Cannabis, Cytochrome P450 Metabolism, and Surgical Anesthesia: A Narrative Review of Pharmacology, Interactions, and the Interpretation of Cannabinoid Testing

Cheryl Kim Straub-Lopez

Forensic Toxicologist • Expert Witness • Consultant

CK Straub-Lopez Consulting LLC (DBA: TOXPERT) · Tucson, Arizona · Available Nationwide

cheryl@toxpert.net · (520) 481-8984 · toxpert.net

"From the Inside. For Your Defense."

Abstract

Cannabis is among the most widely used psychoactive substances, yet its interactions with surgical anesthesia and the interpretation of cannabinoid testing remain incompletely appreciated. This narrative review synthesizes the pharmacology of delta-9-tetrahydrocannabinol (THC) and related cannabinoids, their metabolism by the cytochrome P450 (CYP) enzyme system, and the pharmacokinetic and pharmacodynamic consequences of cannabis use in the perioperative period. Active cannabinoids — THC and its potent metabolite 11-hydroxy-THC — contribute to additive central-nervous-system depression, increased anesthetic requirements, and cardiovascular and airway effects, whereas the inactive metabolite THC-COOH serves only as a long-lived marker of past exposure. Cannabidiol, though non-intoxicating, is a potent CYP inhibitor that can prolong the action of several anesthetic agents. The review emphasizes that cannabinoid

testing is difficult to interpret, particularly around surgery: blood THC is a moving target subject to rapid redistribution and possible re-release from fat stores during fasting and stress, detection windows depend heavily on assay and cutoff concentration, and a positive test reflects past exposure rather than impairment. Current professional guidance favors history-based screening over routine biological testing. Throughout, the strength of the underlying evidence is flagged, distinguishing well-established pharmacology from limited or emerging perioperative data.

Keywords: cannabis; tetrahydrocannabinol; cytochrome P450; anesthesia; perioperative care; drug interactions; cannabinoid testing; pharmacokinetics; forensic toxicology

1. Introduction

Cannabis use has risen sharply with expanding legalization, and a growing share of surgical patients present having recently or regularly used delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), or semi-synthetic cannabinoids such as delta-8-THC. Two practical problems follow. First, cannabinoids interact with anesthesia through both metabolism and direct physiologic effects, influencing drug levels, sedation depth, and cardiovascular and airway risk. Second, cannabinoid testing — often performed or encountered around the time of surgery — is notoriously difficult to interpret, and a positive result is frequently misread as evidence of impairment. This review brings these threads together for a broad clinical and forensic readership, with explicit attention to the strength of the underlying evidence.

2. The Cytochrome P450 System and Why It Matters

The CYP enzymes, concentrated in the liver, metabolize the majority of prescription and recreational drugs. A substrate is a drug the enzyme processes; an inhibitor slows the enzyme so substrate concentrations rise; and an inducer increases enzyme activity so concentrations fall. For prodrugs such as codeine and tramadol, metabolism creates the active drug, so the direction of any interaction is reversed. CYP3A4 alone handles roughly half of marketed drugs, and CYP2D6 is highly variable on a genetic basis; because an individual's genotype and concurrent exposures are usually unknown, the resulting variability is often difficult to predict.[8][2]

3. Cannabinoid Pharmacokinetics

THC is highly lipophilic and is stored in adipose tissue, then released slowly. Plasma THC falls quickly after use, but the terminal elimination phase is long — on the order of about 1.3 days in occasional users and roughly 5 to 13 days in frequent users.[1][2][13]

3.1 Active versus inactive cannabinoids

Cannabinoids act through two G-protein–coupled receptors, CB1 and CB2. CB1 receptors are concentrated in the central and peripheral nervous system and mediate the psychoactive, cardiovascular, and CNS-depressant effects that matter most during anesthesia; the active-versus-inactive distinction used below is therefore framed around CB1 activity. CB2 receptors, by contrast, are expressed mainly on immune and hematopoietic cells—in the spleen, tonsils, and circulating immune cells—and on microglia, where they modulate immune and inflammatory responses with little or no psychoactivity. THC is a partial agonist at both receptors, whereas CBD binds either receptor only weakly and acts largely through non-CB1/CB2 mechanisms. Because CB2 activation is primarily immunomodulatory and anti-inflammatory rather than sedating or cardiodepressant, its direct relevance to anesthetic depth and emergence is limited; interest in CB2-mediated analgesic and anti-inflammatory effects is growing, but the perioperative evidence remains emerging and largely preclinical.[2][10]

The cannabinoids fall into two camps: those active at the CB1 receptor, which contribute to the drug effect, and those that are inactive but useful as test markers. 11-Hydroxy-THC — the active metabolite formed by CYP2C9 and CYP3A4 — is roughly as potent as delta-9-THC (or more) and predominates after edibles, so it adds directly to the central-nervous-system burden during anesthesia. By contrast, THC-COOH (the “carboxy” metabolite) is inactive, does not cross into the brain, and matters only as the long-lasting urine biomarker behind a positive test.[1][2][13]

Among the other cannabinoids, delta-8-THC is a milder isomer of delta-9 (roughly half to three-quarters the potency) that acts at the same CB1 receptor; it would be expected to contribute similarly but less strongly, although the dedicated anesthesia evidence is limited and largely inferred. Two forensic wrinkles deserve emphasis: standard immunoassays often cannot distinguish delta-8 from delta-9, and hemp-derived delta-8 products are loosely regulated with variable content. CBD (cannabidiol) is non-intoxicating at CB1 but, as discussed in the next section, is a potent CYP inhibitor that can prolong the action of midazolam and fentanyl. CBN (cannabinol) is a mildly sedating breakdown product of THC and a marker of aged cannabis.

Other minor cannabinoids such as CBG (cannabigerol) lack dedicated perioperative data and are noted here only for completeness.[3][4][10]

A note on evidence strength. The core pharmacology is well established: that 11-hydroxy-THC is an active metabolite roughly as potent as delta-9, that THC-COOH is inactive and serves only as a detection marker, and that CBD inhibits CYP enzymes. What is weaker is the cannabinoid-specific anesthesia evidence — delta-8's effect on anesthesia is largely inferred from its similarity to delta-9 rather than directly studied, and the data on CBN are limited. The active-versus-inactive classification and the metabolic pathways can be treated as solid, but any compound-specific claim about anesthetic interaction (especially for delta-8 and CBN) should be treated as provisional and verified against primary sources.[2][4][10]

Table 1. Cannabinoid Comparison: Receptor Activity, CYP Metabolism, and Perioperative Relevance

Cannabinoid	CB1 Activity	Key CYP Involvement	Perioperative Relevance	Evidence
Delta-9-THC	Active agonist	Substrate: CYP2C9, 3A4	Primary psychoactive cannabinoid; additive CNS depression, tachycardia, higher anesthetic requirements	Well established
11-Hydroxy-THC	Active (≥ delta-9)	Formed by CYP2C9, 3A4	Potent active metabolite; predominates after edibles; adds to CNS burden	Well established
THC-COOH	Inactive	Downstream of 11-OH-THC	Long-lived urine biomarker; indicates prior exposure rather than current impairment	Well established
Delta-8-THC	Active (milder, ~½–¾)	Similar to delta-9	Same receptor, weaker effect; immunoassay cross-reactivity; loosely regulated products	Limited / inferred
CBD	Inactive at CB1	Potent inhibitor: 3A4, 2C9, 2C19, 2D6	Non-intoxicating but prolongs midazolam and fentanyl; present even in "THC-free" products	Well established

Cannabinoid	CB1 Activity	Key CYP Involvement	Perioperative Relevance	Evidence
CBN	Mildly sedating	THC breakdown product	Marker of aged cannabis; mild sedation	Limited

Abbreviations: CB1, cannabinoid receptor type 1; CYP, cytochrome P450. Active cannabinoids add to clinical effect; inactive species serve only as test markers. · TOXPERT · toxpert.net

4. THC–Anesthesia Pharmacokinetic Interactions

CBD is a potent inhibitor of several CYP enzymes (3A4, 2C9, 2C19, 2D6). When present — including in products marketed as "THC-free" — it can slow the clearance of anesthetic and analgesic agents such as midazolam and fentanyl, prolonging their effect and delaying emergence.[3][4]

Several anesthetic agents are themselves CYP substrates: midazolam and fentanyl (CYP3A4), ketamine (CYP2B6 and 3A4), and lidocaine (CYP3A4 and 1A2). A single measured drug level, viewed without the metabolic context, can therefore mislead. By contrast, remifentanil is cleared by plasma esterases and succinylcholine by plasma pseudocholinesterase, so their handling is largely independent of CYP interactions; inherited pseudocholinesterase deficiency, however, can prolong paralysis from a normal dose.[8][9]

Table 2. Anesthetic and Analgesic Agents: Metabolism and Cannabinoid Interaction

Agent	Metabolic Pathway	Cannabinoid Interaction	Net Effect
Midazolam	CYP3A4	Inhibited by CBD	Prolonged sedation, delayed emergence
Fentanyl	CYP3A4	Inhibited by CBD	Elevated levels, prolonged effect
Ketamine	CYP2B6, CYP3A4	Possible CBD inhibition	Possibly prolonged effect (limited data)

Agent	Metabolic Pathway	Cannabinoid Interaction	Net Effect
Lidocaine	CYP3A4, CYP1A2	Possible CBD inhibition	Altered clearance possible
Propofol	Hepatic (UGT, CYP2B6)	Tolerance / cross-tolerance in regular users	Higher dose needed for same depth
Remifentanil	Plasma esterases	Independent of CYP	Clearance largely unaffected
Succinylcholine	Plasma pseudocholinesterase	Independent of CYP	Unaffected by cannabis; prolonged paralysis if inherited deficiency
Gabapentin / pregabalin	Renal excretion (not CYP-metabolized)	Pharmacodynamic synergy with THC (α2δ channel + CB1)	Supra-additive sedation and psychomotor impairment (preclinical)

Agents cleared by CYP3A4 (midazolam, fentanyl) are most susceptible to CBD-mediated inhibition; ester- and pseudocholinesterase-cleared agents are largely independent of CYP interactions. · TOXPERT · toxpert.net

5. THC–Anesthesia Pharmacodynamic Interactions

Beyond metabolism, cannabis changes how the body responds to anesthesia. Frequent users commonly require higher doses of propofol and other sedatives to reach the same depth, reflecting tolerance and cross-tolerance.[5][7]

Additive central-nervous-system depression with propofol, benzodiazepines, opioids, and volatile agents can produce deeper sedation and delayed emergence. Cannabis smoking is associated with airway hyperreactivity and increased secretions, raising the risk of laryngospasm or bronchospasm. Acutely, THC causes dose-dependent tachycardia and increased myocardial oxygen demand, and the risk of myocardial infarction rises in the hour following use — effects that may be exaggerated by sympathomimetic or anticholinergic agents given during anesthesia.[2][5][6][11]

Gabapentinoids warrant specific mention. Gabapentin and pregabalin are common components of perioperative multimodal analgesia and are increasingly encountered in patients who also use cannabis. Although gabapentin acts through an entirely different target than THC—binding the

α2δ subunit of voltage-gated calcium channels to reduce release of excitatory neurotransmitters, whereas THC is a partial agonist at CB1 receptors—the two converge on overlapping inhibitory pathways. In a mouse neuropathic-pain model, isobolographic analysis found their interaction to be supra-additive (synergistic) rather than merely additive, with a combined ED50 roughly 1.7-fold lower than predicted for a purely additive effect, and the THC-associated effects of sedation, motor incoordination, and catalepsy appearing at amplified levels; antagonist studies further implicate the endocannabinoid system in gabapentin's analgesic action. The practical and forensic implication is that combined sedation and psychomotor impairment can exceed what either agent produces alone—and what a patient might anticipate from prior separate use of each—a point relevant both to perioperative sedative dosing and to the interpretation of apparent impairment. This synergy is documented in animal data and is not flagged on standard gabapentin labeling; corroborating human evidence is limited, so the interaction is best treated as biologically plausible and preclinically demonstrated rather than quantified in surgical patients. [16][17]

Strength of evidence varies across these effects. The acute cardiovascular effects and CBD's enzyme inhibition are well established; the airway-irritability and additive-sedation effects are moderately supported by review articles and consensus guidance; and the increased anesthetic requirement, increased postoperative pain and opioid use, and possible bleeding effects rest on a thinner, largely retrospective or preclinical base. Intraoperative awareness specifically — the concern that a standard dose may prove insufficient — is plausible but sparsely documented, and is one consideration among several rather than the dominant risk.[5][6][7]

6. Detection, Testing, and Interpretation

Detection windows vary widely by matrix and pattern of use. In blood, parent THC is typically detectable for hours to a few days; in oral fluid, roughly one to three days; and in urine (as THC-COOH) from a few days in occasional users to a month or more in heavy users. Across every matrix the same caution applies: the test reports that a substance was present, not that the person was impaired or that use was recent.[1][10][12][13]

6.1 Defining occasional versus frequent use

Following the usage in Huestis's cannabinoid pharmacokinetic work, an **occasional (infrequent) user frequent, chronic, or heavy user** [1]

6.2 Assay method and cutoff concentration

Detection windows are approximate, not fixed. Actual detectability depends heavily on the testing method (an immunoassay screen versus confirmatory GC-MS or LC-MS/MS), the matrix, and especially the cutoff concentration chosen. The common numbers are not interchangeable: a hospital urine drug screen typically reports THC-COOH by immunoassay at a 50 ng/mL cutoff (some laboratories use a more sensitive 20 ng/mL screen, with confirmation at 15 ng/mL), whereas blood testing measures parent THC in far smaller amounts, with forensic per-se thresholds typically in the single digits (often about 2 to 5 ng/mL of whole blood). A “2 ng” blood result and a “50 ng” urine result describe different analytes in different matrices and cannot be compared on a single scale.[1][10][12][13]

6.3 Preoperative testing and the “moving target” problem

Whether to test for cannabis before surgery is a recurring question, and the choice of matrix matters. A urine test detects the inactive metabolite and reflects past use over days to weeks; a positive preoperative urine result does not establish current intoxication or impairment at induction, and on its own rarely changes anesthetic management. A blood test for parent THC better reflects recent use but is not routinely performed and still correlates poorly with the degree of impairment.[1][12][13]

THC is, moreover, unusually hard to interpret in the surgical setting because a blood level is not stable. As a fat-stored drug, THC redistributes rapidly between blood and tissue, so a measured concentration can rise or fall substantially within an hour. In regular users, perioperative fasting, the surgical stress response, and lipolysis may release stored THC back into the blood, while ongoing redistribution lowers it; animal and pharmacokinetic data support this re-release, although its magnitude in humans is uncertain. A single value is therefore only a snapshot tied to its draw time, and for the most meaningful interpretation the sample should be drawn as close to surgery as possible, with the timing of both last use and the draw documented.[1][2][15]

7. What the Guidelines Say

The American Society of Regional Anesthesia and Pain Medicine (ASRA) issued the first formal U.S. consensus guideline on the perioperative cannabis patient in 2023. It recommends screening every surgical patient for cannabis use (type, route, frequency, and timing of last use); considering a delay of elective surgery for acute intoxication; counseling on perioperative risks

and encouraging reduction or abstinence beforehand; anticipating higher anesthetic and analgesic requirements and greater postoperative pain and opioid use in regular users; observing cardiovascular and airway precautions; and using multimodal analgesia while monitoring for withdrawal.[6]

Patient-facing guidance from the American Society of Anesthesiologists (ASA) likewise advises patients to disclose cannabis use, notes that regular use may increase the amount of anesthesia required, and recommends avoiding cannabis on the day of surgery. Notably, both bodies rely on screening by history rather than mandatory biological testing; the American Board of Anesthesiology certifies practitioners and does not issue such guidelines.[5][14]

8. Conclusion

Cannabis interacts with surgical anesthesia in ways that are biologically coherent but unevenly evidenced. The core pharmacology — the activity of THC and 11-hydroxy-THC, the inertness of THC-COOH, CBD's enzyme inhibition, and the long, fat-driven elimination of THC — is well established. The perioperative consequences, from higher anesthetic requirements to cardiovascular and airway risk, are plausible and partly supported but in places rest on limited data. Above all, cannabinoid testing must be interpreted with care: results reflect past exposure rather than impairment, depend heavily on assay and cutoff, and, for blood THC, represent a moving target best sampled close to the time of surgery. History-based screening, attention to the active cannabinoids, and explicit acknowledgment of evidentiary limits together offer the most defensible approach.[5][6][13]

Disclaimer

This article is an educational narrative review and does not constitute patient-specific medical or legal advice. Numeric thresholds (per-se blood limits, immunoassay cutoffs, and frequency-of-use definitions) vary by jurisdiction, laboratory, and study and are presented as typical or approximate values; primary sources should be consulted and verified for any clinical or evidentiary use.

References

1. Huestis MA. Human Cannabinoid Pharmacokinetics. Chemistry & Biodiversity. 2007;4(8):1770-1804.
2. Grotenhermen F. Pharmacokinetics and Pharmacodynamics of Cannabinoids. Clinical Pharmacokinetics. 2003;42(4):327-360.
3. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metabolism Reviews. 2014;46(1):86-95.
4. Alsherbiny MA, Li CG. Medicinal Cannabis — Potential Drug Interactions. Medicines (Basel). 2018;6(1):3.
5. Echeverria-Villalobos M, Todeschini AB, Stoicea N, et al. Perioperative care of cannabis users: A comprehensive review of pharmacological and anesthetic considerations. Journal of Clinical Anesthesia. 2019;57:41-49.
6. Shah S, Schwenk ES, Sondekoppam RV, et al. ASRA Pain Medicine consensus guidelines on the management of the perioperative patient on cannabis and cannabinoids. Regional Anesthesia & Pain Medicine. 2023;48(3):97-117.
7. Imasogie N, Rose RV, Wilson A. High quantities: Evaluating the association between cannabis use and propofol anesthesia during endoscopy. PLoS ONE. 2021;16(3):e0248062.
8. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill; 2018.
9. Gropper MA, ed. Miller's Anesthesia. 9th ed. Elsevier; 2020.
10. Sharma P, Murthy P, Srinivas Bharath MM. Chemistry, Metabolism, and Toxicology of Cannabis: Clinical Implications. Iranian Journal of Psychiatry. 2012;7(4):149-156.
11. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering Myocardial Infarction by Marijuana. Circulation. 2001;103(23):2805-2809.
12. Hadland SE, Levy S. Objective Testing: Urine and Other Drug Tests. Child and Adolescent Psychiatric Clinics of North America. 2016;25(3):549-565.
13. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 12th ed. Seal Beach, CA: Biomedical Publications; 2020.
14. American Society of Anesthesiologists (ASA). Patient guidance on cannabis use and surgery/anesthesia. Schaumburg, IL: ASA.
15. Gunasekaran N, Long LE, Dawson BL, et al. Reintoxication: the release of fat-stored delta-9-tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. British Journal of Pharmacology. 2009;158(5):1330-1337.
16. Kazantzis NP, Casey SL, Seow PW, Mitchell VA, Vaughan CW. THC and gabapentin interactions in a mouse neuropathic pain model. Neuropharmacology. 2018;144:115-121.
17. Nealon CM, Gleeson P, Finn DP. Cannabinoid receptor-mediated antinociception with acetaminophen drug combinations in rats with neuropathic spinal cord injury pain. Neuropharmacology. 2010;58(4-5):758-766.

TOXPERT

From the Inside. For Your Defense.™

Cheryl Kim Straub-Lopez · (520) 481-8984 · cheryl@toxpert.net · toxpert.net