

Perioperative Cannabis as a Potential Solution for Reducing Opioid and Benzodiazepine Dependence

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IMPORTANCE Cannabis is increasingly being used for medicinal purposes but remains outside Western medical practice. Data on perioperative use and outcomes are scarce. Few surgeons receive training regarding legal endorsement, reported medicinal benefits, and potential risks, making it difficult to advise patients. Guidelines and additional research are needed.

OBSERVATIONS It is legal to recommend cannabis, which can be obtained in states with medical cannabis programs. There are many methods of consumption, oral being the safest. Activity is primarily through $\Delta 9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD) via cannabinoid receptors, which may be potentiated when taken together in the plant or plant extract. The known effects of cannabis on inflammation and malignancy are largely limited to laboratory experiments. However, there are higher-quality data to support adjunctive use of cannabis for relief of pain, nausea, and insomnia, which may be useful postoperatively and could potentially decrease reliance on opiates and benzodiazepines. There are prospective trials in surgical patients, but no reported data regarding surgical complications or other surgical outcomes. Currently, cannabis is regulated differently than other controlled substances, and there are issues with purity/homogeneity, making it difficult for surgeons to accept or significantly explore its medical benefits.

CONCLUSIONS AND RELEVANCE Recommendations are made for surgeons advising patients who use cannabis based on the limited existing data. While cannabis likely has some therapeutic benefits, it must be treated as other medical controlled substances to truly elucidate its role in surgical patient care.

JAMA Surg. 2021;156(2):181-190. doi:10.1001/jamasurg.2020.5545
Published online December 2, 2020.

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Cannabis is increasingly being used for medicinal purposes, but few physicians have training regarding its use. Cannabis has reported therapeutic benefits for the treatment of pain, nausea, anorexia, insomnia, inflammation, and malignancy, which may be useful for surgical patients. Some therapeutic benefits also have overlap with opioids and benzodiazepines and could decrease reliance on these pharmacologic agents. In this review, we discuss cannabis terminology, legality regarding endorsement, preparations and manufacturing, and the reported uses specifically as they pertain to surgical patients. We define the gaps in knowledge and conclude with surgical recommendations based on the limited existing data to facilitate communication with patients and decision-making regarding patients who use cannabis. Given the paucity of information related to perioperative complications and safety despite its widespread use, there is a strong need for additional cannabis research with an eye toward surgical issues and concerns.

The distinction between cannabis and industrial hemp is based on $\Delta 9$ -tetrahydrocannabinol (THC) content, with a legal cutoff for hemp of less than 0.3% in the United States.² Despite the fact that many legal authorities have chosen to use the term *marijuana* (or *marihuana*), it is nonetheless a colloquialism rooted in racial stereotypes. Because the use of species epithets is not mandatory, we assert that simply referring to these plants as *cannabis* in the medical milieu is preferred.

Legality: States vs the Federal Controlled Substances Act

The Federal Controlled Substances Act (CSA) lists tetrahydrocannabinols and cannabimimetic agents as schedule I controlled substances, which "have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and high potential for abuse"³ and therefore are illegal.³ However, the law also states that its intent is not to "occupy the field" of state laws on the same subject matter, which has been the source of ongoing debate.³ Notable cannabinoid exceptions to the CSA are dronabinol (trade names: marinol and syndros), a synthetically produced THC that was approved by the US Food and Drug Admin-

Defining Cannabis

Marijuana is a commonly used term for the cannabis genus of flowering plants. The cannabis genus includes up to 4 species; however, only one, *Cannabis sativa*, is recognized in the United States.¹

istration (FDA) in 1989, and nabilone (trade name: casamet), a synthetic THC analog approved in 2005, and cannabidiol (CBD, trade name: epidiolex), derived from cannabis extract, approved in June 2018. Dronabinol and casamet are both schedule II, and epidiolex, while initially schedule V, was descheduled and is no longer subject to the CSA as of April 2020. Industrial hemp was also removed from the CSA in the Agriculture Improvement Act of 2018.² However, the US Drug Enforcement Administration (DEA) repeatedly denied petition to reschedule cannabis with THC content greater than 0.3% as a schedule II medication.⁴

California's initial legislation of cannabis for medical use in 1996 led to filing of a lawsuit, *Walters vs Conant*, which ruled that "the government should be permanently enjoined from (i) revoking any physician class member's DEA registration merely because the doctor makes a recommendation for the use of medical marijuana based on a sincere medical judgment and (ii) from initiating any investigation solely on that ground."⁵ Physicians who recommend cannabis for medical use are legally protected by this ruling, and many state cannabis laws include explicit language protecting physicians.

As of February 2020, 33 states and the District of Columbia have legislation for medical cannabis programs (Table 1 and Figure 1). An additional 16 states have noncomprehensive legislation for medical access to cannabis or CBD, generally permitting the use of low THC/high CBD products for specific medical purposes. Per the state laws described in Table 1, medical clinicians in the United States (with the exception of Texas) do not provide patients with prescriptions for cannabis. Medical clinicians may only recommend or certify cannabis for patients to treat specific conditions or symptoms and do not specify dosage, frequency, or route for consumption. The type of medical professional who may make these recommendations varies by state, and many states require medical professionals to register. Some also require coursework, which may be at a fee. Clinicians must typically verify presence of a qualifying condition or symptom, advise regarding the risks and benefits of cannabis, assert that other medical treatments have been ineffective, and base recommendations on the patient's medical history, current medical conditions, and a bona fide clinician-patient relationship. Common qualifying conditions include cancer, AIDS, multiple sclerosis, Parkinson disease, epilepsy, Crohn disease, anxiety disorder, and posttraumatic stress disorder. Most states also include symptoms such as chronic pain and nausea as qualifying conditions. Patients younger than 18 years may engage in the medical use of cannabis with parental consent. This may require medical recommendations from multiple clinicians or specific types of clinicians. For example, Delaware requires recommendations for minors to be made by specific types of pediatric subspecialists (and does not include pediatric surgeons in this group).

Once a recommendation or certification is made, patients may register for a card to enable access, which costs typically less than \$100. The patient may then obtain cannabis in a number of forms. States have limitations on quantity, transport, and locations where it may be used. Of note, the presence of medical marijuana in an individual's system during working hours may be grounds for disqualification from unemployment benefits and for termination of employment. It also remains illegal to drive while under the influence. There are several states that also permit recreational or "adult" use of cannabis (Table 1). Distinctions between recreational and medi-

cal cannabis include that medical cannabis can be used by minors, it often can be obtained and held in greater quantities (up to 8 lb in Maine), price often excludes state tax, and many states allow cultivation of plants for personal medical use.

Available Preparations and Methods of Consumption

Cannabis can be prepared and consumed in a variety of ways (Table 2).⁶⁻²⁹ Inhalation is the most common form of consumption, by smoking the dried plant or inhaling heated vaporized cannabis extract. Extract with an organic solvent produces semisolid (cannabis wax) or viscous liquid (cannabis oil). Additional agents may be reintroduced for scent/flavor or added to thin the oil to create cannabis liquid, facilitating use with a number of different commercially available vaporizers. However, it should be noted that not all states permit smoking as a method of consumption for medicinal purposes.

Individuals can also eat the plant itself, consume foods and drinks prepared with cannabis extract, or take tablet or gel capsule preparations.²⁹ Oral preparations may also contain additional agents, such as caffeine and other plant-based products. Sublingual or spray tinctures and hard candies for mucosal absorption are also available. Topical preparations also exist. Some manufacturers clearly report internal testing and/or third-party testing³⁰ whereas others do not.

Measurement and Manufacturing Standards of Cannabis

Within the plant itself, biosynthesized acidic cannabinoids are pharmacologically inactive, and undergo decarboxylation induced by heat or light, producing pharmacologically active chemicals (Figure 2).³¹ There is significant variation in the quantities of pharmacologically active contents by preparation.³²⁻³⁵ As such, preparations of cannabis are often labeled with the quantities of Δ^9 -tetrahydrocannabinolic acid (THCA)/THC, cannabidiolic acid/CBD, and cannabiol.^{31,32} These chemicals can be measured in a number of ways, and because cannabis is not regulated by the FDA, there are no true "good manufacturing practices"³⁶ except within Louisiana's medical cannabis program run through their academic and industry partnerships.³⁷ Most states instead have a list of recommended testing procedures for microbial pathogens, residual solvents, pesticides, and potency. Importantly, requirements vary considerably regarding quantification and labeling of cannabinoids. Some states mandate reporting percentage concentration by weight or volume, and others by weight of the unit of sale. By comparison, many states also permit individuals to grow their own plants without any further regulations for testing.

There are concerns regarding accuracy and purity of preparations. Up to 70% of CBD-containing cannabis products are inaccurately labeled, with average deviation of 380% from labeled content.³⁴ Some preparations contain no detectable cannabinoids.³⁵ Products may also contain other pharmacologically active contaminants^{34,38} or vitamin E acetate, which has been associated with electronic cigarette or vaping-associated lung injury (EVALI;

Table 1. States With Comprehensive and Noncomprehensive Medical Cannabis Laws^a

State (year approved) (law text)	Recre- ational (year approved)	Who can recommend	Additional considerations
States with comprehensive medical cannabis laws			
Alaska (1998) (AS 17.37)	Yes (2015)	MD, DO	NA
Arizona (2010) (ARS 36-2801)	No	MD, DO, ND, DHT	NA
Arkansas (2016) (amendment 98)	No	MD, DO	<ul style="list-style-type: none"> Prohibited in health care facilities Prohibited for those knowingly in close physical proximity to anyone younger than 18 years
California (1996) (SB420)	Yes (2016)	MD, DO, DPM	<ul style="list-style-type: none"> Must have patient sign an authorized medical release of information and keep designated form in patient's records
Colorado (2000) (Article XVIII, Section 14)	Yes	MD, DO, DMD, DPM, OD, APP	<ul style="list-style-type: none"> Must register to recommend
Connecticut (2012) (HB 5389)	No	MD, DO	<ul style="list-style-type: none"> Must register to recommend for palliative use
Delaware (2011) (Title 16, Chapter 49A)	No	MD, DO	<ul style="list-style-type: none"> Prohibited in health care facilities
District of Columbia (1998) (DC Act 12-64)	Yes (2014)	MD, DO, DMD, ND, APP	NA
Florida (2016) (Rule Chapter 64-4)	No	MD, DO	<ul style="list-style-type: none"> Must complete examination Patient must complete consent form Low THC can be specified in the recommendation
Hawaii (2000) (SB 862)	No	MD, DO, APP	<ul style="list-style-type: none"> Must register to recommend
Illinois (2014) (410 ILCS 130)	Yes (2020)	MD, DO, APP	<ul style="list-style-type: none"> Must complete state documentation
Louisiana (2015) (LAC:XLIX Chapters 1-31) (RS 40:1046)	No	MD, DO	<ul style="list-style-type: none"> Must take a course Must register to recommend Cannabis only available through state partnered pharmacies
Maine (1999) (LD 1296, Public law, Chapter 407) (2423-B Chapter 558-C)	Yes (2016)	MD, DO, APP	<ul style="list-style-type: none"> Must register to recommend
Maryland (2003) (HB0881 CH0240) (Subtitle 62)	No	MD, DO, DMD, DPM, APP, midwife	<ul style="list-style-type: none"> Must register to recommend Educational course is optional
Massachusetts (2012) (935 CMR 501.000)	Yes (2016)	MD, DO, APP	<ul style="list-style-type: none"> Must complete electronic certification to recommend
Michigan (2008) (Act 283)	Yes (2018)	MD, DO	<ul style="list-style-type: none"> Must complete electronic certification to recommend
Minnesota (2014) (chapter 311, S.F. No. 2470)	No	MD, DO, APP	<ul style="list-style-type: none"> Must complete electronic certification to recommend
Missouri (2018) (Article XIV)	No	MD, DO	<ul style="list-style-type: none"> Can specify whether patient should get more than 4 oz/mo Has cannabis equivalency units
Montana (2004) (SB0333)	No	MD, DO	<ul style="list-style-type: none"> Must monitor response to treatment and possible adverse effects
Nevada (2000) (NAC 453A)	Yes (2016)	MD, DO	NA
New Hampshire (2013) (HB 573)	No	MD, DO, APP	<ul style="list-style-type: none"> Must complete paper certification Previously required a 3-mo clinician-patient relationship; overturned November 2019
New Jersey (2009) (Chapter 153 suppl to P.L. 2009, c. 307)	No	MD, DO, APP; Minors: pediatric specialist	<ul style="list-style-type: none"> Must register to recommend
New Mexico (2007) (SB 0523)	No	MD, DO, APP	<ul style="list-style-type: none"> Cannot recommend as a resident or fellow
New York (2014) (A06357E)	No	MD, DO, APP	<ul style="list-style-type: none"> Must take a course Must be registered to recommend Smoking and cannabis infused foods are prohibited
North Dakota (2016) (NDCC Chapter 19-24.1) (NDAC Chapter 33-44-01)	No	MD, DO, APP	<ul style="list-style-type: none"> Cannot recommend if patient relationship is based solely on recommending cannabis
Ohio (2016) (HB 523)	No	MD, DO	<ul style="list-style-type: none"> Must be registered to recommend

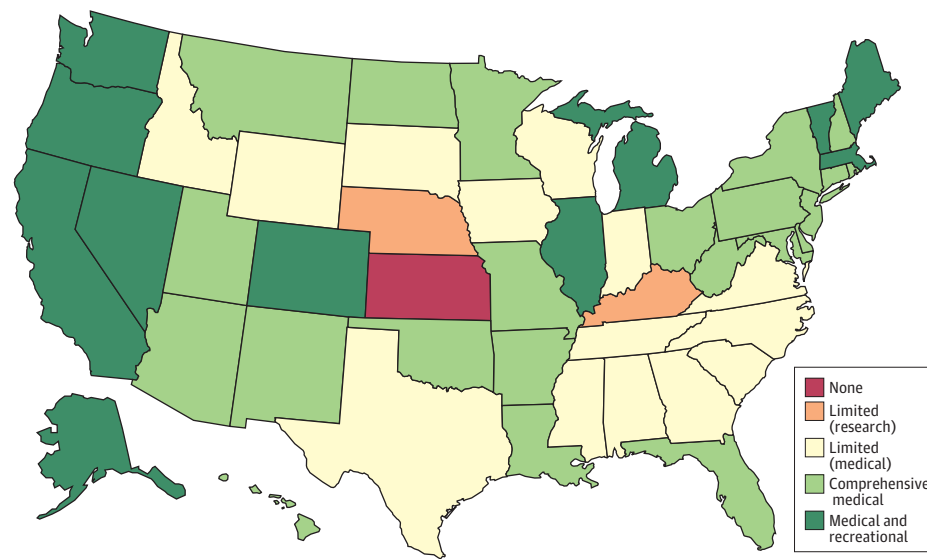
(continued)

Table 1. States With Comprehensive and Noncomprehensive Medical Cannabis Laws^a (continued)

State (year approved) (law text)	Recre- ational (year approved)	Who can recommend	Additional considerations
Oklahoma (2018) (Bill No. 1030)	No	MD, DO, DPM	<ul style="list-style-type: none"> • Cannot recommend as resident or fellow • May recommend short-term 60-d cannabis licenses
Oregon (1998) (Chapter 475B) (Chapter 333)	Yes (2020)	MD, DO	<ul style="list-style-type: none"> • Must be the physician who is the primary responsibility of the patient's care
Pennsylvania (2016) (SB 3)	No	MD, DO	<ul style="list-style-type: none"> • Must take a course • Must register to recommend
Rhode Island (2007) (Title 21, Ch 20, Subch 10, Part 3)	No	MD, DO	<ul style="list-style-type: none"> • Must take a course • Must register to recommend
Utah (2018) (SB 1002)	No	MD, DO, APP	<ul style="list-style-type: none"> • Must register and pay fee to recommend • Cannot recommend to more than 175 patients (with exceptions)
Vermont (2004) (Title 18, Ch 86)	Yes (2019)	MD, DO, APP, ND	<ul style="list-style-type: none"> • Must have 3-mo preexisting relationship with the patient (with some exceptions)
Washington (1998) (Title 69, Ch 69.51A)	Yes (2012)	MD, DO, DMD, DPM, ND, APP	<ul style="list-style-type: none"> • Must take a course • Must register to recommend • Medical cannabis is further classified in to high THC (10-50 mg) and high CBD (<2% THC, and 25 × more CBD)
West Virginia (2017, but not yet operational) (SB 386)	No	MD, DO	<ul style="list-style-type: none"> • Must take a course • Must register to recommend • Medical cannabis cannot be smoked but can be inhaled
States with noncomprehensive medical cannabis laws			
Alabama (2016) (HB61)	NA	MD, DO	Decriminalization of possessing CBD (<3% THC) when it is prescribed by a physician
Georgia (2015) (HB1)	NA	MD, DO	Creates a research program using low THC oil (<5%) with equal or greater amount of CBD for medical resistant epilepsies
Idaho (2015) (Report 133)	NA	MD, DO	Permits CBD with zero THC
Indiana (2017) (HB 1148)	NA	MD, DO (neurologist)	Creates state registry and permits neurologists to recommend CBD at least 5% (<0.3% THC) for patients treatment resistant epilepsy
Iowa (2014) (Section 124E)	NA	MD, DO	Creates state registry, permits possession and use of CBD (<3% THC) in the state, permits selection of 2 manufacturers
Kentucky (2014) (SB 124)	NA	MD, DO, DMD, DPM, APP, veterinarian	Permits cannabidiol use in research through universities with medical schools; additional laws under way to expand access (HB 136)
Mississippi (2014) (HB 2610)	NA	MD, DO	Permits cannabis oil with >15% CBD or 50 mg/mL, and <0.5% THC through the University of Mississippi Medical Center
Nebraska (2019) (Statute 28-463)	NA	NA	Permits medical professionals from studying the treatment of intractable seizures with CBD
North Carolina (2014) (HB 766)	NA	MD, DO (neurologist)	Permits possession of extracts <0.9% THC and >5% CBD for treatment of epilepsy when recommended by a neurologist
South Carolina (2014) (SB 1035)	NA	MD, DO	Permits cannabis oil with >15% CBD by weight or 98% by volume, and <0.9% THC when recommended as treatment for epilepsy by a physician; permits research on CBD
South Dakota (2019) (SB 22)	NA	MD, DO, DMD, DPM, APP, OD, veterinarian	Permits prescriptions for epidiolex
Tennessee (2014) (HB 1883)	NA	NA	Permits cannabis oil with <0.9% THC
Texas (2015) (Chapter 169) (Chapter 487)	NA	MD, DO	Permits physicians to prescribe cannabis with <0.5% THC, creates physician registry
Virginia (2015) (SB 1557)	NA	MD, DO, APP	Permits physicians and APPs to certify use of CBD and THCA oil
Wisconsin (2013) (SB 10)	NA	MD, DO	Permits physicians to certify and pharmacies to dispense CBD for medical conditions
Wyoming (2015) (HB0032)	NA	MD, DO (neurologist)	Permits supervised medical use under a neurologist of cannabis extracts with <0.3% THC and >5% CBD by weight

Abbreviations: APP, advanced practice professional (nurse practitioner or physicians' assistant); CBD, cannabidiol; DMD, doctor of medicine in dentistry or doctor of dental medicine; DPM, doctor of podiatric medicine; MD, doctor of medicine; NA, not applicable; ND, naturopathic doctor; DHT, doctor of homeotherapeutics; OD, doctor of osteopathic medicine; OD, optometrist; THC, Δ9-tetrahydrocannabinol; THCA, Δ9-tetrahydrocannabinolic acid.

^a Refer to legal authorities for the most updated information.

Figure 1. Map of Legality for Cannabis and Cannabis Preparations for Medical and Recreational Purposes in the United States

This map is accurate as of February 2020.

Table 2. Therapeutic Uses of Cannabis and Cannabis Products That May Apply to Surgical Patients, With Supporting Research and Level of Evidence

Use	Dosages studied	Data (level of evidence) ^a
Pain	<ul style="list-style-type: none"> THC: 5-20 mg CBD: 1:0, 3-1 with THC Nabilone: 1-2 mg 	<ul style="list-style-type: none"> Often used with opioids, may decrease opioid needs (3)⁶⁻⁸ 1:1 THC/CBD may decrease severe chronic pain, may decrease breakthrough pain (1)^{7,9,10} Nabilone was not effective (3)¹¹ Impairs memory/cognition (1)⁷⁻⁹
Nausea	<ul style="list-style-type: none"> THC: 30-45 mg Nabilone: 0.5 mg 	<ul style="list-style-type: none"> THC more effective than prochlorperazine for chemotherapy-induced/cancer-related nausea (3)¹² Nabilone did not decrease postoperative nausea/vomiting (1)¹³
Insomnia	<ul style="list-style-type: none"> THC: 5-15 mg CBD: 5-15 mg 	<ul style="list-style-type: none"> Associated with decreased severity of insomnia in patients (4)^{14,15} Does not change sleep quality or polysomnographic parameters in healthy participants (1)¹⁶
Weight gain	<ul style="list-style-type: none"> THC: 5 mg CBD: 2 mg Nabilone: 0.5-1 mg 	<ul style="list-style-type: none"> Increases snacking/carbohydrate intake, but does not increase weight (1)^{17,18} Nabilone (synthetic THC) improved quality of life in lung cancer patients (2)¹⁹
Inflammation	<ul style="list-style-type: none"> CBD: 5 mg-800 mg 	<ul style="list-style-type: none"> Dronabinol (synthetic THC) did not change IL-6 levels (1)²⁰ CBD did not change cortisol levels (4)²¹
Cancer	NA	<ul style="list-style-type: none"> Laboratory data for breast, colon, lung, prostate, lymphoma, leukemia, and malignant glioma (5)²²⁻²⁷ No high-quality data examining patient tumor response rates (4)²⁸

Abbreviations: CBD, cannabidiol; IL-6, interleukin 6; NA, not applicable; THC, Δ9-tetrahydrocannabinol.

^a Based on Oxford Centre for Evidence-Based Medicine Levels of Evidence.

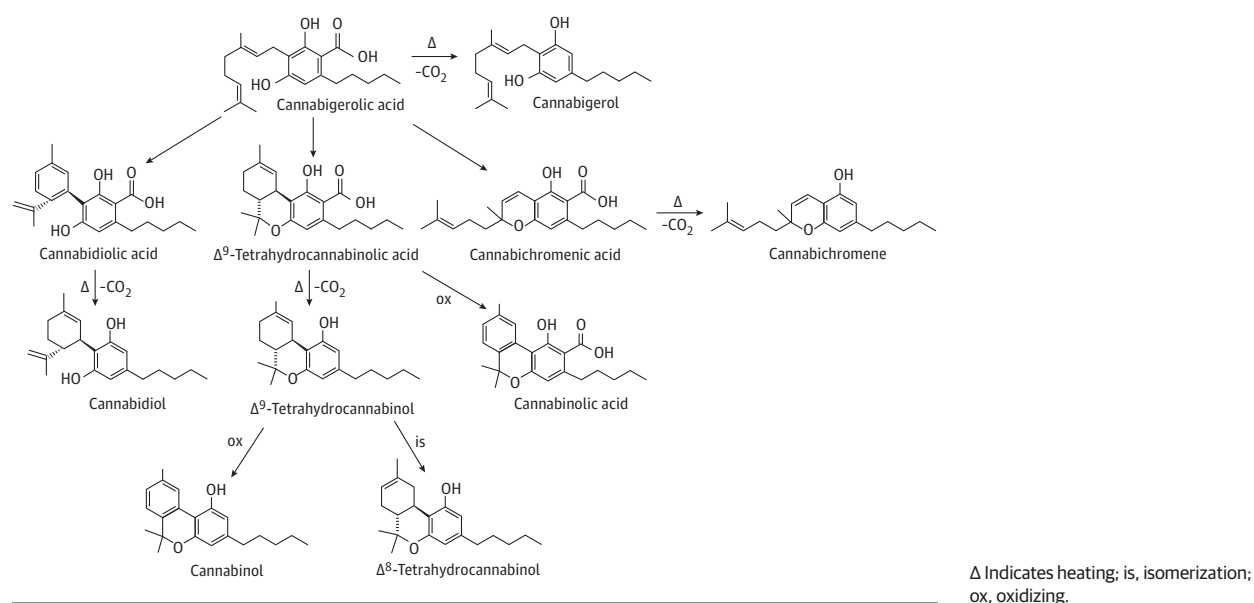
Reported Biologic Effects and Medicinal Uses

Cannabis contains more than 400 compounds, including more than 100 cannabinoids.^{31,40} The primary psychoactive agent is THC,⁴¹ but assuming that the effects of THC are identical to cannabis neglects the potential effects from the other cannabinoids and chemicals in the crude plant.^{32,40} Supporters of medical cannabis cite additional therapeutic benefit when THC and CBD are combined within the plant or plant extract based on the “entourage effect” described below.

There are 2 primary cannabinoid receptors in the body, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), which bind both THC and CBD in the brain and periphery. Cannabinoid receptor 1 is densely populated in the cortex of the brain but has low binding in the medullary nuclei, which mediate respiratory and cardiovascular functions, possibly accounting for its high safety profile.^{42,43} Cannabinoid receptor 1 receptors are also present in lower quantities on B cells.⁴⁴ Cannabinoid receptor 2 is present predominantly in macrophages.⁴³ Endogenous compounds that bind CB1 and CB2 are called endocannabinoids and include anandamide.⁴⁵ Binding of anandamide and its downstream physiologic effects are potentiated by the presence of additional esters, demonstrating the so-called entourage effect.⁴⁶ Similarly, CBD potentiates the effects of THC at CB1 receptors and increases expression of CB1 receptors in the brain.⁴⁷ Further work has identified additional cannabinoid receptors.⁴⁸ Thus, the pharmacologic activities of cannabinoids are not simple and clearly have some dependency on each other as well as additional agents.

Pharmacologic activity varies by method of consumption. Smoking cannabis plant material results in THC and CBD denaturing/destruction, leading to lung availability of only 13% to 30% despite complete decarboxylation, indicating that smoking is an inefficient form of delivery.^{32,33} By comparison, lung availability is as high as 76% when inhaling vaporized cannabis oil.³³ Optimal conversion

described more under the Safety section).³⁹ Because of inaccuracies in labeling, the FDA has submitted warning letters to multiple manufacturers.

Figure 2. Chemical Structures and Pathways of the Main Cannabinoids Present in Cannabis⁴⁰

from THCA to THC occurs at 150 °C (302 °F), which is the lower end of the spectrum for commercial vaporizers.^{32,49} Bioavailability of oral THC is between 10% to 20% when consumed via capsules, baked goods, or mucosal sprays.^{50,51} Transdermal applications are limited owing to the extreme hydrophobicity of cannabinoids, which makes crossing the aqueous layer of the skin's viable tissue the rate limiting step.⁵²

Reported therapeutic effects of cannabis include relief of pain, nausea, anorexia, inflammation, insomnia, and retardation of growth of certain types of cancer, all which may be useful in the surgical patient. These are summarized in Table 2 and are discussed in further detail in subsequent sections. Data also exist regarding its use for the treatment of chronic neuropathic pain, anxiety, multiple sclerosis, movement disorders including Alzheimer disease and Tourette syndrome, inflammatory bowel disease, glaucoma, and seizure disorders, which have been reviewed extensively elsewhere.

Pain/Analgesia

Severe or chronic pain is a top indication for medical cannabis in the United States.⁵³ In a survey-based study of 3845 patients with cancer in Israel treated through their medical cannabis program from 2015 to 2017, average pain scores were decreased, 36% of patients stopped taking opioids, and there was a 51% increase in patients reporting "good quality of life" 6 months after starting treatment.⁶ Multiple randomized clinical trials have also examined oral mucosal spray containing cannabis extract in patients with advanced cancer. Patients treated with THC/CBD spray (but not THC alone) had lower pain scores compared with placebo and also required fewer opioid breakthrough doses.⁹ In larger follow-up studies, patients had overall improved quality of life, and of note, US patients seemed to derive greater benefit.^{7,10} However, memory, cognitive function, and somnolence were worse in the treatment groups^{7,9} and cancer progression was similar in placebo and treatment groups.¹⁰ Dronabinol (oral synthetic THC) has a slight additive effect when combined

with oral morphine for analgesia to electrical stimulation, but cold pain tolerance was actually worse.⁵⁴

Cannabis may influence perioperative anesthesia and analgesia. It has been reported that cannabis users require increased dosage of propofol during induction of anesthesia and that mucosal administration of THC/CBD increases bispectral index.^{55,56} However, pharmacokinetic studies of fentanyl show no potentiation of adverse effects or change in the maximum concentration when coadministered with CBD.²¹ Multiple studies have examined cannabis for postoperative pain. Nabilone (oral synthetic cannabinoid) was ineffective in a randomized trial and unexpectedly was associated with higher pain scores.¹¹ Single treatment with low-dose (5 mg) oral THC after hysterectomy was also ineffective.⁵⁷ Higher doses of THC within cannabis extract decreased frequency of breakthrough pain in a dose escalation study, but sedation also increased.⁸ Of note, none of the perioperative trials describe postoperative outcomes or complications and restrict reporting almost solely to pain and psychotropic responses. A summary of clinical trials examining cannabis in the perioperative/surgical setting is presented in Table 3.^{8,11,13,56,57}

Nausea and Vomiting

In the 1970s, randomized clinical trials demonstrated superiority of oral THC (30-45 mg in divided doses) as an antiemetic compared with placebo⁵⁸ and prochlorperazine¹² for patients receiving cytotoxic chemotherapy. Younger patients had a better response to THC,¹² a finding corroborated in the Israeli study of patients with cancer mentioned previously, in which 91% of patients reported improvement in nausea and vomiting.⁵⁹ By comparison, nabilone (oral synthetic cannabinoid) given preoperatively did not change the incidence of postoperative nausea and vomiting.¹³

Weight Gain and Appetite

After smoking cannabis, healthy patients have 40% increased food intake owing to snacking.¹⁷ However, for patients with advanced cancer cannabis extract capsules with THC/CBD (5 mg/2 mg) and THC

alone (5 mg) daily in divided doses showed no significant impact on appetite or quality of life.¹⁸ A randomized clinical trial of dronabinol (oral synthetic THC) vs megestrol in patients with advanced cancer showed megestrol was superior.⁶⁰ Further, a randomized clinical trial of nabilone (oral synthetic cannabinoid) in patients with advanced cancer showed increased caloric intake of carbohydrates but no change in total caloric intake or patient weight.¹⁹

Insomnia

Cannabis may be used as a sleep aid, which has been noted during studies of cannabis for the treatment of pain and anxiety.¹⁴ The sleep-inducing effects of cannabis may be owing to sedation from THC, but some studies have also attributed this to terpenes found in cannabis.⁶¹ A symptom-charting smartphone application showed significant relief of insomnia with cannabis use, which was associated with higher CBD content.¹⁵ By comparison, a randomized placebo-controlled double-blind crossover study of CBD in health patients showed no difference in subjective sleep quality or polysomnographic parameters.¹⁶

Inflammation

There is *in vitro* evidence that THC and endogenous cannabinoids affect macrophage function by decreasing release of interleukin 6 and nitric oxide in response to lipopolysaccharide, but conversely, they also increase interleukin 1 activity and tumor necrosis factor α .^{62,63} Interleukin-6 levels were measured in the study of dronabinol vs megestrol mentioned previously, with no difference noted.²⁰ Pharmacokinetic studies of CBD also show no differences in plasma cortisol levels.²¹

Cancer

There is laboratory evidence that CBD has antitumor activity in breast cancer cell lines,²² colon cancer cell lines,²³ non-small-cell lung cancer cell lines,²⁴ prostate cell lines,²⁵ lymphoma and leukemia cell lines,²⁶ and malignant glioma cell lines.²⁷ There are case reports of effective CBD use in a variety of malignancies,²⁸ but retrospective studies suggest cannabis use may have adverse effects on the impact of immunotherapy.⁶⁴ To date, there are no published trials or high-quality studies examining the efficacy of cannabis or cannabis products specifically as cytotoxic treatment of cancer.

Overall Safety

The safety profiles of cannabis and THC as stated previously are excellent and generally well tolerated. It is known that THC consumption results in subjective intoxication associated with mild tachycardia.⁴¹ Importantly, however, these effects do not appear to be associated with respiratory depression. In fact, the lethal dose of orally consumed THC in primates has not been identified because none of 22 rhesus monkeys died when administered between 131 to 9000 mg/kg.⁶⁵ These values are orders of magnitude greater than typical dosages of cannabis and THC for medical use. While cannabis smoke contains carcinogens, there is insufficient epidemiologic evidence to support associations of cannabis consumption with malignancy⁶⁶ including head and neck as well as lung cancers.^{67,68} There is also no demonstrable association between cannabis use and myocardial infarction.⁶⁹ It should be noted that states with medical cannabis laws were found to have lower opioid-related mortality rates, a finding that strengthened over time.⁷⁰

Table 3. Perioperative/Surgical Cannabis Clinical Trials

Source	Study population, drug administration	Results
Buggy et al, ⁵⁷ 2003	<ul style="list-style-type: none"> Patients undergoing elective open abdominal hysterectomy (n = 40) Single oral dose of 5-mg THC vs placebo after discontinuing PCA on POD2 	<ul style="list-style-type: none"> No difference in pain scores or time to rescue analgesia "Increased awareness of surroundings" in THC group
Beaulieu et al, ¹¹ 2006	<ul style="list-style-type: none"> Patients undergoing major surgery with morphine PCA postoperatively (n = 41) Oral nabilone, 1 or 2 mg, vs ketoprofen, 50 mg, vs placebo given 1 h preoperatively and every 8 × 24 h postoperatively 	<ul style="list-style-type: none"> Nabilone, 2-mg, group had higher pain scores No difference in other measured variables Study was closed early owing to poor accrual
Holdcroft et al, ⁸ 2006	<ul style="list-style-type: none"> Patients undergoing surgery with morphine PCA postoperatively (n = 65) Single oral dose of cannabis (THC to CBD, 1 to 0.3-0.5) with 5, 10, or 15 mg of THC after PCA was discontinued 	<ul style="list-style-type: none"> Fewer patients required rescue analgesia with increasing THC (25% with 15 mg, 50% with 10 mg, 100% with 5 mg) Sedation increased with dose More adverse events with 15 mg
Levin et al, ¹³ 2017	<ul style="list-style-type: none"> Patients undergoing elective surgery with general anesthesia and at least 3 risk factors for PONV Single oral dose 0.5-mg nabilone vs placebo given preoperatively (n = 340) 	<ul style="list-style-type: none"> No difference in nausea/vomiting No difference in pain scores
Ibera et al, ⁵⁶ 2018	<ul style="list-style-type: none"> Patients undergoing orthopedic surgery (n = 27) Single oromucosal dose of cannabis (THC to CBD ratio approximately 1:1); 21.6-mg THC vs 10.8-mg THC vs 1-mg midazolam/1-mg acetaminophen vs placebo 	<ul style="list-style-type: none"> High dose of cannabis was associated with higher bispectral index

Abbreviations: CBD, cannabidiol; PCA, patient-controlled analgesia; POD, postoperative day; PONV, postoperative nausea/vomiting; THC, δ -9-tetrahydrocannabinol.

Known adverse effects of frequent cannabis smoking (more than once a week) are morning cough, increased sputum production, and wheezing.⁷¹ A condition termed *EVALI*, mentioned previously, was initially reported in August 2019, and can be lethal.³⁹ Electronic cigarette or vaping-associated lung injury predominantly affects young adults (<35 years) and is thought to be from vitamin E acetate within vaporized cannabis liquid. Vitamin E acetate was found in 94% of bronchoalveolar lavage samples from patients with EVALI, and THC or metabolites were also found in 85%.³⁹ Vaporizer cartridges from these patients had vitamin E acetate in 64% of samples, and some contained majority per content vitamin E acetate.³⁵ It is believed that vitamin E acetate is used to dilute cannabis oil owing to ease of obtaining, low expense, and its similarity in liquid and vaporized appearance. The mechanism of injury is thought to be from altering function of surfactant or creation of lung irritants during heating.³⁹ While real safety concerns exist owing to EVALI and improper labeling, these seem to be related to regulation of production rather than the cannabis itself.

Perioperative Safety

There is a very little of information regarding cannabis specifically as it relates to perioperative safety, surgical complications, and surgical outcomes; as stated previously, the previous studies conducted regarding postoperative pain did not report surgical com-

plications. Cannabinoids act on the P450 system, which is involved in the metabolism of many drugs that may need to be adjusted in the perioperative period.⁷² Limited data suggest that cannabis consumption can lead to higher international normalized ratio levels in patients taking warfarin, so coagulation studies the day of surgery should be considered.⁷³

Overall Surgical Recommendations

Based on the information discussed herein, the authors recommend that patients should not inhale the products of combustion prior to undergoing surgery and that smoking of any kind should not be endorsed. Given the concerns regarding vitamin E acetate and EVALI in cannabis preparations intended for vaporization, the safest method of consumption at this time is oral or submucosal. Given the paucity of information but potential to affect induction of anesthesia and the P450 system, we currently recommend oral/submucosal consumption of cannabis products should be held for 10 days prior to surgery. This recommendation is based on the half-life of dronabinol (24-36 hours)⁷⁴ and cannabidiol (56-61 hours).⁷⁵ Patients may resume consumption of cannabis products when other oral home medications are resumed. The risks of cannabis use as they relate to surgical complications are unknown, but long-term benefits appear to outweigh risks primarily for patients with cancer-related pain and nausea. In the symptomatic treatment of surgical patients, cannabis offers the possibility that pain, anxiety, and insomnia may be treated with less use of opioids and benzodiazepines. However, rigorous studies are necessary to definitively prove value of cannabis in attenuating the opioid and benzodiazepine crisis.

Conclusions

To the authors' knowledge, cannabis is the only controlled substance that is referred to as medicine or believed to have thera-

peutic potential in state law that physicians can only recommend but cannot prescribe with a recommended dosage, frequency, route of consumption, or duration of treatment. In many states, physicians must register to recommend cannabis, and patients must also register to comply with the physician recommendations. In many states, patients are also permitted to produce and use cannabis themselves for medicinal purposes without further testing to ensure safety or homogeneity. When it is produced through regulated commercial providers, there are no standard methods for measuring or labeling the therapeutic components. This is in contrast to the FDA-approved cannabinoids dronabinol, nabilone, and cannabidiol.

There are data related to cannabis use for the treatment of pain, nausea, anorexia, inflammation, and insomnia, which are common issues for surgical patients. Studies of cannabis for the treatment pain may importantly decrease opioid and benzodiazepine requirements for patients. However, few of these studies are definitive, and none of the studies on surgical patients report on postoperative complications or outcomes. Thus, there is a large gap in our understanding of how cannabis can be used to help treat surgical patients, and a surgeon's recommendations for patients who already use cannabis must be based on this limited data. There is a critical need for additional research on the effects of perioperative cannabis with specific attention to postoperative outcomes, not only because of its potential benefits but also because of its current widespread use outside Western medicine.

The differences in state laws between cannabis and all other controlled substances and its current listing as a schedule I drug by the DEA add a layer of difficulty to studying its potential benefits in high-quality prospective clinical research. Should surgeons choose to further explore the potential medical benefits of cannabis, research will necessarily be restricted to FDA-approved cannabinoids and to industrial hemp/hemp extracts with less than 0.3% THC. High-quality research of cannabis containing THC will likely not be possible unless it is treated as all other medications to ensure proper dosing, safety, and homogeneity.

ARTICLE INFORMATION

Accepted for Publication: August 8, 2020.

Published Online: December 2, 2020.
doi:10.1001/jamasurg.2020.5545

Author Contributions: Drs Stewart and Fong had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: Stewart.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: Stewart.

Obtained funding: Fong.

Administrative, technical, or material support: Stewart.

Supervision: Fong.

Conflict of Interest Disclosures: Dr Fong reports serving as a scientific consultant for Medtronic, Johnson and Johnson, Olympus, Avra Robotics, Perfint Robotics, and Intuitive Surgical. No other disclosures were reported.

Additional Contributions: We thank Goldie Solodar of City Sessions in Denver, Colorado, whose expertise and editing assistance were used in the preparation of this manuscript. Ms Solodar did not receive compensation for her assistance and provided written permission that her name could appear under the Acknowledgment section of this manuscript.

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