

Cannabis for Pain: Pearls & Pitfalls

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Speakers*

Contributors

Mikhail Kogan, MD*

Medical Director, Center for Integrative Medicine
Associate Professor of Medicine
George Washington University, School of Medicine

Leslie Mendoza Temple, MD*

Medical Director, Integrative Medicine Program
Endeavor Health
Clinical Professor of Family Medicine
University of Chicago Pritzker School of Medicine

Jessica Wright, PharmD, BCACP*

Pharmacogenomics Pharmacist,
Department of Pharmacy
Assistant Professor of Pharmacy
Mayo Clinic

Siddhant Yadav, MD* (Moderator)

Assistant Professor of Medicine,
Department of Medicine
Mayo Clinic

Linda Huang, PharmD, BCPS, BCACP

Clinical Pharmacist
Department of Pharmacy
Mayo Clinic

Abhinav Singla, MD

Assistant Professor of Medicine
Department of Medicine
Mayo Clinic

Basant Katamesh, MBChB

Research Fellow
Department of Medicine
Mayo Clinic

Ann Vincent, MD

Professor of Medicine
Department of Medicine
Mayo Clinic

Disclosures

Leslie Mendoza Temple, MD

Scientific Advisory Board Member

Ashford International, an independent lab testing and consumer platform for CBD hemp products.

Mikhail Kogan, MD

Royalties, Medical Marijuana Book, 2021 and 2023, Pingium Random House

Jessica Wright, PharmD, BCACP

Nothing to disclose

Siddhant Yadav, MD

Nothing to disclose

Objectives



1. Summarize evidence base for medical cannabis in pain management.
2. Share clinical pearls to increase knowledge base on dosing, routes, frequency.
3. Describe pharmacology and gene-drug interactions related to cannabis
4. Describe pearls and pitfalls when recommending medical cannabis for managing pain.
5. Describe US/international legislative environment.
6. Medical cannabis education recommendations

Case 1: The depressed patient with neuropathy and spinal stenosis pain

75 year old male of **South Asian descent**
PMH: Atrial fibrillation, depression, diabetes, lumbar spinal stenosis, burning neuropathy in feet.

Medications: 4-5 hydrocodone/acetaminophen, gabapentin, fluoxetine, diltiazem, warfarin, lisinopril, aspirin, metformin, and vit B12 daily. Medications make him constipated, sleepy and foggy-brained.

Procedures: 4 epidurals in 7 years; several rounds of physical therapy, and declined surgical intervention. Acupuncture, chiropractic care and massage are intermittent due to finances/transportation limits and provide temporary relief, but it's not enough.



Case 2: The depressed patient with neuropathy and spinal stenosis pain

- **Is cannabis an option for him?**
- Any drug interactions of concern?
- Would pharmacogenomics testing be of value for him?



A Multicriteria Decision Analysis Comparing Pharmacotherapy for Chronic Neuropathic Pain, Including Cannabinoids and Cannabis-Based Medical Products

David J. Nutt,^{1,*} Lawrence D. Phillips,² Michael P. Barnes,³ Brigitta Brander,⁴ Helen Valerie Curran,⁴ Alan Fayaz,⁴ David P. Finn,⁵ Tina Horsted,⁶ Julie Moltke,⁶ Chloe Sakal,⁷ Haggai Sharon,⁸ Saoirse E. O'Sullivan,⁹ Tim Williams,¹⁰ Gregor Zorn,¹¹ and Anne K. Schlag⁷

Abstract

Background: Pharmacological management of chronic neuropathic pain (CNP) still represents a major clinical challenge. Collective harnessing of both the scientific evidence base and clinical experience (of clinicians and patients) can play a key role in informing treatment pathways and contribute to the debate on specific treatments (e.g., cannabinoids). A group of expert clinicians (pain specialists and psychiatrists), scientists, and patient representatives convened to assess the relative benefit–safety balance of 12 pharmacological treatments, including orally administered cannabinoids/cannabis-based medicinal products for the treatment of CNP in adults.

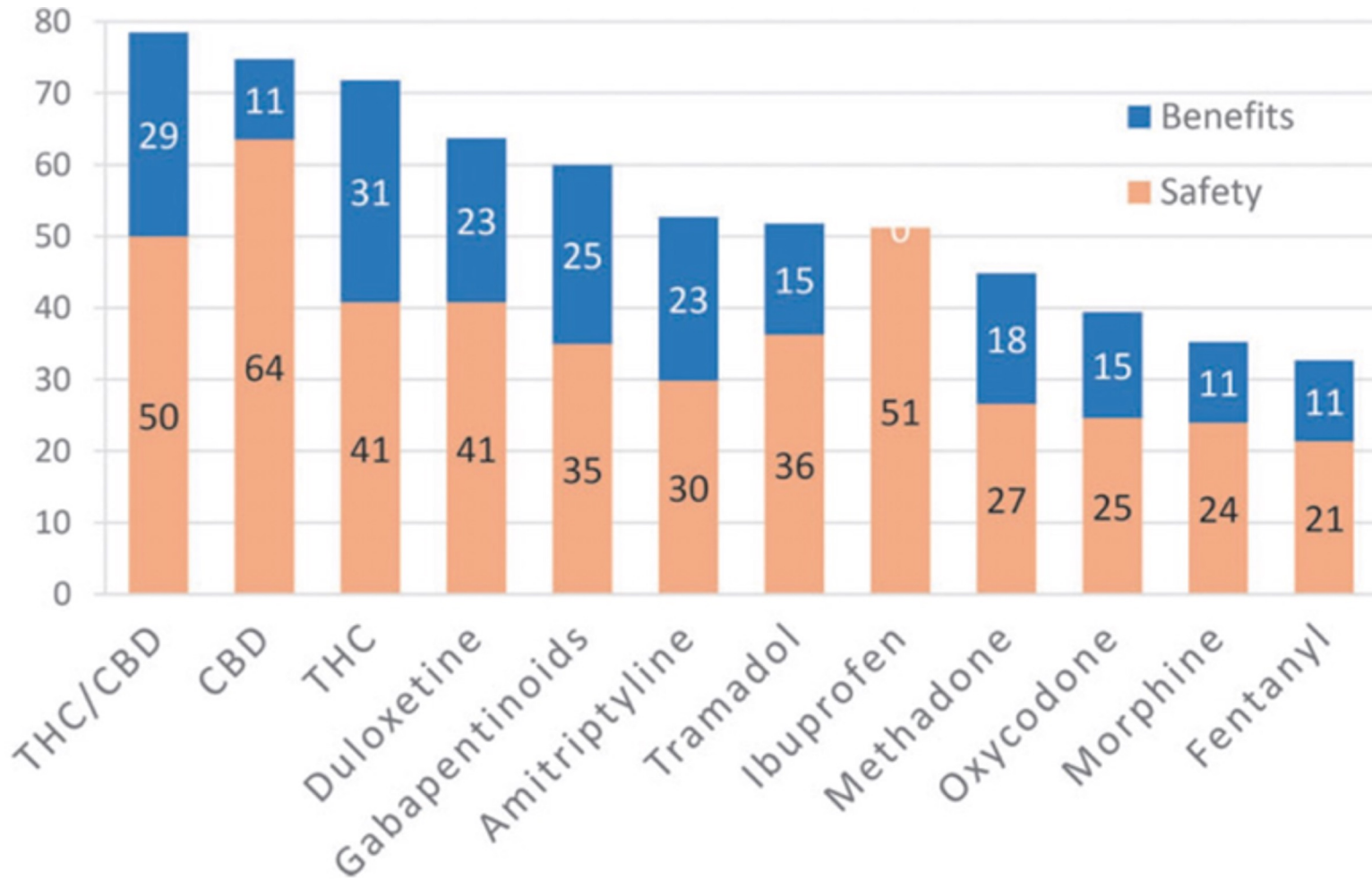


FIG. 3. The overall weighted preference values for the neuropathic pain pharmacotherapies. More blue means more benefit, more red indicates more safety.

© 2021 Nutt et al.

Case 2: The depressed patient with neuropathy and spinal stenosis pain

- Is cannabis an option for him?
- **Any drug interactions of concern?**
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What drug interactions are of concern?

- **Fluoxetine** inhibits CBD metabolism via CYP2C19 →
Increased CBD side effects
- **Diltiazem** inhibits THC + CBD metabolism via CYP3A4 →
Increased THC + CBD side effects
- CBD inhibits **warfarin** metabolism via CYP2C9 →
Increased INR
- **Hydrocodone/acetaminophen** plus **gabapentin** →
Additive CNS depressant effects

Up to Date, Inc. Accessed January 5, 2024. <http://www.uptodate.com>.

CNS Depressants

Cannabis can add to risk of CNS depressant side effects

CNS depressants: **opioids**, benzodiazepines, phenothiazines, sedative hypnotics, barbiturates, **gabapentin**, etc.

Up to Date, Inc. Accessed January 5, 2024. <http://www.uptodate.com>.

Drug interaction take home point

Several mechanisms for drug-cannabis interactions:

1. Additive CNS depressant side effects
2. Cannabis interacting with drugs
3. Drugs interacting with cannabis

Nasrin S, Watson CJW, Perez-Paramo YX, Lazarus P. Cannabinoid Metabolites as Inhibitors of Major Hepatic CYP450 Enzymes, with Implications for Cannabis-Drug Interactions. *Drug Metab Dispos.* 2021 Dec;49(12):1070-1080. doi: 10.1124/dmd.121.000442. Epub 2021 Sep 7. PMID: 34493602.

Case 2: The depressed patient with neuropathy and spinal stenosis pain

- Is cannabis an option for him?
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Prevalence of CYP2C19 & CYP2C9 variants

	Reduced CYP2C9	Reduced CYP2C19	Increased CYP2C19
Central/South Asian	40%	49%	21%
Near Eastern	39%	25%	29%
European	37%	28%	32%
African American/Afro-Caribbean	24%	35%	28%
Sub-Saharan African	27%	34%	24%
American (Native to the Americas)	17%	23%	14%
East Asian	16%	59%	3%
Pacific Islander	9%	94%	2%

Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, Klein TE. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther. 2021 Sep;110(3):563-572. doi: 10.1002/cpt.2350. Epub 2021 Jul 22. PMID: 34216021; PMCID: PMC8457105.

Pharmacogenomic Profile and Plan

- CYP2C9 *3/*3 (Poor Metabolizer)
- CYP2C19 *1/*2 (Intermediate Metabolizer)
- CYP3A4 *1/*1 (Normal Metabolizer)

- Further reduced starting dose and/or frequency of cannabis for this patient

Importance of Pharmacogenomics

Genetic variants exist that alter CYP function at baseline, including:

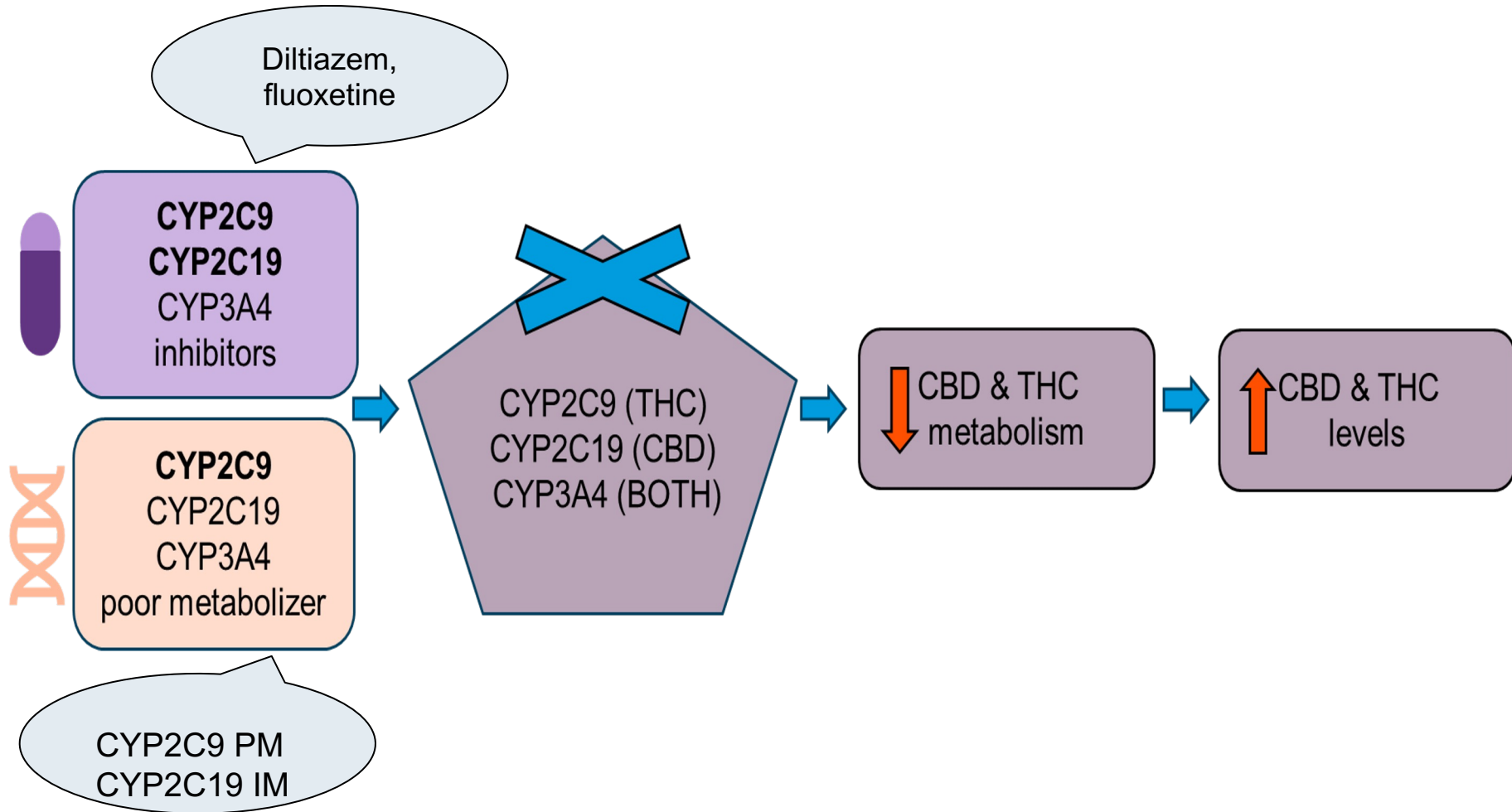
Increases THC & CBD levels: CYP2C9, CYP2C19, CYP3A4 poor or intermediate metabolizer

Decreases CBD levels:

CYP2C19 rapid and ultrarapid metabolizer

Wright J, Huang L, El-Fetouh Katamesh B, Yadav S, Singla A, Vincent A. Cannabinoid pharmacogenomics concepts and strategies for the practicing clinician. *Minnesota Medicine Magazine*. 2024;107(1):30-33.

Adding gene + drug interactions



What does this all mean?

- Theoretical and real-world scenarios may vary greatly.
- Pharmacogenomics testing may be a predictor (i.e. certain biogeographical groups, prior medication intolerances, etc.)
- Possibility for compounded effects from drug-drug and gene-drug interactions, added complexity of interactions between cannabinoids, terpenoids and other compounds in cannabis
- Adjusting starting dose of cannabis could help reduce risk of adverse effects from drug-drug and gene-drug interactions.

Case 2: The patient who smokes cannabis daily because edibles “don’t work”

52y man with fibromyalgia and PTSD insists that smoking joints are the only dosage form that works for his symptoms (pain, anxiety).

He often feels queasy.

“Edibles don’t work.”



Regarding heart disease & cannabis

Association of Cannabis Use With Cardiovascular Outcomes Among US Adults

Abra M. Jeffers, Stanton Glantz, Amy L. Byers and Salomeh Keyhani

Originally published 28 Feb 2024. Journal of the American Heart Association. 2024.

n=434,104, age 18-74y adults, mean=45.4 yrs
4% used daily; 7.1% avg 5 days/month; 88.9%
nonusers

60% white, 11.6% black, 19.3% Hispanic, 8.9%
Other; 51.1% women

Smoking cannabis = 73.8% of users in study

Association of Cannabis Use With Cardiovascular Outcomes Among US Adults

Abra M. Jeffers, Stanton Glantz, Amy L. Byers and Salomeh Keyhani

Originally published 28 Feb 2024. Journal of the American Heart Association. 2024;0:e030178

“Cannabis use has a strong independent effect in the general population and a strong association with cardiovascular outcomes independent of the effects of using tobacco cigarettes or e-cigarettes.”

A limitation of the study: no mention of the need to compare smoked cannabis vs. edibles/topical cannabis.

Cannabis Hyperemesis Syndrome

Episodic vomiting after prolonged excessive cannabis use with symptom onset >6 months, which is relieved by sustained cessation of cannabis. Other treatments:

- Hot water hydrotherapy
- Topical capsaicin
- Droperidol
- Benzodiazepines
- Haloperidol
- Propranolol
- Aprepitant



Cannabis: Routes of administration



Inhalation

Onset: minutes

Bioavailability

- THC: 10-35%
- CBD: 11-45%

Oral

Onset: 1-2 hours

Bioavailability

- THC: 4-12%
- CBD: ~6%

Buccal/Sublingual

Onset: around 30 minutes

Bioavailability

- Mixed cannabinoids: ~13-15%

Transcutaneous

Onset: variable between patches vs topical creams vs lotion

Bioavailability

- may differ based on the thickness of skin layers

Suppository

Onset: faster than oral

Bioavailability

- may be 4x compared to oral due to bypassing first metabolism

Cannabis route pearls

- **Edibles:** Takes 1-2 hours to 'kick in', lasts 6-12 hrs, great for bedtime use.
- **Oral tinctures:** 15-30 min onset
- **Smoke/vape:** immediate onset, exits faster
- **Suppositories:** rectal/vaginal- variable
- **Patch:** apply 1/2-1 patch every 12 hours
- **Topicals:** use thin layer twice daily

Practicalities in initiating THC-containing cannabinoids

- **Quantity:** Take cannabis edible (1/4th piece) at bedtime, or 1 hour before bedtime to help sleep & sleep off intoxicating effects if any.
- **Initial Timing:** Start the cannabis regimen on a night where there's not much going on the next day (i.e. Friday evening).
- **Meds Timing:** Separate pain, sleep or other psychotropic medications by 1-2 hours, ok to keep dose the same when initiating medical cannabis regimen.
- **Meds Dosing:** Reduce dose of sleep and pain meds gradually as appropriate with cannabis intake.

Edibles: Be wary of accidental ingestion- especially for kids



Some experts say cannabis product packaging may appear similar to other snacks, which can confuse kids.
skodonnell via Getty Images

THC Dosing pearls

- Let the THC quantity drive the dose.
- Starting dose for cannabis naïve: 1.25-2.5 mg THC plus variable CBD content.
- Edibles: Increase by 1-2.5 mg THC increments nightly or;
- Tinctures: Start with the same dose of THC in oral tincture. Increase the mg of THC 2-3 hours following the previous dose if needed in increments of 1 to 5 mg THC each time, depending on patient.

Case 3: The chronic cannabis user who gets an infection

48y woman using medical cannabis nightly, and occasionally in the afternoons for chronic low back pain and insomnia. Tolerating cannabis well.

Diagnosed with complicated UTI. Started on sulfamethoxazole-trimethoprim DS 1 tab twice daily x 7 days. Has tolerated antibiotic without side effects in the past.

Dizziness ensues after 3 days of treatment while also using cannabis as usual.



Cannabis side effects

PSYCHIATRIC	CENTRAL NERVOUS SYSTEM / COGNITION	RESPIRATORY/ CARDIOVASCULAR	GASTROINTESTINAL
Anxiety in naive users	Dizziness/loss of balance	Tachycardia	Nausea/vomiting
Panic attacks in naive users	Cognitive impairment	Hypotension	Cannabis hyperemesis syndrome
Increased risk of psychosis in vulnerable and naive users	Hallucination	Airway inflammation (inhaled route)	Appetite changes
Potential for cannabis addiction and dependency	Somnolence	Decreased lung function (inhaled route)	Dry mouth
Euphoria	Driving impairment	Increased risk of coronary artery disease	Abdominal cramping/pain

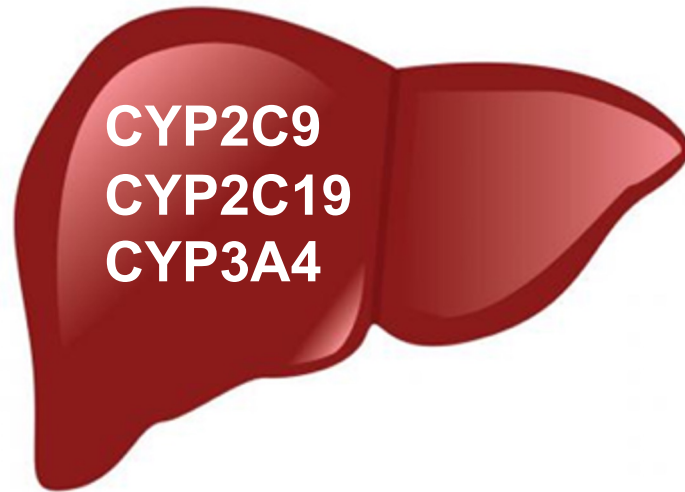
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Basic Cannabinoid Metabolism Concepts

- CYP450 family of enzymes
- **THC**: Primarily metabolized by CYP2C9 & CYP3A4
- **CBD**: Primarily metabolized by CYP2C19 & CYP3A4
- Medications that act on these enzymes when used with cannabinoids can be inhibitors or inducers

Wright J, Huang L, El-Fetouh Katamesh B, Yadav S, Singla A, Vincent A. Cannabinoid pharmacogenomics concepts and strategies for the practicing clinician. *Minnesota Medicine Magazine*. 2024;107(1):30-33.

Examples of Inhibitors



CYP2C9 inhibitors

- Sulfamethoxazole
- Fluconazole
- Miconazole

CYP2C19 inhibitors

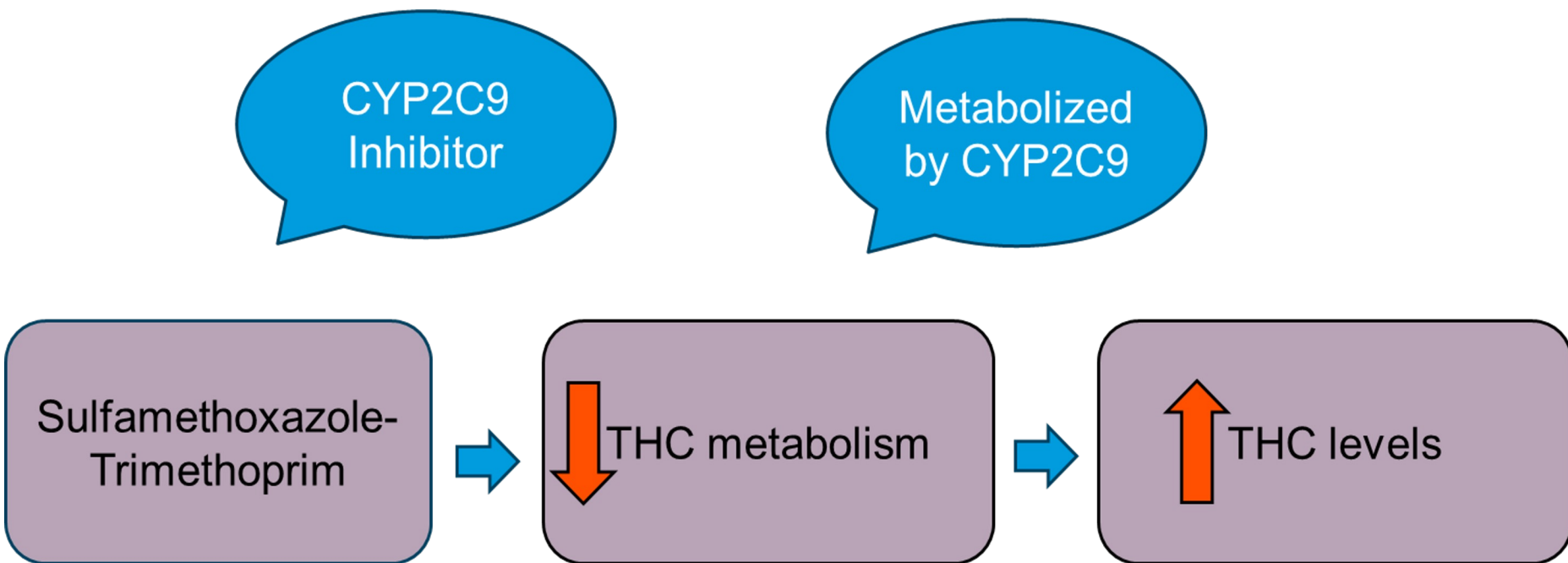
- Omeprazole
- Esomeprazole
- Fluoxetine
- Fluconazole
- Fluvoxamine
- Ketoconazole

CYP3A4 inhibitors

- Diltiazem
- Verapamil
- Fluconazole
- Ketoconazole
- Nirmatrelvir / ritonavir

Up to Date, Inc. Accessed January 5, 2024. <http://www.uptodate.com>.

Mechanism



Up to Date, Inc. Accessed January 5, 2024. <http://www.uptodate.com>.

Take-home points

- ❖ Drug interactions can still occur even in patients who are stable and otherwise have tolerated cannabis.
- ❖ Remember common medications that interact with cannabis.



Cannabinoid Pharmacogenomics Concepts And Strategies For The Practicing Clinician

Jessica Wright, Linda Huang, Basant El-Fetouh Katamesh, Siddhant Yadav, Abhinav Singla, Ann Vincent

QR code for full text article:



Article on pp. 32-35



Drug-cannabis interaction databases

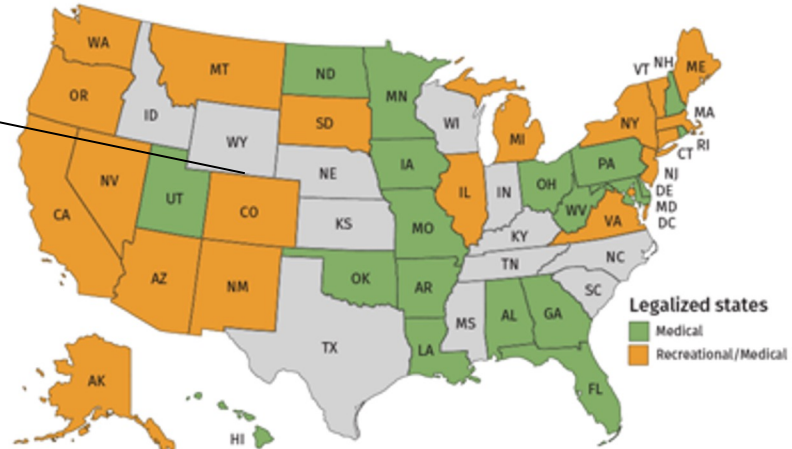
****It's a place to start, but may not contain all interactions.****

- U Penn site: <https://cann-dir.psu.edu/drug-research/result>
- Lexicomp and Micromedex
 - Search cannabidiol for CBD
 - Search dronabinol in place of THC

When in doubt, consult a pharmacist.

Policy: U.S and International

**Total population in states
with cannabis laws:
208 million***



*www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws/medical-marijuana-patient-numbers/

www.mjbizdaily.com

*In exceptional circum

Cannabis legalisation, March 2021



7 Proposed Federal Cannabis Laws in the U.S.

Legal Industry | Attorney Analysis | Health

Where things stand: a summary of pending federal cannabis legislation

By Jean E. Smith-Gonnell and Cole White

February 7, 2024 3:13 PM CST - Updated 2 months ago



Commentary | Attorney Analysis from Westlaw Today, a part of Thomson Reuters.



REUTERS/Luisa Gonzalez [Purchase Licensing Rights](#)

- Marijuana Opportunity Reinvestment and Expungement (MORE) Act
- Strengthening the Tenth Amendment Through Entrusting States (STATES) 2.0 Act
- The States Reform Act
- Marijuana 1-to-3 Act of 2023
- Harnessing Opportunities by Pursuing Expungement (HOPE) Act of 2023
- Clean Slate Act of 2023
- Free to Grow Act of 2023

Determining Medical Cannabis Education Competencies: A Delphi Process

Developing core competencies for educating medical students on medical cannabis



Zolotov Y, Temple LM, Isralowitz R, Isaac J, Kogan M



Students at the University of Minnesota celebrate their induction into medical school. The U.S. has disproportionately few Black and Hispanic doctors. Some of the barriers to entering the profession start before even getting into medical school, recent research finds, including financial pressures and racism.

Anthony Souffle/Star Tribune via Getty Images

6 Recommended Core Competencies for Medical School Curriculum

1. Understand the basics of the endocannabinoid system.
2. Describe the main components of the Cannabis plant and their biological effects.
3. Review the legal and regulatory landscape of cannabis in the US.
4. Describe the evidence base for health conditions that are commonly managed with cannabis.
5. Understand the potential risks of medical cannabis use.
6. Understand basic clinical management with medical cannabis.

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GIVEN EXPECTED UPCOMING PUBLICATION**

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Thank you!

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Q&A

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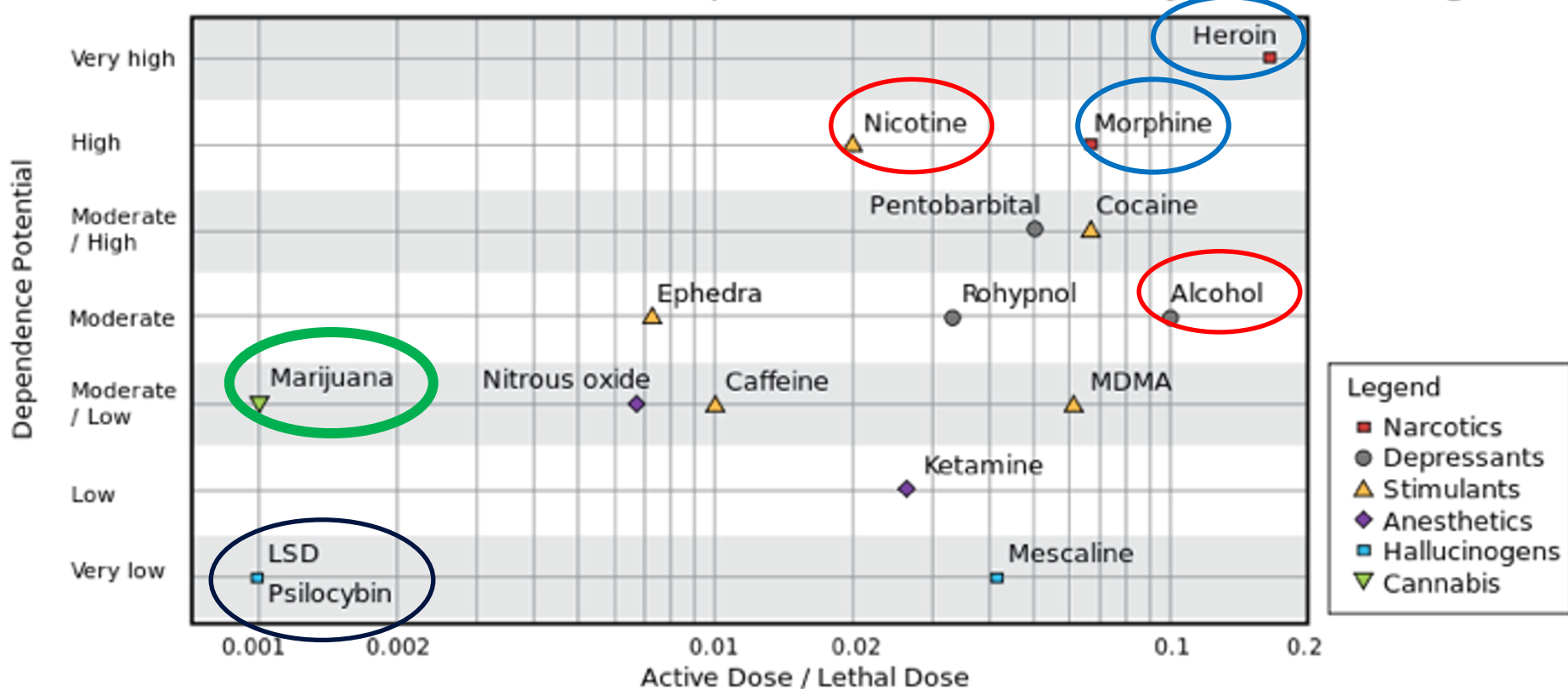
Professor of Medicine, Department of Medicine
Mayo Clinic



Bonus Slides

Cannabis Toxicity/Addiction is low but not zero

Active/Lethal Dose Ratio and Dependence Potential of Psychoactive Drugs



RS Gable, et al. The Toxicity of Recreational Drugs. *American Scientist*. 94(3), May 2006.

<https://www.americanscientist.org/article/the-toxicity-of-recreational-drugs>

Lifetime Dependence Risks

- 32% for nicotine
- 23% for heroin
- 17% for cocaine
- 15% for alcohol
- 9% for marijuana

Robson P. Abuse potential and psychoactive effects of delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Expert Opin Drug Safe.* 2011;10(5):675-685.
Bostwick, JM. Blurred boundaries: the therapeutics and politics of medical marijuana. *Mayo Clin Proc.* Feb. 2012;87(2);172-186.

Labels today vary significantly with inadequate information

THE GOLD STANDARD	
AK-47	
THC	17.434%
CBD	<.01%
CBG	.197%
CBN:	<.01%
CBC:	<.01%
Moisture Content:	5.891%
Total Cannabinoid:	17.64%
Total Active Cannabinoid:	2.181%
THC-Acid	15.262%
THC - dcrb	2.171%
CBD-Acid	<.01%
CBD - dcrb	<.01%
CBG-Acid	.197%
CBG - dcrb	<.01%
Cannabis Flower	
65% Sativa	

Harvested **Net Weight 2 grams** Lot/Batch #

Proposed labeling

FIGURE 5 Sections of a sample UCIL.

CANNABIS INFORMATION

Product form: **Inhaled extract**

Product weight: **0.5g (0.018 oz)**

Total THC in product: **350mg**

SCAN FOR MORE INFO →

QR code

Product and serving information

CANNABINOID PROFILE

Total THC	70.1%
THCA	2.3%
Total CBD	4.4%
CBDA	1.4%

Other cannabinoids:
CBN 0.1%, CBG 0.05%

Terpenes & flavonoids:
Limonene 0.2%, β -Pinene 0.2%

THC and CBD measurements (required)

Other cannabinoid, terpene and flavonoid measurements (optional)

INACTIVE INGREDIENTS: PEG 400, coconut oil.

Ingredients/ Inactive ingredients

WARNINGS: Keep out of reach of children and pets. This product may be addictive. The potency of some cannabis extracts requires cautious inhalation to avoid overconsumption. Do not drive or operate machinery while intoxicated. This product may pose significant health risks to preg-

Health warnings