OPEN

NARRATIVE REVIEW ARTICLE

Cannabinoids and General Anesthetics: Revisiting Molecular Mechanisms of Their Pharmacological Interactions

Marco Echeverria-Villalobos, MD,[1] Catherine A. Fabian, MD,[2] Justin G. Mitchell, MD,[3] Elvio Mazzotta, MD,[1] Juan C. Fiorda Diaz, MD,[1] Kristen Noon, MD,[1] and Tristan E. Weaver, MD[1]

Cannabis has been used for recreation and medical purposes for more than a millennium across the world; however, its use's consequences remain poorly understood. Although a growing number of surgical patients are regular cannabis consumers, little is known regarding the pharmacological interactions between cannabis and general anesthetics; consequently, there is not a solid consensus among anesthesiologists on the perioperative management of these patients. The existing evidence about the molecular mechanisms underlying pharmacological interactions between cannabinoids and anesthetic agents, both in animal models and in humans, shows divergent results. While some animal studies have demonstrated that phytocannabinoids (tetrahydrocannabinol [THC], cannabidiol [CBD], and cannabinol [CBN]) potentiate the anesthetic effects of inhalation and intravenous anesthetics, while others have found effects comparable with what has been described in humans so far. Clinical studies and case reports have consistently shown increased requirements of GABAergic anesthetic drugs (isoflurane, sevoflurane, propofol, midazolam) to achieve adequate levels of clinical anesthesia. Several potential molecular mechanisms have been proposed to explain the effects of these interactions. However, it is interesting to mention that in humans, it has been observed that the ingestion of THC enhances the hypnotic effect of ketamine. Animal studies have reported that cannabinoids enhance the analgesic effect of opioids due to a synergistic interaction of the endogenous cannabinoid system (ECS) with the endogenous opioid system (EOS) at the spinal cord level and in the central nervous system. However, human data reveals that cannabis users show higher scores of postoperative pain intensity as well as increased requirements of opioid medication for analgesia. This review aims to improve understanding of the molecular mechanisms and pharmacological interactions between cannabis and anesthetic drugs and the clinical outcomes that occur when these substances are used together. (Anesth Analg 2025;140:1401–13)

Out of the over 480 different elements in the cannabis plant, more than 120 phytocannabinoids and phytochemicals have been identified in cannabis-derived recreational products. The most widely used and studied phytocannabinoids are delta-9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), cannabinol (CBN), and cannabigerol (CBG), being Δ9-THC the primary psychoactive compound.[1]

Marijuana, marihuana, hashish, hemp, weed, or cannabis are some of the names used to refer to any product derived from the *Cannabis* plant; however, in this review, we will identify as cannabinoids all compounds derived from the plant (phytocannabinoids), as well as the synthetic cannabinoids, which are lab-made compounds structurally similar to the compounds naturally derived from the plant cannabinoids. To date, cannabis is legal in 38 of 50 states for medical use, and 24 states, in addition to Guam, the Northern Mariana Islands, and DC, have legalized the use of recreational and medical cannabis. Based on the TCH content, cannabis plants are categorized according to the Federal legal status as (a) marijuana, the cannabis plant and products containing a THC concentration >0.3% (Schedule I substance), and (b) hemp, which is the cannabis plant and products containing <0.3% of THC.[2] The widespread use of these compounds, mainly for recreational purposes, requires that anesthesiologists and perioperative care teams should familiarize themselves with the potential effects of cannabis use in surgical patients.

From the [1]Department of Anesthesiology, The Ohio State University Wexner Medical Center, Columbus, Ohio; [2]Department of Anesthesiology. University of Michigan Hospital, Ann Arbor, Michigan; and [3]Department of Anesthesiology & Perioperative Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, California.

Accepted for publication September 24, 2024.

Conflicts of Interest, Funding: Please see DISCLOSURES at the end of this article.

Reprints will not be available from the authors.

Address correspondence to Marco Echeverria-Villalobos, MD, Department of Anesthesiology, The Ohio State University, Wexner Medical Center, Doan Hall 520, 410 W 10th Ave, Columbus, OH 43210. Address e-mail to Marco.Echeverriavillalobos@osumc.edu.

DOI: 10.1213/ANE.0000000000007313

Cannabinoids are pleiotropic compounds with multiple physiological effects of their own and derived from their drug-drug interaction with drugs involved in the perioperative management of cannabinoid-using patients that can complicate the course of anesthesia and the postoperative period. However, there is still a lack of clinical studies to elucidate discrepancies between what has been reported in animal studies and the reported findings in humans (research studies and case reports) resulting from the potential interactions between cannabis and anesthetic agents in patients with acute exposure and chronic use. Regulatory obstacles may have hampered serious and rigorous clinical studies as cannabis is a Schedule I compound, by the US Drug Enforcement Agency.[3] Published animal studies have shown conflicting data. Some demonstrate that phytocannabinoids THC, CBD, and CBN potentiate the anesthetic effects of inhalational anesthetics, decreasing the anesthetic requirements, shortening induction, and prolonging emergence times. Other studies showed results that aligned more with the reported effects on humans.[4,5] In contrast, in humans, THC has been reported to reduce the sedative and anesthetic effects of propofol and sevoflurane. Therefore, existing evidence shows that cannabis users may require higher doses of intravenous hypnotics and volatile anesthetic agents to achieve adequate anesthetic depth, as well as postoperative opioids.[6–10] Other confounding factors complicating the study of these interactions and their outcomes are differences in animal species, the poor standardization of cannabis compounds, and their chemical configuration and strength inconsistency. A synergistic interaction between cannabinoids and opioids that potentiates the antinociceptive activity of opioids was observed in animal models.[11]

The objective of this narrative review is to provide an understanding of the molecular mechanisms and pharmacological interactions between cannabis and anesthetic drugs and the clinical outcomes that occur when these substances are used together, which consequentially affects anesthesia planning and perioperative care.

DISCUSSION

Basic Pharmacology of the Exocannabinoids and the Endocannabinoid Systems

Phytocannabinoids or Exocannabinoids. The most characterized and studied phytocannabinoids or exocannabinoids are THC and CBD. Although THC is the main psychomimetic component, its synthetic analogs were the first cannabinoids used for medicinal purposes (Nabilone, Dronabinol). On the contrary, CBD is the main nonpsychoactive component in the Cannabis plant and is used to treat several medical conditions. Exocannabinoids must interact with the endocannabinoid system once they enter the body to produce their effects. Early studies with phytocannabinoids discovered that these compounds inhibit adenyl cyclase when binding to specific receptors widely disseminated in the central and peripheral nervous systems and other organs.[12,13] In humans, Δ^9-THC biotransformation occurs primarily in the liver by a 2-phase process of hydroxylation and oxidation through the CYP2C9 enzymes of the cytochrome P450 system. In contrast, CBD hydroxylation is performed by the subsystem CYP2C19 and the oxidation phase by the CYP3A4.[1]

The Endocannabinoid System. The endocannabinoid system (ECS) consists of endogenous cannabinoids or ligands, the cannabinoid receptors (C1B-R and CB2-R), which are adenylyl cyclase G-protein-coupled receptors (GPCRs), and the enzymatic system responsible for the synthesis and degradation of endocannabinoid ligands.[14–16] The ECS is one of the most pervasive cerebral signaling systems, participating in numerous physiologic responses such as pain, memory, stress response, motivated behavior, and neural growth and development.[17,18]

Cannabinoid Receptors. Phytocannabinoids, endocannabinoid ligands, and synthetic cannabinoids (K2 or spice) exert physiologic effects via GPCRs. CB1 receptors (CB1-Rs) are primarily expressed in some central neural structures like brain cortex, hippocampus, dentate gyrus, striatum, amygdala, basal ganglia outflow, nucleus accumbens, thalamus, hypothalamus, periaqueductal gray, brainstem, and cerebellum; and due to their location on interneurons (GABAergic, CCK-positive) and presynaptic axons they actively participate in the modulation of neurotransmission; CB1-Rs are also expressed in neurons connecting into the area postrema, contributing to the antiemetic effects elicit by some phytocannabinoids, as well as in the peripheral and the enteric nervous system.[19] Moreover, CB1-R is found in other body tissues, including the cardiovascular, immunologic, adrenal, ocular, and gastrointestinal systems.[20] Additionally, CB1-Rs are expressed in dopaminergic, cholinergic, glutamatergic, and serotoninergic neuronal systems, modulating the release of other neurotransmitters such as dopamine, acetylcholine, glutamate, and serotonin.[21,22] CB2 receptors are found in the immune system (T cells, macrophages, and B cells), spleen, subcutaneous adipose tissue, thymus, tonsils, right lung lobe, left colon, and left lobe of the liver, suggesting a potential immunomodulatory function (Figure 1).[23] Recent investigations revealed that CB2-Rs are expressed in the human brain at low levels in the hippocampal CA2/3 pyramidal neurons and glial cells, and its expression is upregulated in response to neuroinflammation.[19,24]

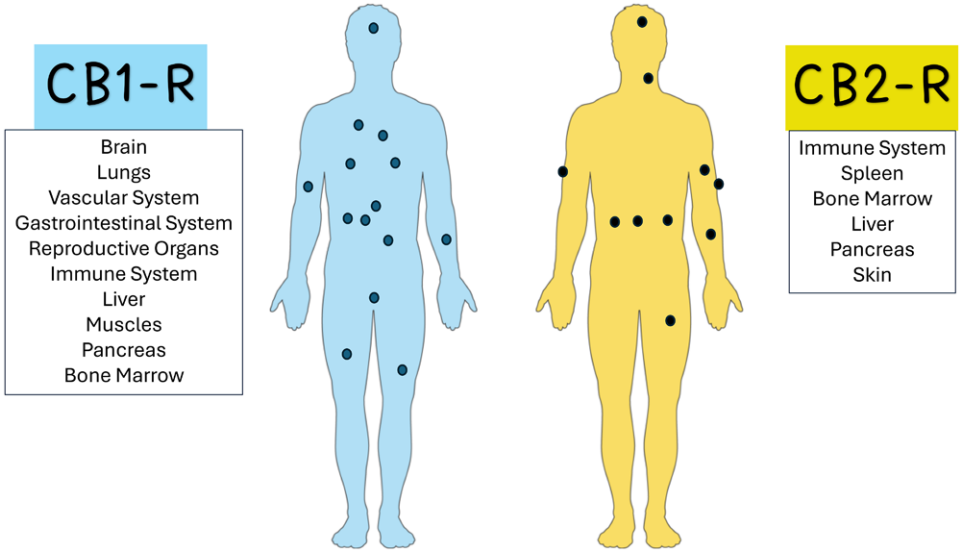

Figure 1. Distribution of cannabinoid receptors. CB1: The majority of CB1 receptors are expressed in the brain. Still, they are also located in other organs and tissues, such as the lungs, vascular system, gastrointestinal system, reproductive organs, immune system, liver, pancreas, muscle, and bone marrow, where they modulate local tissue functions. CB2: The principal expression of CB2 is in the immune system, such as the spleen and bone marrow, where it shows immunomodulatory functions and other tissues (liver, pancreas, and skin).

CB2-Rs have been detected in the cerebellar microglial cells, modulating microglial activation and reducing the neuroinflammatory response.[25] Preclinical and clinical data have shown that frequent or heavy cannabis consumption is associated with the downregulation of the brain's CB1-Rs and lower levels of circulating endocannabinoids. However, abstinence for 2 to 14 days may restore the CB1-R expression.[26] An orphan cannabinoid receptor, the G protein-coupled receptor-55 (GPR55), has been identified more recently. It is highly expressed in the dorsal root ganglion (DRG), neurons, vascular endothelial cells, and immune cells, and once activated by THC and AEA, promotes the increase in intracellular Ca^{2+}.[27] Synthetic cannabinoids are full agonists of CB1-R, eliciting potent physiologic responses that explain the significant toxic effects that can cause the death of its users.[28]

Cannabinoid Ligands. Endocannabinoid ligands are synthesized from phospholipids located in the cellular membranes of several brain cells, such as postsynaptic neurons, astrocytes, and microglial cells. They are released by cell depolarization or on-demand after CB-R activation.[29,30] Once synthesized, endocannabinoids bind retrogradely to the presynaptic CB1-R, restraining the release of neurotransmitters at the presynaptic terminals by inhibiting voltage-gated Ca^{2+} channels or activating the inward current of potassium channels.[31] The main endocannabinoid ligands, arachidonoylethanolamide (also known as anandamide or AEA) and 2-arachidonoylglycerol (2-AG), are derived from arachidonic acid, being AEA an amide, and 2-AG an ester, and both are produced in a 2-step process at the postsynaptic level. The actions mediated by the ECS depend on the concentration of the ligands, which is tightly balanced by their synthesis and biodegradation.[32] AEA shows higher binding affinity to CB1 receptors but is a partial agonist eliciting a weaker intracellular response than 2-AG, which has a low binding affinity and full agonism to CB1 and CB2 receptors (Table 1). The most abundant endocannabinoid ligand in the brain is 2-AG, binding only to cannabinoid receptors, while AEA activates TRVP1 receptors, inhibits L-type Ca^{2+} channels, and downregulates 2-AG synthesis, impacting synaptic transmission.[33] AEA shows a high affinity for nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs), which are involved in the transcription of genes that regulate neuroinflammation, energy production, and lipid metabolism.[34] 2-AG also plays a vital role in neuroinflammation by synthesizing arachidonic acid, a primary source for cyclooxygenase-mediated prostaglandin biosynthesis.[1,35] The concentration of endocannabinoids is regulated by the enzyme fatty acid amide hydrolase (FAAH), AEA amidohydrolase, and monoacylglycerol lipase (MAGL), which act by degrading AEA and 2-AG, respectively (Figure 2).[36]

Exocannabinoids and Endocannabinoids Interaction. Exogenous cannabinoids (phytocannabinoids and synthetic analogs) and endocannabinoid ligands (AEA and 2-AG) target both types of CB receptors with varying selectivity. THC is a partial agonist of CB1 and CB2 receptors, while CBD shows a low affinity for cannabis receptors CB1 and CB2; however, it can signal other receptors such as TRPV1, GPR55, 5-HT_1, and adenosine (Table 1).[26,37]

Proposed Molecular Mechanisms of the Pharmacological Interactions Between Cannabinoids and Anesthetic Drugs in Animals and Humans

Studies performed in animal models to investigate the pharmacological interactions between cannabinoids

Table 1. CB1/CB2 Receptors Agonists and Antagonists

CB receptors	Exogenous agonists	Endogenous agonists	Antagonists
nonselective CB1-R/CB2-R affinity/efficacy	Δ9-Tetrahydrocannabinol (THC) • Low CB1/CB2 affinity (CB1>CB2) • Partial agonist of CB1/CB2 • Efficacy CB1>CB2	Anandamide (AEA) • High affinity for CB1 • Low affinity for CB2 • Partial agonist of CB1 • Efficacy CB1>CB2 2- Arachidonoglycerol (2-AG) • Low affinity CB1>CB2 • Full agonist of CB1 and CB2 • Efficacy CB1>CB2	Cannabidiol (CBD) • Low CB1 affinity • noncompetitive antagonist of CB1/CB2 (inverse agonist) • Negative allosteric modulators of CB1
Selective CB1-R affinity/efficacy	No exogenous phytocannabinoids are selective agonists of CB1-R. Synthetic cannabinoids with a pharmacological structure similar to THC are the only selective CB1-R agonists • Nabilone (used for chemotherapy-induced nausea and vomiting)	No endogenous cannabinoid is a selective agonist of CB1-R.	Synthetic cannabinoids are the only selective CB1-R antagonists.
Selective CB2-R affinity/efficacy	Only synthetic cannabinoids are selective CB2-R agonists.	No endogenous cannabinoid is a selective agonist of CB2-R.	Only synthetic cannabinoids are CB2-selective antagonists.

Agonist (full agonist): A molecule that binds to the receptor site and elicits a response causing a conformational change. Partial agonist: Molecule that binds to the receptor, allowing a partial activity that provokes a reaction that is less than the maximum effect of a full agonist. Inverse agonist: Molecule that binds to a receptor, prompting a physiological response opposite to the agonist effect. Inverse agonists can blunt receptor activity. Antagonists: Molecule that binds to the receptor, preventing the agonist molecules from binding and do not produce any response. High affinity to a receptor describes the binding of a ligand to the receptor, which results from greater attractive forces. In contrast, in low affinity, the binding to receptors requires less attractive force. Efficacy refers to the capacity of a molecule or ligand to produce a pharmacological response when it binds to the receptor. An agonist's potency depends on high affinity, efficacy, or both.

Abbreviations: CB1-R, cannabinoid-1 receptor; CB2-R, cannabinoid-2 receptor.

and the most used drugs in anesthesia have yielded contradictory results, with some of them showing that cannabis consumption decreases the requirements of intravenous and inhaled anesthetics. In most preclinical studies, animals were subjected to daily cannabis consumption, which resembles chronic use in humans, before they were exposed to the volatile or intravenous anesthetic agent. However, the magnitude of this effect varies among cannabinoids.[1,21]

Current reports on the interaction of anesthetic drugs and phytocannabinoids or synthetic cannabinoids in humans are limited to case reports and small clinical studies. Interestingly, the existing evidence does not show the disparities reported in animal studies. In contrast, clinical studies and case reports have consistently highlighted the tolerance to intravenous and volatile agents during induction and maintenance of anesthesia, elevated processed EEG index, and an unknown cross-tolerance to analgesics (Table 2).[53,54]

Cannabinoids Interaction With Inhaled and Intravenous GABAergic Anesthetics.

Animal Data. Several studies in different animal species (dogs, mice, rats) have found that the acute or chronic administration of THC produces a dose-dependent reduction in the MAC of the most used volatile anesthetics, halothane, isoflurane, and sevoflurane. GABA is the major inhibitory neurotransmitter in the brain. The proposed mechanism is that cannabinoids like CBD bind to postsynaptic CB1-Rs and activate GABAA receptors (GABAA-R) via the 2-AG ligand, facilitating GABA binding to the receptor and potentiating its inhibitory actions on neurotransmission.[39,55] Other preclinical studies found that selective activation of presynaptic CB1-R by THC, through 2-AG, inhibits GABA release in the synaptic cleft, precluding the neurotransmitter's inhibitory effects.[39,56] Meanwhile, other authors have described that CBD favors glutamate release by interacting with several receptors, such as TRPV1, GPR55, and 5-HT1A.[33,57] Synthetic cannabinoids can also affect the anesthetic requirements of inhalation agents, most probably through their action as full presynaptic CB1-R agonists, inhibiting the release of GABA.[58]

Regarding intravenous anesthetics, trials in mouse models had reported that the administration of cannabis avoided the hypnotic effect of propofol. At the same time, sedation required increasing doses of propofol, and similar results were reported with the combination of THC and thiopental. This effect was attributed to the previously described interaction of THC with presynaptic CB1-R, downregulating the production and release of GABA and inhibiting the synaptic GABAergic inhibitory neurotransmission.[6] Also, neurochemical and neuroanatomic evidence has shown that postsynaptic CB1-R activation releases 2-AG, which potentiates GABAA-R and postsynaptic GABA current in multiple brain areas, such as the hypothalamus, hippocampus, cortex, striatum, and cerebellum (Figure 3).[39] Patel et al[59] demonstrated

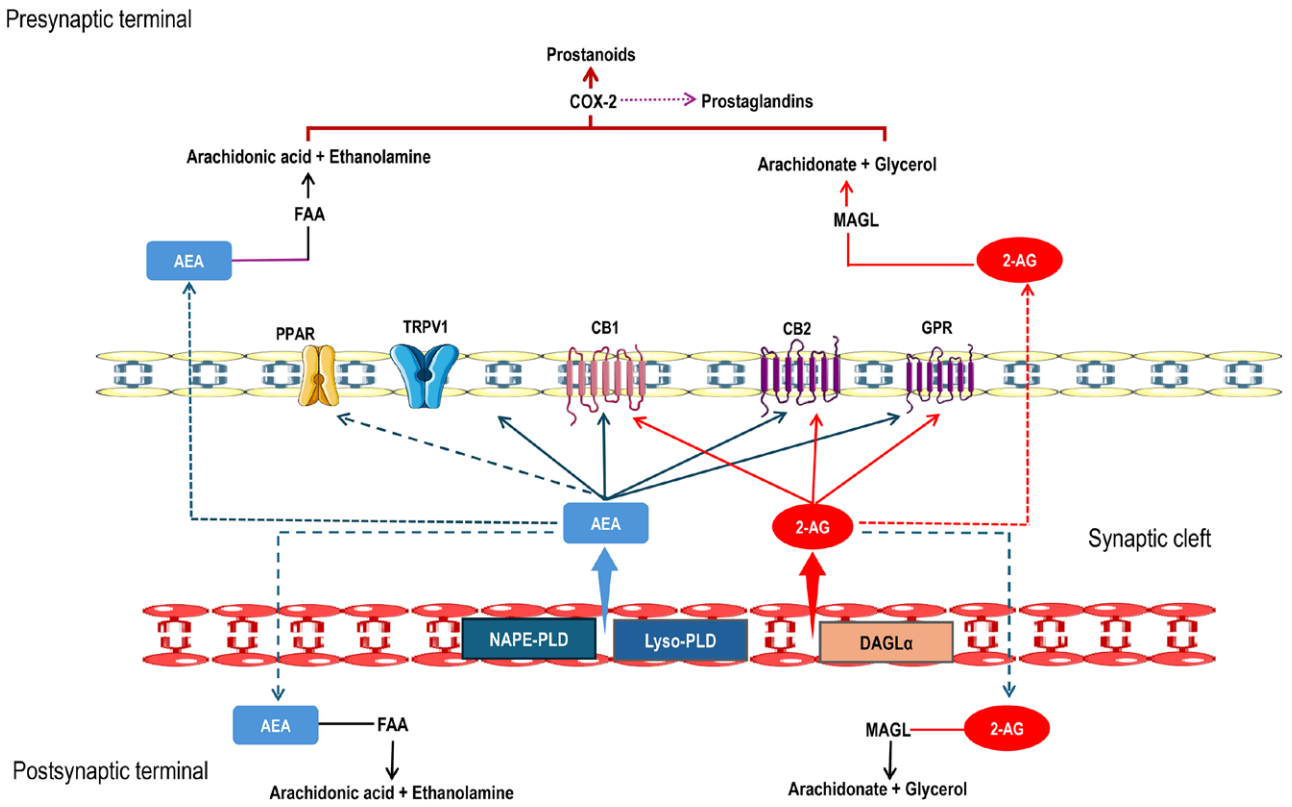

Figure 2. Synthesis and degradation of endocannabinoids. Endocannabinoids are produced on demand in the retrograde postsynaptic neuron signal, and their synthesis is initiated by glutamate receptor activation. The ligand 2-arachidonylglycerol (2-AG) is synthesized by the enzymes 2-acylglycerol [AG] and diacylglycerol [DAG] (DAGL) and, once synthesized, diffuses into the synaptic cleft and activates CB1 and CB2 receptors in a retrograde fashion, situated in the presynaptic terminal; signaling of 2-AG is terminated by the enzyme monoacylglycerol lipase (MAGL) degradation in the presynaptic terminal. 2. Anandamide (AEA) is synthesized by the enzyme N-acyl phosphatidylethanolamine [NAPE], NAPE-specific phospholipase D [NAPE-PLD], and then diffuses into the synaptic cleft to activate CB1 and CB2 receptors. AEA also activates transient receptor potential channel 1 (TRPV1). AEA is broken down postsynaptically by fatty acid amino hydrolase (FAAH) into arachidonic acid and ethanolamine. Both 2-AG and AEA have endocannabinoid transporters facilitating their reuptake and subsequent postsynaptic degradation.

that propofol is a strong inhibitor of FAAH activity, increasing the brain content of AEA. This is one of the main mechanisms explaining its sedative, anesthetic, and antiemetic effects.

Human Data. Another exciting line of research is the antagonistic interaction of THC with propofol and thiopental that has been reported in humans, where recent or heavy cannabis consumption increases the requirements of both agents to achieve an adequate level of sedation or anesthesia. Cannabis users may require higher doses of intravenous hypnotics and inhalation anesthetic drugs, perhaps due to the interaction between exocannabinoids, cannabinoid receptors, ligands, GABA deposits, and GABA-A receptors, as was shown in animal models.[60]

These findings suggest that some of the central effects seen after CB1-R activation by endocannabinoids are mediated by interactions with the GABAergic neurons, either inhibiting presynaptic GABA release or modulating GABA receptor functioning to a large extent in cannabis users, depending on the prevalence of the exocannabinoid that has been consumed. THC interaction with presynaptic CB1-R promotes the formation of the 2-AG ligand, which impedes the release of GABA in the synaptic cleft, interfering with the formation of the complex GABA-GABAA-R in the postsynaptic terminal and interfering with the GABAergic neurotransmission. This must be the mechanism by which the consumption of cannabis or cannabis products with high THC content causes an increase in the requirements of GABAergic anesthetics both for the induction and for the maintenance of adequate levels of anesthesia. Conversely, CBD activates the postsynaptic CB1 receptor, stimulating the GABAA receptor via 2-AG and increasing the postsynaptic neuron's GABA and Cl-current (Figure 3).[38] Besides, CBD inhibits FAAH, enhances AEA levels, and signals on the presynaptic CB1-R, dampening glutamate release and postsynaptic NMDA-R activity and decreasing neuron excitability.[42] Therefore, patients receiving CBD for medical purposes should not require high doses of GABAergic anesthetics to achieve adequate anesthesia depth, as in the case of recreational cannabis use due to high levels of THC.

Table 2. Pharmacological Interactions of Cannabis and Cannabinoids With Anesthetic Drugs in Humans

Anesthetic drugs	Mechanisms of pharmacologic interactions	Clinical outcomes
Inhalational anesthetics (isoflurane, sevoflurane)	• THC binds to presynaptic CB1-R inhibiting the release of GABA → ↓ inhibitory neurotransmission[38] • CBD activates postsynaptic CB1-R → promote GABA current by activating GABAA-R enhancing inhibitory neurotransmission[39] • CB1-R activation by preoperative CB exposure → ↓ release of acetylcholine in neocortex[40,41] • Presynaptic CB1-R activation suppresses GABA and glutamate release → interferes with synaptic transmission and plasticity in the hippocampus[42]	• THC ↑ requirements of GABAergic inhalation and intravenous anesthetics to achieve adequate anesthesia depth • CBD by improving GABAergic transmission might ↓ anesthetic drug requirements • Transient postoperative cognitive deficit affecting memory and learning process • CBD might ↓ anesthetic agents' requirements
Intravenous GABAergic anesthetics (Propofol, BDZ)	• CB provokes changes in CYP enzymatic system expression and activity → Accelerated metabolic degradation of propofol[43–45] • Propofol inhibits FAAH →↑AEA levels that activate CB1-R in: ○ Dorsal vagal complex, NTS, AP in brain	• ↑ propofol requirements to maintain clinical anesthesia • Antiemetic effects → ↓PONV
Ketamine (NMDA-R antagonist)	• Coupling of THC with presynaptic CB1-R leads to a) ↓ glutamate release into synaptic cleft (presynaptic effect)[46] b) ↓ intracellular NMDA-R signaling and expression (postsynaptic effect)[47,48] Ketamine ↑ AEA in presence of nociceptive stimulus →↑ CB1-R activation[48]	• Neuroprotective effect by preventing intracellular Ca^{2+} influx and cell death during ischemic conditions • ↑ antinociceptive effect of ketamine • ↓ requirements of GABAergic anesthetics to maintain clinical anesthesia
Opioids	ECS and EOS are both activated by external cannabinoids and opioids.[13,49–52] • ECS and EOS share anatomical and neurochemical distribution in the SDH and in the brain • Interaction of CBs with κ and δ opioid receptors triggers synthesis and release of endogenous opioids	• This interaction has a synergistic effect on nociception as well as on opioid withdrawal. • The antinociceptive synergistic effect of CB and opioids is more consistent in chronic than acute pain
Neuromuscular blockers	No interactions between CB and NMB have been described in hums	Hitherto, no adverse events have been published

Abbreviations: AEA, anandamide; AP, area postrema; BDZ, benzodiazepines; CB, cannabis and cannabinoids; CB1-R, cannabinoid-1 receptor; CYP, cytochrome P-450 enzymatic system; ECS, endogenous cannabinoid system; EOS, endogenous opioid system; GABA-A-R, γ-aminobutyric acid – a-receptor; NA, nucleus accumbens; NMDA, n-methyl-d-aspartate; NMJ, neuromuscular junction; NTS, nucleus tractus solitarii; NMB, neuromuscular blockers; N_2O, nitrous oxide; STP, sodium thiopental; THC, tetrahydrocannabinol; VT, ventral tegmentum.

Another mechanism involved in the reported increase in the requirements of GABAergic anesthetics is the upregulation of the hepatic enzyme system P-450 in cannabis users. Cannabinoids directly activate and inhibit nuclear receptors in the hepatic microsomes, leading to CYP expression and activity changes and accelerating propofol's metabolic degradation. Therefore, higher induction and maintenance doses are required to maintain adequate drug blood levels and anesthesia depth.[43] THC is metabolized in the liver by cytochrome P-450 enzymes such as CYP2C9, CYP3A4, and CYP2B6.[44] Likewise, propofol is metabolized by glucuronidation via uridine diphosphate (UDP) glucuronosyltransferase 1A9 and by the cytochrome enzymes CYP2B6 and CYP2C9.[45] However, the outcomes of these pharmacologic interactions are often difficult to predict in real clinical scenarios due to the presence of confounding social habits among cannabis users, such as alcohol abuse, which could predispose to liver dysfunction and disease. Therefore, further well-designed research studies are required to better understand these effects' extent.

Flisberg et al[61] published the first prospective randomized controlled clinical trial comparing the propofol requirements between cannabis users (CBU) and noncannabis users (non-CBU) during laryngeal mask insertion. A higher total dose of propofol was required to achieve bispectral index (BIS) values <60 and satisfactory LM insertion in the CBU group in comparison with the non-CBU patients (263.2 ± 69.5 mg vs 314.0 ± 109.3 mg, $P < .04$). However, considering that the average weight in both groups was 80 kg, the total doses of propofol are equivalent to 3.29 ± 0.86 mg/kg vs 3.92 ± 0.12 mg/kg. Similar findings have been reported in patients undergoing transesophageal echocardiography (TEE) under sedation with midazolam.[22] Sedative doses of fentanyl, midazolam, and propofol increase by ~14%, ~20%, and ~220% in cannabis users, which makes cannabis exposure an independent predictor of higher propofol requirements.[62] Likewise, cannabis users may be more susceptible to experiencing (and requiring medication for) sleep disorders, anxiety, and depression.[63]

Cannabinoid Interaction With the NMDA System. *Animal Data.* Glutamate is the primary excitatory neurotransmitter in the CNS, which plays a primary role in synaptic transmission, neuronal connectivity, and other processes of brain development, such as neurogenesis, cell differentiation, and migration.[64] The ECS interplays with the NMDA-glutamatergic system to maintain a physiologic balance of the excitotoxic effects of Ca^{2+} influx into the neurons to

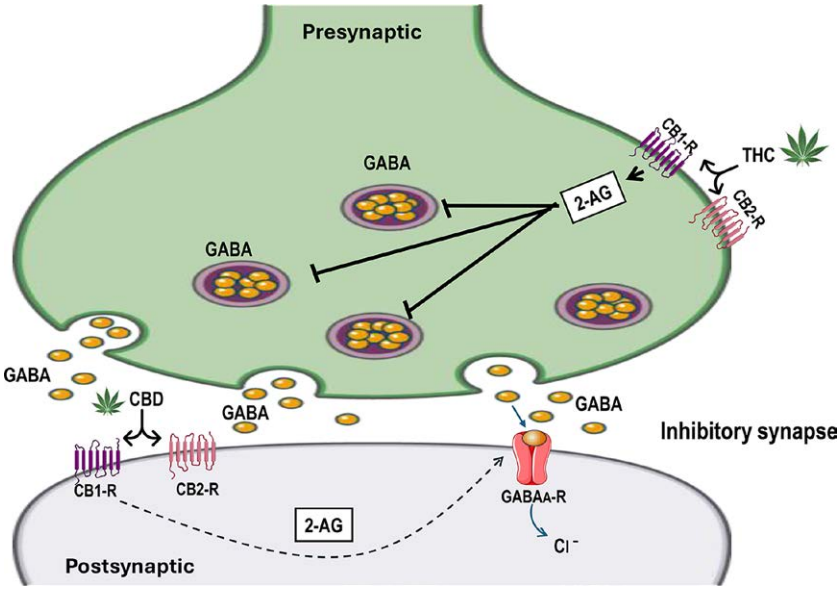

Figure 3. Cannabinoid interaction with the GABA signaling. The major phytocannabinoids, tetrahydrocannabinol (THC), and cannabidiol (CBD) modulate the release of GABA and the activity of GABAA receptors (GABAARs), correspondingly. THC activation of presynaptic CB1-R inhibits the release of GABA into the synaptic cleft in the brain (hippocampal interneurons). Meanwhile, CBD activates postsynaptic CB1-Rs and enhances GABAergic activity by potentiating $GABA_AR$ currents through the action of endocannabinoid ligand 2-AG.

ensure adequate neurotransmission. THC stimulation CB1-R attenuates presynaptic glutamate release into the synaptic cleft (presynaptic effect). It interferes with the postsynaptic signaling system regulated by the NMDA receptor (NMDAR) system and intracellular NMDA receptor signaling and expression (postsynaptic effect).[46] This interaction blocks intracellular Ca^{2+} influx, which prevents cell death and is one of the pathways involved in ketamine's neuroprotective effects (Figure 4).[47] In addition, it has been demonstrated that ketamine induces the release of ligand AEA and CB1-R activation in the presence of a nociceptive stimulus, suggesting that this pathway could be one of ketamine's antinociceptive effects.[48]

Human Data. Two case reports have shown that cannabis users may demand elevated doses of intravenous and inhaled anesthetics during anesthesia induction and maintenance.[48,65,66] Interestingly, after N_2O (an NMDA receptor antagonist) was initiated in both cases, there were clinical signs of more adequate levels of anesthesia and hemodynamic stability.[67,68] Therefore, the addition of an NMDA receptor antagonist like N_2O or ketamine (with no direct interaction with GABA receptors) may contribute to attenuating the increased requirements of GABAergic anesthetic agents such as propofol, midazolam, sevoflurane, and isoflurane in active cannabis users.[48]

Cannabinoid Interaction With Opioids. The ECS and the EOS are both activated by cannabinoids and opioids. CB1-R and mu-opioid receptor (MOR) share an anatomical and neurochemical distribution pattern, as well as common signaling pathways in the dorsal horn neurons of the spinal cord and specific brain structures, including the central medial thalamic nuclei, periaqueductal gray, medial basal hypothalamus, raphe nuclei, caudate putamen, dorsal hippocampus, and substantia nigra.[69,70] This molecular interaction not only plays a vital role in antinociception but also in drug reward and opioid withdrawal.[70] Moreover, the cross-talk between CB1-R and MOR plays an essential role in other physiologic and pathologic processes such as sedation, hypothermia, hypotension, and inhibition of motor activity.[71] Furthermore, the combined subanalgesic doses of THC and morphine not only produce an antinociceptive synergy but, at the same time, prevent the development of tolerance due to chronic exposure to morphine.[71]

Animal Data. Studies conducted in different animal models have demonstrated the existence of a functional interaction between the ECS and the endogenous opioid system (EOS), resulting in a potentiation of the opiate analgesic effects when combined with CB-R agonists.[72] Some of these studies have demonstrated the opioid-sparing effect of cannabinoids, showing that the coadministration of low doses of cannabinoids and opioid receptor agonists enhanced the analgesic effect compared to the effects of either drug.[49] To explain the synergistic effects between opioids and cannabinoids, some contributing factors have been identified: (a) cannabinoid and opioid receptors have overlapping locations in brain regions, and both signaling systems intervene in standard physiological processes such as nociception, rewarding, and motor activity, (b) the receptors of both systems belong to the G-protein-coupled receptor family and their transduction systems are also similar, (c) exogenous cannabinoids may provoke the production and release of endogenous opioid peptides in the

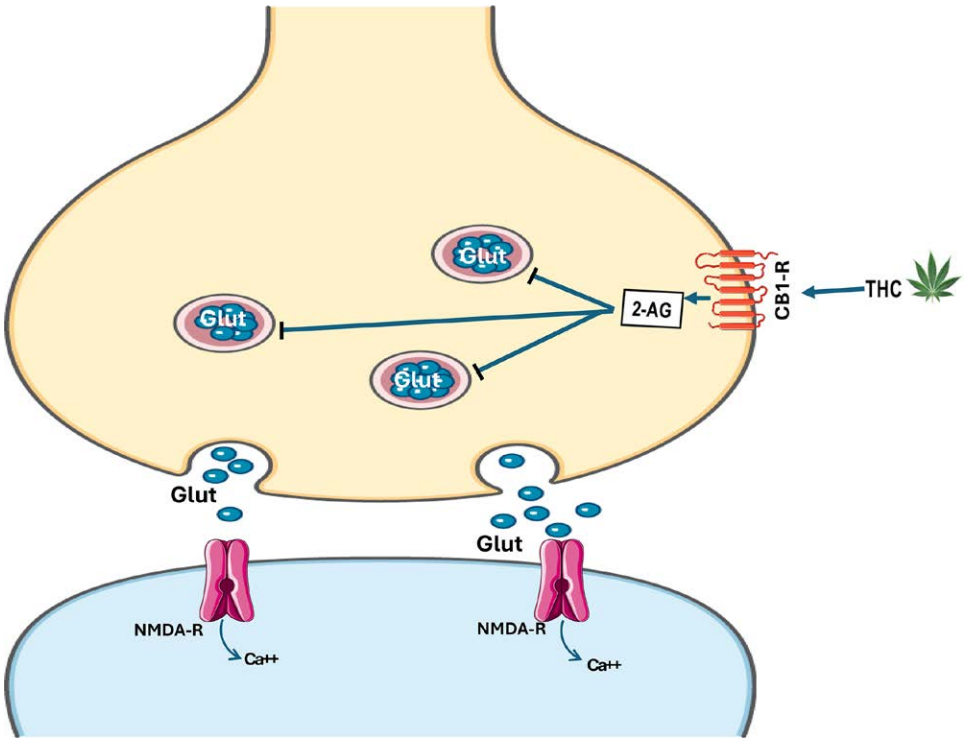

Figure 4. Interaction of THC with postsynaptic NMDA-R signaling. In glutamatergic neurons, the binding of THC to presynaptic CB1-R causes the release of 2-AG, which inhibits the release of glutamate into the synaptic cleft. This interferes with the binding of Ca++ with the postsynaptic N-methyl-D-aspartate receptor (NMDA-R) and, consequently, dampens the excitotoxic signaling mediated by the NMDA-R, attenuating the influx of Ca^{++} into the neuron.

brain and peripheral nervous system; thus, the intracellular signaling mechanisms triggered by the interaction of cannabinoids with K and δ opioid receptors increase the synthesis and release of K and δ endogenous opioids, and d) repeated doses of THC increase the μ-receptor density in many different areas of the brain, reaching the maximal expression 3 days after neural injection of THC and fading after 14 days.[37,49–52]

Human Data. Despite what the studies in animals have shown, the findings of recent meta-analyses that included prospective studies in healthy volunteers with experimental pain, acute postoperative, lumbar pain, and patients with cancer pain demonstrated that opioid-sparing properties in cannabis users are inconsistent, with no beneficial effects on opioid dosage or pain intensity in acute pain. However, various RCTs conducted on patients with cancer pain taking opioids for a long term reported improved pain scores with the addition of an extract of THC (nabiximols) compared with the placebo group.[51] A meta-analysis conducted by Abdallah et al[73] reported that patients receiving cannabinoids for the treatment of acute postoperative pain showed no differences in opioid medication and rest pain intensity up to 24 hours after surgery compared to the control group. Another meta-analysis studying the response to orally and intramuscularly administered cannabinoids for acute pain of various etiologies found a significant reduction in pain levels in those patients who received intramuscular cannabinoids. In contrast, no differences were observed in pain intensity with the placebo group when cannabinoids were given orally. The meta-analysis also included RCTs examining the effect of dronabinol or smoked cannabis in patients with various causes of chronic noncancer pain, and most studies reported a significant reduction in the level of pain when compared with placebo.[74] The reported opioid-sparing effect in humans when cannabis and opioids are combined, especially in cancer and chronic pain, could be explained by the mechanisms above proposed for the synergistic interaction between cannabinoids and opioids.

Cannabinoids and Neuromuscular Transmission. Several studies in animal models and humans have described the presence of CB1-R, CB2-R, and TRPVI-R and the synthesis of endocannabinoids (AEA and 2-AG) in the neuromuscular junction of striated peripheral muscle. CB1-R and ligands AEA and 2-AG are also present in the muscle nerve endings and the sarcolemma, regulating the release of acetylcholine and Ca^{2+} at the nerve terminal and the contractile tension of the skeletal muscle.[75] In mammalians, THC increases both the frequency and amplitude of miniature end-plate potentials (MEPP) at the presynaptic level, prolonging the duration of end-plate potentials (EPP).[76] CBD inhibits voltage-gated sodium channels (Nav 1.4), decreasing skeletal muscle contraction.[77] However, no adverse pharmacological interactions between cannabinoids and neuromuscular blockers have been reported in humans.

Other Perioperative Outcomes Derived From the Interactions of Cannabinoids

Cannabinoids, Opioids, Acute and Postoperative Pain. Despite the proven effectiveness of cannabis in chronic pain, there is increasing evidence that cannabis use may be detrimental in the acute pain setting, with most human studies reporting that cannabis users are more prone to experience poor postoperative pain control, with higher pain scores, and more opioid requirements for analgesia than noncannabis users.[73,78–80] Some molecular mechanisms of interaction between cannabinoids and opioids could explain this contradictory response in acute postoperative pain to that observed in chronic pain. Different distributions of CB1-R in nerve fibers may be plausible explanations for this physiologic response. Mackie et al[81] demonstrated that small-diameter diameter Aδ fibers contain fewer CB1-R and more μ-opioid receptors (MOR) than large-diameter fibers. Moreover, chronic cannabis use leads to CB1-R downregulation and desensitization, resulting in reduced drug effects.[82,83] The results of a recent meta-analysis have confirmed that postoperative pain intensity and opioid consumption as oral morphine equivalents (OME) were significantly higher in cannabis users compared with nonusers at 24 hours and 36 hours after surgery.[73] In an observational, prospective pilot study, Dupriest et al[78] found that there were significantly higher pain scores 24 hours after craniotomy surgery in cannabis users than in noncannabis users patients (4.58 vs 3.89; $P = .056$). Wiseman et al[80] reported that cannabis users presented greater pain intensity and higher opioid requirements at 12 and 36 hours postoperatively compared with nonusers. Two retrospective propensity score matched-cohort studies showed that cannabis users presented significantly higher postoperative pain scores than nonusers (median 4.68 vs 3.88) and required more opioid medication.[79,84]

Cannabinoids and Postoperative Nausea and Vomiting. Another potential interaction between the ECS and anesthetic agents involves the physiologic mechanisms of PONV. Although cannabinoids have been used in the treatment of chemotherapy-induced nausea and vomiting (CINV), some evidence shows that their interaction with some anesthetic agents may contribute to the occurrence of PONV.[85–87] Cannabis shows a paradoxical pharmacological behavior, having antiemetic effects when used at low doses, whereas chronic high-dose consumption could result in cyclical vomiting.[88] Therefore, anesthesia providers must consider the combination of chronic cannabis consumption and general inhalation anesthesia a high-risk factor for PONV. Preclinical and clinical studies have demonstrated that some cannabinoids have central and peripheral antiemetic effects by activating the CB1-R in the brain and the enteric nervous system (ENS). CB1-R and endocannabinoid ligands, AEA and 2-AG, exist in significant concentrations in the brainstem, most of all in the dorsal vagal complex, which encompasses the nucleus tractus solitarii, the dorsal motor nucleus of the vagus nerve, and the area postrema.[89] Likewise, CB1-Rs are found in the myenteric plexus of the stomach and duodenum.[75,90] Some studies showed that the antiemetic and emetic postoperative effects of some anesthetic agents are linked to the levels of AEA in the brain.[91] AEA decreases in the brain after inhaled anesthetic exposure, whereas small increments are seen after total intravenous anesthesia (TIVA) with propofol.[91] A recent retrospective cohort study analyzing an extensive database of 27,388 general surgery cases lasting 30 minutes or longer identified that regular cannabis consumption was associated with an increased risk of PONV and a slight increase in the marginal probability of PONV.[92] Propofol inhibition of FAAH increases the amount of AEA in the brain; therefore, propofol's antiemetic properties can be attributed to the cannabinoid system through the CB1-R-AEA interaction in the dorsal vagal complex.[93]

Cannabinoids and Postoperative Effects on Cognitive Function, Memory, and Learning. GABA and glutamate neurotransmitters are essential to synaptic transmission and plasticity in the hippocampus. These processes are necessary components of the learning and memory processes and include the storage and conservation of information required for the development of recent memory (spatial or nonspatial) and long-term memory.[40] Endogenous cannabinoids are regulatory factors for the interaction between the frontal cortex and the hippocampus, which is involved in the mechanism of memory and learning.[41] The activation of CB1-R, highly expressed in the hippocampus, by exogenous cannabinoids such as Δ^9-THC inhibits the release of GABA in the GABAergic interneurons and glutamate in the axonal terminals, disrupting the synchronized activity of these cortical and subcortical neural circuits.[56,94] Barbieri et al[95] reported that the acute use of synthetic CB1 and CB2 agonists impairs synaptic plasticity in CA1 hippocampal cells. It is well known that cholinergic activity in the prefrontal cortex and hippocampus is essential in regulating cognitive functions, including memory and learning. Some reports indicate that activation of the CB1-Rs may inhibit the release of acetylcholine in the human neocortex, leading to cholinergic system dysregulation and transmission in some cerebral regions, such as the hippocampus and neocortex, which could be associated with the

cognitive deficits observed in cannabis users after general anesthesia.[96]

Cannabinoids and Neuraxial Anesthesia. To date, there is a notable lack of clinical studies involving cannabis users undergoing neuraxial anesthesia. The existing evidence is insufficient to establish any pharmacological interaction between cannabis use and neuraxial anesthesia.

CONCLUSIONS

Cannabis legalization at the state level, as well as the use of medical cannabinoids, may continue to increase in the upcoming years. As a result, the chances of perioperative health care providers treating cannabis recreational or medical users in any surgical setting will increase. Acute and chronic cannabinoid exposure results in pharmacological interactions with medications that are of everyday use during the perioperative period, such as opioids, inhalation, and intravenous anesthetics. Although the exact mechanisms of drug interactions between cannabinoids, inhaled agents, intravenous anesthetics, and opioids during the perioperative period may not be well understood, the effects resulting from the interplay between cannabinoids and neuronal transmission and excitation at different levels of the nervous system are unquestionable.

Outlining the results reported in clinical studies and case reports, the contradictions resulting from the pharmacological interactions between cannabinoids and anesthetic drugs in animals and humans are notable. All of the existing evidence in humans shows that an increase in anesthetic requirements for both inhalational agents and intravenous anesthetics dependent on GABAergic neurotransmission accompanies the presence of cannabinoids at the time of anesthesia. The opposite has been reported when cannabis users use NMDA receptor antagonist agents such as ketamine or N_2O. CBs have been successful in treating chemotherapy-induced nausea and vomiting. Nonetheless, cannabis users undergoing general anesthesia may present PONV. Postoperative delirium, cognitive dysfunction, and alterations in recent and long-term memory and learning have also been described in cannabis users undergoing general anesthesia. No adverse events attributable to the interaction between CBs and neuromuscular relaxants and neuraxial anesthesia have been published in humans.

Most of the current clinical evidence about the interactions between CB and the drugs used in anesthesia is based on a few prospective and retrospective studies with small sample sizes, as well as clinical case reports; therefore, future research requires the design of prospective, randomized studies that allow these interactions and their perioperative consequences to be determined more accurately, retrospective cohort studies with data extracted from national databases that can provide more extensive clinical, epidemiological information about the incidence of perioperative outcomes of these interactions, and the design of practical clinical guidelines or consensus documents for the perioperative care of cannabis users since there is not sufficient evidence for guidelines. ■

ACKNOWLEDGMENTS

The authors acknowledge Jillian Tishko for their editing collaboration (Ms Tishko provided authorization to be named on this publication).

DISCLOSURES

Conflicts of Interest: None. **Funding:** None. **This manuscript was handled by:** Ken B. Johnson, MD.

REFERENCES

1. Maccarrone M. Phytocannabinoids and endocannabinoids: different in nature. *Rend Lin Sci Fis Nat*. 2020;31:931–938.
2. Johnson R. Defining hemp: a fact sheet. *Cong Res Ser*. 2019;44742:1–12.
3. Haney M. Perspectives on cannabis research—Barriers and recommendations. *JAMA Psych*. 2020;77:994–995.
4. Schuster J, Ates M, Brune K, Gühring H. The cannabinoids R (−)-7-hydroxy-delta-6-tetra-hydrocannabinol-dimethylheptyl (HU-210), 2-O-arachidonoylglycerylether (HU-310) and arachidonyl-2-chloroethylamide (ACEA) increase isoflurane provoked sleep duration by activation of cannabinoids 1 (CB1)-receptors in mice. *Neurosci Lett*. 2002;326:196–200.
5. Uršič M, Babič A, Vake T, Snoj T. The impact of cannabidiol on the induction of isoflurane anesthesia and recovery in wistar rats. *Cannabis Cannabinoid Res*. 2021;7:289–293.
6. Brand P-A, Paris A, Bein B, et al. Propofol sedation is reduced by δ9-tetrahydrocannabinol in mice. *Anesth Analg*. 2008;107:102–106.
7. Ruesch D, Brand P, Schneider H, Hoecker J, Wulf H. Potentiation of GABA-A receptors by propofol is inhibited by Delta9-tetrahydrocannabinol: 7AP5-3. *Eur J Anaesthesiol*. 2008;25:102.
8. Holmen IC, Beach JP, Kaizer AM, Gumidyala R. The association between preoperative cannabis use and intraoperative inhaled anesthetic consumption: a retrospective study. *J Clin Anesth*. 2020;67:109980.
9. Bicket MC, Ladha KS, Boehnke KF, et al. The association of cannabis use after discharge from surgery with opioid consumption and patient-reported outcomes. *Ann Surg*. 2024;279:437–442.
10. Moon AS, LeRoy TE, Yacoubian V, Gedman M, Aidlen JP, Rogerson A. Cannabis use is associated with increased use of prescription opioids following posterior lumbar spinal fusion surgery. *Global Spine J*. 2024;14:204–210.
11. Cichewicz DL, McCarthy EA. Antinociceptive synergy between Δ9-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther*. 2003;304:1010–1015.
12. Howlett A, Fleming R. Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response in neuroblastoma cell membranes. *Mol Pharmacol*. 1984;26:532–538.
13. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*. 1993;365:61–65.

14. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sci*. 2004;74:1317–1324.
15. Cichewicz DL, Welch SP. Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral Δ9-tetrahydrocannabinol. *J Pharmacol Exp Ther*. 2003;305:812–817.
16. Welch SP. Interaction of the cannabinoid and opioid systems in the modulation of nociception. *Int Rev Psychiatry*. 2009;21:143–151.
17. Busquets-Garcia A, Bains J, Marsicano G. CB1 receptor signaling in the brain: extracting specificity from ubiquity. *Neuropsychopharmacology*. 2018;43:4–20.
18. Meyer HC, Lee FS, Gee DG. The role of the endocannabinoid system and genetic variation in adolescent brain development. *Neuropsychopharmacology*. 2018;43: 21–33.
19. Mackie K. Cannabinoid receptors: where they are and what they do. *J Neuroendocrinol*. 2008;20:10–14.
20. Morales P, Reggio PH. An update on non-CB1, non-CB2 cannabinoid related G-protein-coupled receptors. *Cannabis Cannabinoid Res*. 2017;2:265–273.
21. Lu H-C, Mackie K. Review of the endocannabinoid system. *Biol Psych*. 2021;6:607–615.
22. Morales P, Hurst DP, Reggio PH. Molecular targets of the phytocannabinoids: A complex picture. In: Kinghorn AD, Falk H, Gibbons S, Kobayashi Ji, eds. *Phytocannabinoids: Unraveling the Complex Chemistry and Pharmacology of Cannabis sativa*. Springer International Publishing; 2017:103–131.
23. Nomura DK, Morrison BE, Blankman JL, et al. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. *Science*. 2011;334:809–813.
24. Bie B, Wu J, Foss JF, Naguib M. An overview of the cannabinoid type 2 receptor system and its therapeutic potential. *Curr Opin Anaesthesiol*. 2018;31:407–414.
25. Komorowska-Müller JA, Schmöle A-C. CB2 receptor in microglia: The guardian of self-control. *Int J Mol Sci* . 2020;22:19.
26. Haney M. Cannabis use and the endocannabinoid system: a clinical perspective. *Am J Psychiatry*. 2022;179:21–25.
27. Sharir H, Abood ME. Pharmacological characterization of GPR55, a putative cannabinoid receptor. *Pharmacol Ther*. 2010;126:301–313.
28. Howlett AC, Thomas BF, Huffman JW. The spicy story of cannabimimetic indoles. *Molecules*. 2021;26:6190.
29. Alger BE, Kim J. Supply and demand for endocannabinoids. *Trends Neurosci*. 2011;34:304–315.
30. Viader A, Blankman JL, Zhong P, et al. Metabolic interplay between astrocytes and neurons regulates endocannabinoid action. *Cell Rep*. 2015;12:798–808.
31. Araque A, Castillo PE, Manzoni OJ, Tonini R. Synaptic functions of endocannabinoid signaling in health and disease. *Neuropharmacology*. 2017;124:13–24.
32. Matias I, Di Marzo V. Endocannabinoid synthesis and degradation, and their regulation in the framework of energy balance. *J Endocrinol Invest*. 2006;29:15.
33. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. *Int J Mol Sci* . 2018;19:833.
34. Pistis M, Melis M. From surface to nuclear receptors: the endocannabinoid family extends its assets. *Curr Med Chem*. 2010;17:1450–1467.
35. Lu H-C, Mackie K. An introduction to the endogenous cannabinoid system. *Biol Psychiatry*. 2016;79:516–525.
36. Luchicchi A, Pistis M. Anandamide and 2-arachidonoylglycerol: pharmacological properties, functional features, and emerging specificities of the two major endocannabinoids. *Mol Neurobiol*. 2012;46:374–392.
37. Babalonis S, Haney M, Malcolm RJ, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend*. 2017;172:9–13.
38. Sigel E, Baur R, Rácz I, et al. The major central endocannabinoid directly acts at GABAA receptors. *Proc Natl Acad Sci USA*. 2011;108:18150–18155.
39. James SP, Bondugji D. Gamma-Aminobutyric Acid (GABA) and the endocannabinoids: understanding the risks and opportunities. *Nat Drugs Plants*. 2022 May:1.
40. Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. *Neuron*. 2002;35:625–641.
41. Drew WG, Miller LL. Cannabis: neural mechanisms and behavior–a theoretical review. *Pharmacology*. 1974;11:12–32.
42. Rodríguez-Muñoz M, Sánchez-Blázquez P, Merlos M, Garzón-Niño J. Endocannabinoid control of glutamate NMDA receptors: the therapeutic potential and consequences of dysfunction. *Oncotarget*. 2016;7:55840–55862.
43. Nasrin S, Watson CJ, Bardhi K, Fort G, Chen G, Lazarus P. Inhibition of UDP-glucuronosyltransferase enzymes by major cannabinoids and their metabolites. *Drug Metab Dispos*. 2021;49:1081–1089.
44. Smith RT, Gruber SA. Contemplating cannabis? The complex relationship between cannabinoids and hepatic metabolism resulting in the potential for drug-drug interactions. *Front Psychiatry*. 2023;13:1055481.
45. Zendulka O, Dovrtelová G, Nosková K, et al. Cannabinoids and cytochrome P450 interactions. *Curr Drug Metab*. 2016;17:206–226.
46. Sánchez-Blázquez P, Rodríguez-Muñoz M, Garzón J. The cannabinoid receptor 1 associates with NMDA receptors to produce glutamatergic hypofunction: implications in psychosis and schizophrenia. *Front Pharmacol*. 2014;4:169.
47. Pertwee R. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153:199–215.
48. da Fonseca Pacheco D, Romero TRL, Duarte IDG. Ketamine induces central antinociception mediated by endogenous cannabinoids and activation of CB1 receptors. *Neurosci Lett*. 2019;699:140–144.
49. Nielsen S, Sabioni P, Trigo JM, et al. Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. *Neuropsychopharmacology*. 2017;42:1752–1765.
50. Viganò D, Rubino T, Vaccani A, et al. Molecular mechanisms involved in the asymmetric interaction between cannabinoid and opioid systems. *Psychopharmacology (Berl)*. 2005;182:527–536.
51. Nielsen S, Picco L, Murnion B, et al. Opioid-sparing effect of cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies. *Neuropsychopharmacology*. 2022;47:1315–1330.
52. Corchero J, Oliva JM, García-Lecumberri C, Martin S, Ambrosio E, Manzanares J. Repeated administration with δ9-tetrahydrocannabinol regulates μ-opioid receptor density in the rat brain. *J Psychopharmacol*. 2004;18:54–58.
53. Oz M, Tchugunova Y, Dinc M. Differential effects of endogenous and synthetic cannabinoids on voltage-dependent calcium fluxes in rabbit T-tubule membranes: comparison with fatty acids. *Eur J Pharmacol*. 2004;502:47–58.
54. Allard B. From excitation to intracellular Ca2+ movements in skeletal muscle: Basic aspects and related clinical disorders. *Neuromusc Dis*. 2018;28:394–401.

55. Ruffolo G, Gaeta A, Cannata B, et al. GABAergic neurotransmission in human tissues is modulated by cannabidiol. *Life*. 2022;12:2042.
56. Laaris N, Good CH, Lupica CR. Δ9-tetrahydrocannabinol is a full agonist at CB1 receptors on GABA neuron axon terminals in the hippocampus. *Neuropharmacology*. 2010;59:121–127.
57. Lazarini-Lopes W, Do Val-da Silva RA, da Silva-Júnior RM, Leite JP, Garcia-Cairasco N. The anticonvulsant effects of cannabidiol in experimental models of epileptic seizures: From behavior and mechanisms to clinical insights. *Neurosci Biobehav Rev*. 2020;111:166–182.
58. Ibancovichi JA, Chávez-Monteagudo JR, Sánchez-Aparicio P, De Paz-Campos MA. Repeated administration of the cannabinoid WIN alters the isoflurane-sparing effect of morphine and dexmedetomidine. *Veter Sci*. 2023;10:310.
59. Patel S, Wohlfeil ER, Rademacher DJ, et al. The general anesthetic propofol increases brain N-arachidonylethanolamine (anandamide) content and inhibits fatty acid amide hydrolase. *Br J Pharmacol*. 2003;139:1005–1013.
60. Nelson L, Guo T, Lu J, Saper C, Franks N, Maze M. The sedative component of anesthesia is mediated by GABA A receptors in an endogenous sleep pathway. *Nat Neurosci*. 2002;5:979–984.
61. Flisberg P, Paech M, Shah T, Ledowski T, Kurowski I, Parsons R. Induction dose of propofol in patients using cannabis. *Eur J Anaesthesiol*. 2009;26:192–195.
62. Thakkar H, Mahindajit A, Taylor D, Roberts L, Cooke J. Conscious sedation for transoesophageal echocardiography in cannabis users. *Heart Lung Circ*. 2017;26:S254.
63. Zhang BH, Saud H, Sengupta N, et al. Effect of preoperative cannabis use on perioperative outcomes: a retrospective cohort study. *Regional Anesth Pain Med*. 2021;46:650–655.
64. Cohen K, Weizman A, Weinstein A. Modulatory effects of cannabinoids on brain neurotransmission. *Eur J Neurosci*. 2019;50:2322–2345.
65. de Fonseca FR, Del Arco I, Martín-Calderón JL, Gorriti MA, Navarro M. Role of the endogenous cannabinoid system in the regulation of motor activity. *Neurobiol Dis*. 1998;5:483–501.
66. Liu Q, Bhat M, Bowen WD, Cheng J. Signaling pathways from cannabinoid receptor-1 activation to inhibition of N-methyl-D-aspartic acid mediated calcium influx and neurotoxicity in dorsal root ganglion neurons. *J Pharmacol Exp Ther*. 2009;331:1062–1070.
67. Richtig G, Bosse G, Arlt F, von Heymann C. Cannabis consumption before surgery may be associated with increased tolerance of anesthetic drugs: A case report. *Int J Case Rep Images*. 2015;6:436–439.
68. Symons I. Cannabis smoking and anaesthesia. *Anaesthesia*. 2002;57:1142–1143.
69. Parolaro D, Rubino T, Vigano D, Massi P, Guidali C, Realini N. Cellular mechanisms underlying the interaction between cannabinoid and opioid system. *Curr Drug Targets*. 2010;11:393–405.
70. Vigano D, Rubino T, Parolaro D. Molecular and cellular basis of cannabinoid and opioid interactions. *Pharmacol Biochem Behav*. 2005;81:360–368.
71. Scavone J, Sterling R, Van Bockstaele E. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience*. 2013;248:637–654.
72. Navarro M, Carrera M, Fratta W, et al. Functional interaction between opioid and cannabinoid receptors in drug self-administration. *J Neurosci*. 2001;21:5344–5350.
73. Abdallah FW, Hussain N, Weaver T, Brull R. Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis. *Regional Anesth Pain Med*. 2020;45:509–519.
74. Gazendam A, Nucci N, Gouveia K, Abdel Khalik H, Rubinger L, Johal H. Cannabinoids in the management of acute pain: A systematic review and meta-analysis. *Cannabis Cannabinoid Res*. 2020;5:290–297.
75. Suhre W, O'Reilly-Shah V, Van Cleve W. Cannabis use is associated with a small increase in the risk of postoperative nausea and vomiting: a retrospective machine-learning causal analysis. *BMC Anesthesiol*. 2020;20:1–8.
76. Morsch M, Protti DA, Cheng D, et al. Cannabinoid-induced increase of quantal size and enhanced neuromuscular transmission. *Sci Rep*. 2018;8:1–8.
77. Ghovanloo M-R, Choudhury K, Bandaru TS, et al. Cannabidiol inhibits the skeletal muscle Nav1. 4 by blocking its pore and by altering membrane elasticity. *J Gen Physiol*. 2021;153:e202012701.
78. Dupriest K, Rogers K, Thakur B, Venkatachalam AM, Stutzman SE. Postoperative pain management is influenced by previous cannabis use in neurosurgical patients. *J Neurosci Nurs*. 2021;53:87–91.
79. Sajdeya R, Rouhizadeh M, Cook RL, et al. Cannabis use and acute postoperative pain outcomes in older adults: a propensity matched retrospective cohort study. *Regional Anesth Pain Med*. 2024:rapm–2024-105633.
80. Wiseman LK, Mahu IT, Mukhida K. The effect of preoperative cannabis use on postoperative pain following gynaecologic oncology surgery. *J Obstet Gynaecol Can*. 2022;44:750–756.
81. Massi P, Vaccani A, Romorini S, Parolaro D. Comparative characterization in the rat of the interaction between cannabinoids and opiates for their immunosuppressive and analgesic effects. *J Neuroimmunol*. 2001;117:116–124.
82. Liu CW, Bhatia A, Buzon-Tan A, et al. Weeding out the problem: the impact of preoperative cannabinoid use on pain in the perioperative period. *Anesth Analg*. 2019;129:874–881.
83. Salottolo K, Peck L, Tanner Ii A, et al. The grass is not always greener: a multi-institutional pilot study of marijuana use and acute pain management following traumatic injury. *Patient Safety Surg*. 2018;12:1–8.
84. Ekrami E, Sari S, Kopac O, et al. Association Between Cannabis Use and Opioid Consumption, Pain, and Respiratory Complications After Surgery: A Retrospective Cohort Analysis. *Anesth Analg*. 2022;139:724–733.
85. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. *Eur Neurol*. 2017;78:320–329.
86. Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain*. 2018;159:1932–1954.
87. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2018;3:CD012182.
88. Ruffle JK, Bajgoric S, Samra K, Chandrapalan S, Aziz Q, Farmer AD. Cannabinoid hyperemesis syndrome: an important differential diagnosis of persistent unexplained vomiting. *Eur J Gastroenterol Hepatol*. 2015;27:1403–1408.
89. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science*. 2005;310:329–332.
90. Kleine-Brueggeney M, Greif R, Brenneisen R, Urwyler N, Stueber F, Theiler LG. Intravenous

delta-9-tetrahydrocannabinol to prevent postoperative nausea and vomiting: a randomized controlled trial. *Anesth Analg*. 2015;121:1157–1164.
91. Van Sickle MD, Oland LD, Ho W, et al. Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. *Gastroenterology*. 2001;121:767–774.
92. Levin DN, Dulberg Z, Chan A-W, Hare GM, Mazer CD, Hong A. A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. *Can J Anaesth*. 2017;64:385–395.
93. Schelling G, Hauer D, Azad SC, et al. Effects of general anesthesia on anandamide blood levels in humans. *Anesthesiology*. 2006;104:273–277.
94. Lupica CR, Hu Y, Devinsky O, Hoffman AF. Cannabinoids as hippocampal network administrators. *Neuropharmacology*. 2017;124:25–37.
95. Barbieri M, Ossato A, Canazza I, et al. Synthetic cannabinoid JWH-018 and its halogenated derivatives JWH-018-Cl and JWH-018-Br impair Novel Object Recognition in mice: Behavioral, electrophysiological and neurochemical evidence. *Neuropharmacology*. 2016;109:254–269.
96. Steffens M, Szabo B, Klar M, Rominger A, Zentner J, Feuerstein T. Modulation of electrically evoked acetylcholine release through cannabinoid CB1 receptors: evidence for an endocannabinoid tone in the human neocortex. *Neuroscience*. 2003;120:455–465.