. E-cigarette use appears to be associated with other less-acute pulmonary adverse effects that are yet to be fully understood. Cannabis affects many organ systems with alterations in cardiovascular, respiratory and neurological function. Specifically, there is emerging evidence that cannabis use may reduce the efficacy of sedative agents and postoperative pain management efforts.

Summary
There is a very wide variety of cannabis products currently available, with respect to both route of administration as well as cannabinoid content. Patients using cannabis products prior to anesthesia may present with altered physiology that place them at increased risk for cardiovascular and respiratory complications. They may also be tolerant to the effects of propofol and opioid for pain management, thus consideration should be given to use of a multimodal regimen.

Keywords
anesthesia, cannabis, e-cigarette, Δ-9-tetrahydrocannabinol vaping

INTRODUCTION

Cannabis is the most widely used illicit drug worldwide, with an estimated 188 million people reporting its use in the prior year [1]. The term 'cannabis' commonly refers to the *Cannabis sativa* L plant; its subspecies (*C. sativa* and *Cannabis indica*); and its isolated constituents and their synthetic congeners. In the United States, despite its continued classification as a schedule I drug [with the exception of a limited number of Food and Drug Administration (FDA)-approved cannabinoids, discussed below], the prevalence of past-year cannabis use has steadily increased in recent years, from 10.1% in 2007 to 15.9% in 2018 [2]. Meanwhile, past month marijuana use among adolescents aged 12–17 years has remained relatively stable around 7–8% despite these broader patterns of use; similarly stable annual use prevalence was seen in Canadian adolescents from 15 to 17 years old prior to the legalization of cannabis in 2018 [1,3]. However, other analyses suggest that the increased availability of legal cannabis is accompanied by greater prevalence of cannabis use among adolescents [4,5]. It may also drive increased unintentional cannabis exposures: following the legalization of recreational marijuana in Colorado, the rate of marijuana-related children's hospital visits and calls to a regional poison center approximately doubled and the median age of all patients was around 2 years, with approximately 50% of cases involving edible cannabis products [6].

Thus, anesthesiologists are increasingly likely to encounter patients with a history of cannabis use that may impact their perioperative care. This review will focus on the described physiological effects and perioperative management implications of recreational cannabis use, particularly among pediatric patients where such evidence is available, including those related to use of e-cigarette, or vaping, products. The perioperative management of pediatric patients using medicinal marijuana has recently been reviewed elsewhere [7▪].

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Curr Opin Anesthesiol 2020, 33:318–326
DOI:10.1097/ACO.0000000000000872

KEY POINTS

- Anesthesiologists are increasingly likely to encounter pediatric patients using cannabis products for therapeutic and recreational purposes.
- The physiologic effects of individual cannabinoids vary with dose, use frequency and route of administration, as well as the exact composition of the product being used, which may be unknown to the patient.
- E-cigarette use may result in lung injury as seen with the 2019 outbreak of EVALI; however, it is likely that there is an accumulation of more subtle pulmonary effects that have yet to be fully described and which may impact anesthesia care.
- Although often derived from plant material, currently available cannabis products are vastly different from those available 20 years ago, and the full risks of using nonapproved cannabis products are unknown and not negligible.

CANNABINOID PHARMACOLOGY

The cannabis plant contains more than 750 identified constituents, over 100 of which are classified as phytocannabinoids, although other substances derived from cannabis may have physiological effects in humans [8,9]. The most well known and primary cannabinoid, Δ-9-tetrahydrocannabinol (THC), is responsible for the psychotomimetic and intoxicating effects of cannabis; however, other cannabinoids, such as cannabidiol (CBD) may also be psychoactive, with reported anxiolytic and somniferous properties in addition to anti-inflammatory and neuroprotective actions [10–12].

The cannabinoids exert many of their physiological effects via interaction with the receptors CB1 and CB2, upon which the endogenous cannabinoids (endocannabinoids) also act [13]. CB1 receptors are primarily found within the central nervous system (CNS) on presynaptic nerve terminals, where they likely modulate neurotransmitter release, but are also found in a wide variety of other tissues including immune cells [14,15]. They are the most common G protein-coupled receptors in the mammalian brain but are expressed at relatively low levels within the brainstem, possibly contributing to the low toxicity of cannabis [15,16▪]. CB2 is often considered the 'peripheral' cannabinoid receptor and is recognized for its expression on immune cells but CB2 receptors have also been identified on fibroblasts, chondrocytes, neurons (typically in postsynaptic regions) and microglia among various other cell types [14,17]. CB2 activation may oppose the effects of CB1 and is thought to be important in neuroprotection [18,19]. Additionally, cannabinoids interact with multiple noncannabinoid receptors including but not limited to transient receptor potential vanilloid 1 (TRPV1), serotonin, acetylcholine, glycine and opioid receptors [20].

Although cannabis has historically been a controlled substance internationally, several cannabinoids have been developed and approved as pharmaceuticals for human use. These include dronabinol (Marinol, AbbVie Inc., North Chicago, IL, U.S.A.; Syndros, Insys Therapeutics, Inc., Chandler, AZ, USA), a synthetic THC approved for the treatment of nausea and vomiting associated with chemotherapy or anorexia in patients with AIDS [21]; nabilone (Cesamet), a synthetic cannabinoid for the treatment of chemotherapy-associated nausea and vomiting; nabiximols (Sativex, Cesamet, GW Pharma, Cambridge, United Kingdom), an oromucosal spray containing approximately a 1 : 1 ratio of THC : CBD approved in Canada and many European countries for the treatment of spasticity in multiple sclerosis [22]; and cannabidiol (Epidiolex, GW pharmaceuticals), an FDA-approved cannabinoid for the management of seizures associated with Lennox–Gastaut or Dravet syndromes in patients 2 years of age and older [23]. Only the latter has specifically been approved for use in pediatric patients. The possession, purchase and use of cannabis have been legalized for adults to varying degrees by countries throughout the world, such as Canada, Uruguay and South Africa, as well as states within the United States including Massachusetts, Washington and Illinois, among others [1,3,4,24–27].

As markets have expanded, there has been a proliferation in available cannabis products and routes of delivery. Cannabis is commonly inhaled via combustion of plant material or concentrates, but both may also be inhaled via high-temperature vaporization using vaporizers, dabbing and e-cigarettes, or ingested as an extract, often in a cannabis-supplemented food or beverage [28]. Indeed, as the initial legalization of cannabis for adult use in the state of Colorado, the share of cannabis sales constituted of plant material has decreased while that for concentrates has grown by over 50% [29]. Meanwhile, the potency of both concentrates and whole plant material in Colorado has increased, reaching 68.6 and 19.6% THC in 2017, respectively [29]. This continues nationwide trends of increasing cannabis plant potency from 3.4% THC in 1993 to 12.2% in 2014 [30,31]. A single cannabis-infused cookie may contain over 400 mg of THC, exponentially more than the 2.5 mg twice daily starting and 20 mg maximum daily dose of dronabinol [21,32].

THC is detectable in plasma for over 24 h after a single dose [33,34]. Among frequent users, THC may be detectible in blood for over 30 days after the last

administration [35]. THC and CBD undergo significant first pass metabolism, being metabolized by hepatic cytochrome P450 enzymes including CYP2C9, CYP2C19 and CYP3A4, among others [36–40]. Thus, drug–drug interactions may occur owing to inhibition or induction of metabolic enzymes or transporters, in addition to pharmacodynamic drug–drug interactions.

E-CIGARETTES AND VAPING

Electronic cigarettes, also known as electronic nicotine delivery systems (ENDS), and vaporizers were approved for use in US markets in 2007. Appearances vary, ranging from traditional cigarettes to pipes to pens or USB flash drives, and vaporizers may further be camouflaged as watches or even built into clothing (Fig. 1) [41]. The basic design typically includes a battery power source, a heating element and a reservoir for the 'e-liquid', which consists of a solvent, flavorings and the active drug that become aerosolized upon heating [42]. Common solvents include propylene glycol, known to cause renal and CNS toxicity following intravenous exposure, and vegetable glycerin; both are generally well tolerated as food additives but may have significant adverse effects on pulmonary tissues when inhaled [43]. Numerous toxic compounds have been identified in e-cigarette aerosol, such as organic volatile compounds, aldehydes, carcinogenic nitrosamines, polycyclic aromatic hydrocarbons, and metals including lead, and the exact composition and thus exposure risk may vary between manufacturers and flavors [42,44▪,45]. Nicotine itself may alter brain development and function and serum levels of the nicotine metabolite, cotinine, were similar between passive exposure to e-cigarette aerosol and tobacco cigarette smoke [46–48].

Despite these findings, the use of e-cigarettes has been increasing as they are perceived to be less harmful than tobacco smoking [49]. They were initially marketed to support smoking cessation; however, may not result in nicotine abstinence [50–52]. The use of electronic cigarettes among adolescents appears to be associated with an increased prevalence of tobacco smoking, and is growing. A 2018

FIGURE 1. Examples of e-cigarette models. Data from [42].

survey of US high school students found that over one-fifth endorsed current use of e-cigarettes whereas 4.9% of middle school students reported current e-cigarette use [53]. With increasing availability and use, monthly calls to US poison centers increased from 1 in September 2010 to 215 in February 2014, and 51% of calls involved children less than 5 years in age [54]. From January 2017 to August 2019, the incidence of emergency department visits related to e-cigarette use gradually increased over 20-fold among patients between 10 and 19 years of age [55▪▪]. In 2016, almost one-third of US middle and high school students who had ever used an e-cigarette reported having used THC through this device [56]. These present a particular challenge from a drug enforcement standpoint as the contents of e-cigarette cartridges are not identifiable by visual or olfactory characteristics of the liquid or aerosol.

In the summer of 2019, numerous cases of an acute respiratory illness associated with e-cigarette use were reported, beginning with a cluster of five previously healthy adolescents admitted with dyspnea, fatigue and hypoxemia [57]. As of October, 2019, there were over 1600 reported cases of e-cigarette, or vaping, product use-associated lung injury (EVALI), among whom the median age was 24 years (range: 13–75 years) [58]. A large majority (85%) of patients reported using THC-containing products, as well as frequent use and acquisition of these products through informal sources [59]. Patients with EVALI presented with a history of vaping or e-cigarette use and respiratory symptoms (98%), most commonly shortness of breath (87%) or cough (83%), gastrointestinal symptoms (81%) and constitutional symptoms (100%) including subjective fever (81%), without evidence of pulmonary infection on initial work-up [57]. Patients were found to have pulmonary opacities on chest radiographs and ground-glass opacities on chest computed tomography (CT) [60▪]. Among 12 adolescents treated for EVALI at one institution from June to August 2019, laboratory testing revealed signs of acute inflammation, including leukocytosis and elevated inflammatory markers as well as increased neutrophils and lipid-laden macrophages in broncheoalveolar lavage samples [61]. Treatment has included supportive care and the administration of high-dose steroids to treat pulmonary inflammation [61]. Since its peak in September of 2019, the number of EVALI cases reported to the Centers for Disease Control and Prevention appears to be dropping.

E-cigarettes may have other pulmonary effects of lesser acuity than EVALI. E-cigarette use is associated with asthma in adolescents, and this relationship appears stronger when e-cigarettes are used in combination with smoking marijuana or marijuana and tobacco cigarettes [62]. Similarly, surveys of e-cigarette use in adolescents have identified increased symptoms of chronic bronchial irritation including chronic cough or phlegm [63,64]. Cellular changes reported in association with e-cigarette aerosol exposure include increased biomarkers of chronic bronchitis; increased protease levels in sputum, which may result in damaging proteolysis in lung tissues; impaired macrophage function and the appearance of lipid-laden macrophages; and inhibition of ciliary-beating epithelial cells [43]. A single 15-min exposure to e-cigarette aerosol may impair gas exchange and reduce expiratory flow [65]. Despite the recent awareness of EVALI, we likely will not detect the development of lung diseases because of e-cigarette use at a population level for several more decades [43]. There are currently no reported studies of e-cigarette use and anesthesia.

CANNABINOID EFFECTS BY SYSTEM

Cardiovascular

The cardiovascular effects of cannabinoids depend on the dose, duration and frequency of use as well as the route of administration. In humans, THC exposure most commonly results in an increase in heart rate that may be accompanied by a variable change in blood pressure; in animal models, cardiac output is reduced following THC administration and appears attributable to reduced venous return rather than inhibition of myocardial contractility [66–69]. Heart rate increases after marijuana smoke exposure peak 10–30 min after smoking, possibly reflecting a compensatory sympathetic response to THC-induced vasodilation [70–72]. Among marijuana users, repeated daily oral administration of high-dose synthetic THC was found to induce tolerance to its intoxicating effects, but not to the cardiovascular effects of tachycardia and hypotension [66]. However, there are several case reports of young patients intoxicated with cannabis who display tachycardia and hypertension, including a 17-year-old patient who presented with seizures, tachycardia, hyperthermia and hypertension ultimately attributed to dabbing [73], and a 34-year old healthy man who remained tachycardic and hypertensive throughout his anesthetic, presumably owing to use of cannabis the night before surgery [74]. Active marijuana use has also been associated with Takotsubo cardiomyopathy, and there are numerous reports of severe cardiovascular complications related to cannabis use in young patients [16▪,75,76].

Although low doses of THC have been found to be cardioprotective when given to mice prior to a

myocardial infarction (MI), a cohort review found that marijuana smokers had an almost five-fold higher risk of acute MI during the first hour after exposure, then decreasing after that [77,78]. Similarly, among patients previously hospitalized with MI, a longitudinal prospective follow-up study on mortality found that those using cannabis less than once weekly had a 2.5-fold increased risk of dying, with up to a four-fold risk among patients using marijuana more frequently [79]. In addition to ST-elevation MI, stroke (particularly ischemic stroke) has been described in association with acute cannabis use [80,81]. Marijuana smoke exposure results in increased levels of carboxyhemoglobin, and thus reduced oxygen-carrying capacity [82]. THC and CBD, though to a lesser degree, have been found to reduce platelet counts and increase platelet aggregation, which may contribute to thrombosis [83,84]. A large retrospective cohort study found that patients with a history of cannabis use disorder were found to have a significantly higher rate of postoperative MI than patients without this diagnosis [85]. The adjusted odds of acute cerebrovascular accident were over three times higher in patients with a cannabis use disorder but this finding did not reach statistical significance after adjustment.

Respiratory

Smoking cannabis or ingesting oral THC results in airway dilation in healthy participants; however, in asthmatic subjects aerosolized THC may produce bronchoconstriction [86,87]. In patients with chronic obstructive pulmonary disease (COPD), vaporized cannabis produces minimal effect on airway function or exertional breathlessness [88]. CBD does not appear to produce bronchodilation after ingestion of even large doses [89]. In animal models, airway hyper-reactivity was observed following repeated exposure to cannabis smoke after only 7 days compared with 2 months for tobacco smoke, and inflammation was more severe and presented earlier in the cannabis-exposed group [90]. In humans, heavy smoking of cannabis over a period of approximately 6–10 weeks resulted in reduced FEV_1 and airway conductance [91]. Long-term marijuana smoking is associated with increased respiratory symptoms of cough and wheezing but has not been clearly associated with airway obstruction or increased airway hyperreactivity once tobacco use history has been accounted for [92–96]. In a large retrospective review of electronic medical records, cannabis use was associated with an increased risk of respiratory disease diagnosis including COPD, asthma and pneumonia [97]. Several case reports describe adverse respiratory events after anesthesia in adults and adolescents that the authors attribute to a history of cannabis use [98–102].

Gastrointestinal, endocrine and immune

Cannabinoids are effective treatments for nausea and vomiting associated with chemotherapy, yet nausea is also a common side effect of cannabinoids reported in clinical trials [103]. THC has not been found to prevent postoperative nausea and vomiting [104]. Cannabis use may result in delayed gastric emptying [105]. Cannabinoid hyperemesis syndrome, characterized by recurrent nausea, vomiting and abdominal pain, is an increasingly recognized complication of frequent cannabis use [106].

Acute THC administration resulted in insulin resistance and impaired glucose tolerance in cannabis-naïve subjects [107]. However, a large health survey found that a history of marijuana use was associated with a lower prevalence of diabetes [108]. Although cannabinoid receptors are expressed on many immune cells and have anti-inflammatory effects in preclinical investigations, systemic immunocompromise because of cannabis use has not been described [109,110].

Neurologic and psychiatric

Cannabis has both beneficial and detrimental CNS effects. Cannabis has been used for centuries as an antiseizure medication [111]. Both CBD and THC have anticonvulsant properties and the first antiepileptic cannabinoid, Epidiolex, was recently approved by the FDA [24,112,113]. Many measures of cognitive performance are impaired in adult chronic users of cannabis, but most appear to improve following abstinence [114].

Acute administration of THC induces both anxiety and psychotic symptoms [115,116]. while at a population level, cannabis use is associated with a significantly increased risk of psychosis [117]. Cannabis use increases the risk of suicidal ideation and attempts among both adolescents and adults [117,118], and marijuana was the most common substance present among suicides in Coloradoans aged 10–19 years in 2016, a trend that has been increasing along with the availability of marijuana in the state [81].

Pain

Pain management is a commonly promoted and studied use of medical cannabis. There is evidence for that cannabis reduces chronic noncancer pain [119]. However, several meta-analyses have found that these effects may not be large enough to be

clinically relevant [119,120▪▪]. In a 2018 meta-analysis, cannabinoids were found to reduce pain intensity significantly more than placebo, but the magnitude of the effect only equated to a reduction of 2.9–100 mm on a visual analogue scale, which is far below the minimum clinically important difference, and the calculated number needed to benefit from cannabis treatment was 24 [119]. Another meta-analysis evaluating cannabis for neuropathic pain found the number needed to benefit was 11; however, the number needed to harm with nervous system adverse events was 3 and with psychiatric events was 10 [121▪▪].

A meta-analysis of seven studies found there is currently no role for cannabinoids in the management of acute pain, as they are not superior to placebo and neither synergistic nor additive with opioids for analgesia [122]. There is emerging observational evidence that the chronic use of cannabis is associated with increased postoperative pain and opioid use after surgery [60▪,123,124]. Patients who used cannabis during their recovery after musculoskeletal trauma reported that it reduced their pain and the need for prescription pain medication; however, these patients used more total opioids and for greater duration than patients who did not use cannabis during their postoperative recovery [125▪].

Response to anesthetics

Administration of THC resulted in prolongation of ether, ketamine and pentobarbitone anesthesia in mice [126,127]. A synthetic THC analogue had a similar effect on isoflurane anesthesia in mice [128]. Halothane anesthesia was prolonged with reduced minimum alveolar concentration in dogs following THC injection [129]. In contrast, acute THC administration was found to reduce the sedative effect of both propofol and thiopental in mice [130]. CBD had little effect on ketamine or thiopental anesthesia but did increase the duration of pentobarbitone anesthesia in mice, likely reflecting a metabolic rather than neurologic interaction [127]. Patients who were administered nabiximols prior to anesthesia displayed higher bispectral index (BIS) values but no other evidence of inadequate depth of anesthesia [131].

There is growing evidence that adult patients who use cannabis regularly are resistant to sedative-hypnotic agents; however, the impact of cannabis (including vaporized THC) use on the response to anesthetic agents has not been described in pediatric patients. Case reports describe the administration of larger than anticipated doses of anesthetics to patients who endorse a history of cannabis use [74,132]. In a prospective study, Flisberg *et al.* in 2009 found that patients who reported at least weekly use of cannabis over the prior 6 months required a larger dose of propofol to achieve placement of a laryngeal mask airway than patients who did not use cannabis, but had no difference in the dose required to reach a BIS value below 60 [133]. A retrospective review of adult patients undergoing outpatient endoscopy found that those who reported regular use of cannabis required significantly more propofol and midazolam to maintain sedation than those reporting no or sporadic cannabis use [134]. This diminished response to propofol may be explained at least in part by the observation that propofol administration, unlike sevoflurane, preserves blood levels of the endocannabinoid, arachidonoylethanolamide, and also inhibits the enzyme that degrades it, which may also contribute to the antiemetic properties of propofol [135,136].

CONCLUSION

Patients who regularly use THC-containing products may present several challenges for the anesthesiologist and use of these products, as well as their THC concentration, continues to increase, particularly among adolescents. Chronic cannabis use including vaping of THC may result in tachycardia or bradycardia, hypertension or hypotension and possibly myocardial infarction or stroke; the cardiovascular effects of cannabis may vary greatly with chronicity and dose. Patients who smoke or vape these products may develop pulmonary symptoms similar to those found in patients who smoke tobacco, putting them at increased risk for coughing, bronchospasm and airway obstruction. They are also at risk for drug–drug interactions including altered performance of anticoagulant and antiplatelet drugs as well as unpredictable interactions with sedative–hypnotic drugs. In addition, they may experience increased postoperative pain or opioid use compared with nonusers, although it is currently unclear whether this reflects a form of cross-tolerance to opioid analgesics or hyperalgesia. Future research should include study of the analgesic effects of prescription cannabinoids for postoperative pain management in patients with a history of cannabis use.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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