Medical Cannabis: Understanding the Pharmacology

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The United States View of Cannabis/Marijuana

- Cannabis vs Marijuana
- Federal law: currently prohibits the use, sale, and possession of marijuana
- State Law: many states have legalized marijuana for "medical" use with an Rx
 - This makes **the** prescribers responsible for the Rx
 - big responsibility
 - Prescribe a drug that is Schedule I

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- <u>Schedule I No medical use and not able to be prescribed Marijuana, heroin, ecstasy, LSD</u>
- <u>Schedule II C</u>ocaine, methamphetamine, opium and morphine







Phytocannabinoids

Δ9-Tetrahydrocannabinol (THC)

- Binds strongly to CB1 inducing the euphoric/Psychoactive effects
- Improve nausea/vomiting
- Anticonvulsant, but can also be proconvulsant
- The psychotropic effects of Δ^9 -THC limit tolerability, and are the reason many use it for recreation

Cannabidiol (CBD)

- Low affinity for CB1 receptors, no euphoric/psychoactive effects
 - Additional molecular targets that regulate neuronal excitability – still being studied
- Neuroprotective and anti-convulsant, and anti-inflammatory
- · Well tolerated
- THC:CBD ratio is key Therapeutic and adverse effects depend on THC concentration
- International standard uses a limit of 0.3% TCH to define hemp vs drug









Indications for Cannabidiol (CBD) Alone Epilepsy/Seizures - Used to reduce frequency · Dravet syndrome and Lennox-Gastaut Syndrome · Treatment-resistant epilepsy in children/young adults • Cannabidiol (Epidiolex), artisanal CBD (eg: Charlottes Web) Chronic Pain and Inflammatory (arthritis and MSK pain) • Cancer pain, HIV-associated neuropathic pain Chemotherapy-induced nausea and vomiting Image adapted from AdobeStock_274546918.jpeg Insomnia and sleep disorders Spasms and pain (especially in multiple sclerosis) Huntington's disease Anxiety Parkinson's disease - Dystonia and Dystonia Sleep Anxiety, PTSD, Schizophrenia or schizophreniform disorder. Pain Dependency and withdrawal of cannabis Inflammation . Addiction: lower cravings (tobacco, opioids) Copyright © 2025, Dr. Andrea Efre

Indications of Medical Cannabis	
Epilepsy/seizures (children and adults)	Chronic Pain and Cancer related pain
 CBD or CBD/THC, or THC Nasal spray for immediate seizure treatment 	 Neuropathic pain (MS, HIV and traumatic or spinal injury)
 Multiple sclerosis (MS related pain, spasticity, urinary symptoms and sleep) 	 Analgesic effect: improve pain and decrease prescription drug use (Furrer et al., 2021); (Vivace et al., 2021); (Lynch & Campbell, 2011).
 Nabiximols (Sativex) (Santarossa et al, 2022, Kopel et al, 2014) 	 80% of patient would consider using THC and 90% amenable to CBD (Karakash et al., 2025)
 People with MS (n=242) use marijuana primarily for chronic pain and secondarily for sloop (link et al. 2022) 	 Improeved pain and sleep scores at 3, 6 and 12 month intervals in chronic pain (Datta et al, 2025)
	• Fibromyalgia
 Headaches 	 Systematic review: safe and effective alternative
 Headache and migraine ratings were reduced by nearly 50% after using 	for short term paid reduction in treating fibromyalgia (Strand et al, 2023)
cannabis, without overuse headaches (Cuttler et al, 2020).	 Improved Quality of Life over 3 months for patients with chronic pain and anxiety disorders (Lent et al., 2024)
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High yield THC = not medicinal 30-90% THC = recreational













Pharmacokinetics of CBD

Mechanism: Anandamide uptake inhibitor, Inhibits adenosine uptake, Inhibits FAAH and release of proinflammatory cytokines and expression of transcription factors. Inhibits calcium, potassium, and sodium channels by noncompetitive antagonism

Metabolism: Hepatic, via CYP1A1, 1A2, 2C8, 2C9, **2C19, 3A4,** and **2D6**; UGT1A9 and UGT2B7; undergoes hydroxylation

Distribution: Time dependent, fatty tissues and highly perfused organs such as brain, heart, lung, and liver

Elimination: Feces and urine; t1/2: 18–32 h

(Page et al, 2020)

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Inhalation:

- Onset: Onset: 3-5 min
- Bioavailability: Duration: 2-3 h
- Bioavailability: 11%-45%

Oral: Onset

- Onset: hours
- Duration: 12–24 h
- Bioavailability: 6%-33%

Transdermal: not known Transrectal: not known





Cannabinoid Interactions with Cardiac Medications

- Beta Blocker
- Cannabinoids and CBD alone may increase serum concentrations of beta-blockers such as metoprolol (Lopressor®)
- Potentially leading to enhanced hypotensive effects and bradycardia

Calcium Channel Blockers

- Cannabinoids may elevate levels of calcium channel blockers
- Diltiazem and verapamil are metabolized by CYP3A4
- Increased concentrations lead to hypotension, bradycardia, dizziness

Statins

- Cannabinoid use may increase plasma concentrations of statins metabolized by CYP3A4, such as atorvastatin (Lipitor®)
- Potentially enhancing adverse effects like myopathy.

Cannabinoid Interactions with Cardiac Medications

Clopidogrel (Plavix) (Inhibit platelet aggregation)

- Is a Pro-Drug and uses CYP enzyme metabolism to convert to its active metabolite
- CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 are used for activation (Sangkuhl, et al,. 2010)
- By inhibiting conversion from pro-drug to active drug clopidogrel never gets to work
- Therefore, Decreased antiplatelet effect of clopidogrel = higher incidence of adverse cardiovascular events
- · Risk or stroke, clots, re-occlusions
- Drugs that inhibit the CYP2C19 (like CBD and PPIs) prevent the drug from becoming an active metabolite

Cilostazol (Pletal) Antiplatelet

- PDE3 inhibitor
- Indicated for Intermittent claudication
- It can treat intermittent problems with blood flow in the legs (claudication) by enabling people to walk longer distances with less pain
- Cannabis inhibits metabolism
- Thereby increase the level or effect of cilostazol
- Cannabis inhibits CYP3A4and 2C19 metabolism.
- Increase the risk of adverse events like headache, diarrhea, hypotension, tachycardia and possible cardiac arrhythmias

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Cannabinoid Interactions with Cardiac Medications

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Direct Oral AntiCoagulants (DOACs)

- Dabigratran (Pradaxa), apixaban (Eliquis), rivaroxaban (Xarelto,) and edoxaban (Savaysa).
- CYP3a4 and CYP2C19
- Inhibited metabolism
- Increased levels of DOACs, resulting in higher risk for bleeding,
- Warranting close monitoring of these anticoagulants with CBD as well.

Digoxin

- May interact with CBD through inhibition of P-gp
- potential to increase digoxin's area under the curve. As digoxin has a narrow therapeutic index, patients should be monitored patients more closely. Some patients may require a digoxin dose reduction by 15% to 30% or a modification in their therapeutic regimen.

Additional Potential Drug-to-Drug Interactions

- Levothyroxine: Cannabis can increase levothyroxine metabolism making the medication less effective
- Anti-epileptic medications: carbamazepine, topiramate, phenytoin, valproate, and benzodiazepines (Devinsky, et al, 2018)
- Phenytoin (which is CYP2C9, 2C19, and 3A4 inducer)
- Clobazam (increased risk of benzodiazepine toxicity)
- Theophylline, clozapine and olanzapine (reduced efficacy).
- Antibiotics: sulfamethoxazole (Bactrim) with cannabis may increase effects of cannabis – may increase THC levels (boost the psychoactive effect)
- Rifampin is a strong CYP3A4 inducer decreases cannabis effects
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Interactions are different based on strength of inducer or inhibito

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Potential Drug-to-Drug Interactions

- Sildenafil: Myocardial infarction (possible CYP3A-4 and CYP2C9 interaction)
- Opioids: Cross-tolerance and excessive CNS depression
- Barbiturates: Excessive CNS depression
- · Benzodiazepines: Excessive CNS depression
- Protease inhibitors: Reduced effectiveness related to decreased plasma drug levels (possible CYP3A-4 interaction)
- SSRIs: Psychiatric disturbance (possible CYP2C9 interaction) eg fluoxetine
- Theophylline: Reduced effectiveness related to decreased plasma drug levels (increased clearance) (Horvath et al, 2019).

 Tricyclic antidepressants: Tachycardia, delirium (possible CYP2C9 interaction)

- Anticholinergics: Tachycardia, delirium
- Adrenergic agonists: Hypertension and Tachycardia
- Naltrexone: Enhanced euphoria
- Disulfiram: Hypomania
- Lithium: Increased plasma concentrations
- Neuroleptic antipsychotics: Reduced effectiveness; increased extrapyramidal effects
- Corticosteroids: Enhanced immunosuppression
- Propofol: Diminished effectiveness

Anesthesia, Sedation and Pain – Considerations for pre-op clearance and pre-procedure discussions

- Significantly higher quantities of propofol are needed for sedation (Kosirog, 2024) (Imasogie et al, 2021)
- Requires more anesthesia and higher doses of propofol for induction and sedation (Everett et al, 2021) and (Horvath et al, 2019) (Imasogie et al, 2021) (Echeverria et al, 2019)
- THC prolongs the action of some intravenous anesthetics such as pentobarbital, thiopental, ketamine, propanidid and alfaxolone/alfadolone (Althesin®) (Echeverria et al 2019)
- Pain control is more difficult to achieve in patients who use marijuana (Aleissa et al, 2020)
 - Marijuana group had needed more post-operative opioids (58.3 vs. 35 mg, p = 0.021) and had higher pain scores (5 vs. 4, p = 0.011) (Aleissa et al, 2020)

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Signs of Cannabis Intoxication

- Change in vision, reduce tear flow
- Conjunctival injection (red eye)
- Nystagmus and Slow pupillary response to light
- Dry mouth
- Cough, Bronchitis, pneumothorax or pneumomediastinum
- Ataxia, slurred speech, stumbling
- Dizziness or fainting symptoms
- Nausea or vomiting







Cardiovascular Complications of Marijuana Use

- New 2025 study: Myocardial Infarction and Cardiovascular Risks Associated with Cannabis Use: A Multicenter Retrospective Study
- 4.6 million patients <50yrs from 53 healthcare organizations (HCO) throughout the United States -
- The primary outcome was MI. Cannabis users aged 50 and younger were six times as likely to have an MI than those not using cannabis
- · Adverse CV events, including MI, ischemic stroke, HF and mortality.
- Cannabis use poses a substantial and independent risk for:

• ACS or MI following cannabis (within one hour of consumption) in young, healthy individuals, who present with chest pain

 Cannabis has also been implicated in endothelial dysfunction, proinflammatory cytokine release, and oxidative stress, all of which contribute to coronary microvascular dysfunction and plaque destabilization (Kamel, et al., 2025)

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Pre-Proof JACC Advances (Kamel, et al., 2025)









Pulmonary Side Effects

- Chronic marijuana smokers have similar respiratory changes to tobacco smokers:
 - · Airway irritability, cough (daily), phlegm
 - · Bronchospasm, uvular edema, airway obstruction
- Large airway inflammation (Horvath et al 2019)
- Bullous emphysema (most linked to abuse/overuse)
- Limited evidence on COPD or emphysema (need more research) ? associated wit tobacco
- Risk for respiratory symptoms/lung injury increased in adolescents who vape cannabis (Boyd et al, 2021)
- CDC: Smoked cannabis can harm lung tissues and cause scarring and damage to small blood vessels.
- An association between cannabis and lung cancer remains unclear, as most cannabis users smoke the cannabis with tobacco, which is a known cancer causative agent (Gracie, & Hancox, 2021), (Benchekroun et al, 2021), (Betser et al, 2021)



GI Adverse Effects (evaluate for overuse)

Gastroparesis

- Cannabinoid agents have significant effects on gastric motility (gastroparesis) and colonic motility (constipation) (Camilleri, 2018)
- THC has been implicated in gastroparesis development – delayed gastric emptying without mechanical obstruction (Cammarano and Villaluz, 2021)
- Slow gastric emptying means gastric contents remain after NPO prior to procedures
- Take aspiration precautions for anesthesia/procedures in those patients who use marijuana

(Cammarano and Villaluz, 2021)

Cannabinoid Hyperemesis Syndrome (CHS)

- · Associated with Compulsive hot-water bathing
- Cessation of cannabis symptoms should resolve, if they continue it is probably Cyclic Vomiting Syndrome CVS

Cannabis Use Disorder

- CDC Approximately one in three cannabis users <u>have</u> <u>cannabis use disorder</u> (CUD)
 - Cannabis-induced <u>psychosis</u>, <u>anxiety disorder</u>, <u>sleep disorder</u>, <u>cannabis hyperemesis syndrome</u>.
 - Chronic bronchitis (smoke or vape)
 - <u>Fertility issues</u>
- No treatments available to facilitate CUD treatment but some Medications are in trial

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E-cigarette, or Vaping Associated Lung Injury (EVALI) Vaping Associated Lung Injury (VALI)

- · Mostly in recreational use
- Majority of vapers with EVALI reported using THC and/or CBD (formulated with oils, such as vitamin E acetate)
- 17% reported using only nicotine vaping products, which are not routinely mixed with vitamin E acetate
- Vaping cessation counselling and follow-up (Odish et al, 2020)

- EVALI is a heterogeneous collection of pneumonitis patterns that include:
 - Acute eosinophilic pneumonia
 - Organizing pneumonia
 - · Lipoid pneumonia
 - · Diffuse alveolar damage or hemorrhage
 - Acute respiratory distress syndrome (ARDS)
 - Hypersensitivity pneumonitis
 - · Peribronchiolar granulomatous pneumonitis
 - Rare giant-cell interstitial pneumonitis (Henry, et al 2020).
 - The CDC has an Algorithm for management of Outpatient EVALI. Located at www.CDC.gov

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International Approaches

- The UK, Canada and some European countries are tracking information and establishing data through registries
- Canada government site tracks cannabis and Cannabis research and data including data on related side effects https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis.html
- The Quebec Cannabis Registry: Investigating the Safety and Effectiveness of Medical Cannabis
- UK Medical Cannabis Registry a privately funded organization of the Curaleaf Clinic
- French Addictovigilance Network https://addictovigilance.aphp.fr/about-us/
 - Mandatory reporting all cases related to drug dependence, drug abuse or psychoactive substances misuse cases
 - Report acute cardiovascular events associated with marijuana (Latif & Garg, 2020).
 - Hyperemesis syndrome (Bouquet et al, 2021)



Nurse/Provider Considerations

- Identify patients who use marijuana and monitor for adverse effects
- Subjective data collection (admission) remember to ask about all forms of marijuana
- Medically, there is a difference between THC and CBD and whole plant
- Based on type of cannabis used Evaluate risk vs benefits
- Consider the pharmacokinetics/interactions with Rx medications
- Medication reconciliation
 - Be aware marijuana affects the metabolism of other medication
 - Effect medications requiring balance: including cardiac drugs
 - Sedation and anesthesia adaptions may need to be made
 - Consider increased monitoring of competitive medications







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