

Cannabis: Potential Drug Interactions

Virginia Code § 54.1-3319(A) requires a pharmacist to conduct a prospective drug review before each new prescription is dispensed or delivered to a patient or a person acting on behalf of the patient. That review must include screening for potential drug therapy problems due to drug-drug interactions. As legal allowances for the use of cannabis increase, the Board of Pharmacy offers the following guidance to assist pharmacists performing prospective drug reviews, including the screening for drug-drug interactions.

What is cannabis and how is it used?

Cannabis is a psychoactive drug. The primary psychoactive component of cannabis is delta-9-tetrahydrocannabinol (THC).¹⁻² Along with THC, cannabis contains over 500 chemicals with over 100 of those being cannabinoids.¹ Cannabis can be consumed several different ways by joints, pipes, bongs, blunts, oils, edibles, or vaporizer pens.² There are three cannabis plants with psychoactive properties, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.³ Cannabis is often used as a recreational drug or can be used for medical purposes in disease states including pain, glaucoma, Parkinson's Disease, fibromyalgia, PTSD, and many others.⁴

How can cannabis affect other medications?

Cannabis contains over 100 cannabinoids, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), that bind to cannabinoid receptors throughout the body.⁵⁻⁷ These cannabinoids also interfere with the metabolism of many prescription medications through the cytochrome P450 enzyme system.⁵⁻⁷ When a metabolic enzyme is inhibited, it results in increased concentrations of enzyme substrate in the body. In contrast, when a metabolic enzyme is induced, it results in decreased concentrations of enzyme substrate in the body. Both THC and CBD are present in high concentrations within the cannabis plant and are inhibitors and substrates of multiple CYP450 enzymes.⁵⁻⁷

THC, the primary psychoactive component of cannabis, is metabolized by CYP2C9 and CYP3A4 enzymes.⁵⁻⁷ CBD is metabolized by CYP3A4 and CYP2C19. Thus, drug interactions may occur when cannabis is used in combination with inducers and inhibitors of the respective enzymes. THC also acts as an inhibitor of CYP1A2, CYP2B6, CYP2C9, and CYP2D6. CBD inhibits CYP3A4, CYP2B6, CYP2C9, CYP2D6, and CYP2E1.⁵⁻⁷ Currently, cannabis-drug interactions are mostly theoretical or come from case reports due to the lack of clinical trial results that evidences the effects of the interactions and the probability of their occurrence.⁵ Additive effects can occur with other drugs such as tachycardia and hypertension with sympathomimetics, drowsiness and ataxia with central nervous system depressants, and confusion with anticholinergics.⁷

What are the potential drug interactions of cannabis?

Potential Drug Interactions with Cannabis⁸				
CYP3A4 Substrate + Inhibitor		CYP2C19 Substrate + Inhibitor		CYP2C9 Inhibitor
CBD + Drug Levels	Drug +/- CBD Levels	CBD + Drug Levels	Drug +/- CBD Levels	CBD + Drug Levels
Benzodiazepines*	Protease Inhibitors*	Benzodiazepines*	PPIs*	Sulfonylureas*
Corticosteroids*	Ketoconazole	PPIs*	Azole Antifungals*	NSAIDs*
Statins*	Loperamide	Azole Antifungals*	Cimetidine	Buprenorphine
Alfuzosin	Amiodarone	Clopidogrel	Clopidogrel	Montelukast
Budesonide	Verapamil	Cyclophosphamide	Efavirenz	Rosiglitazone
Cyclosporine	Cimetidine	Warfarin	Rifampin	Phenobarbital
Disopyramide	Aprepitant	Escitalopram	Carbamazepine	Phenytoin
Ergotamine	Imatinib	Meclobemide	Phenobarbital	Rosuvastatin
Fluticasone	Nefazodone	Pentamidine	Phenytoin	Warfarin
Quinidine	Enzalutamide	Proguanil	St. John's Wort	Diclofenac
Sildenafil	Phenytoin	Sertraline	Fluvoxamine	Dronabinol
Tadalafil	Carbamazepine	Thalidomide	Fluoxetine	Tolbutamide
Vardenafil	Topiramate	Propranolol		Valsartan
	Phenobarbital	Carisoprodol		Losartan
	Rifampicin			
	Efavirenz			
	Pioglitazone			

*Most, if not all drugs in the class are affected

What interactions have demonstrated clinical relevance?

Clinical Relevance of Drug Interactions with Cannabis⁵		
Drug	Mechanism	Effects
Level 1 Interaction: Very High Risk		
Warfarin	CYP2C9 Inhibition	Increased INR with concomitant use of CBD resulting in GI bleeding. Monitor INR closely for warfarin adjustments. Avoid combination if possible.
Level 2 Interaction: High Risk		
Buprenorphine	CYP3A4 Inhibition	Increased concentrations of buprenorphine. Avoid combination if possible or adjust buprenorphine doses. ¹
Tacrolimus	CYP3A4 Inhibition	Increased tacrolimus concentrations. Avoid combination if possible or adjust tacrolimus doses. ¹
Level 3 Interaction: Medium Risk		
Clozapine	CYP3A4 and 2C19 Induction	Decreased clozapine concentrations. Consider dose adjustment. ¹
Methadone	CYP3A4 and 2C19 Inhibition	Increased methadone levels resulting in increased somnolence. Consider dose adjustment. ¹
Clobazam	CYP2C19 Inhibition	Increased clobazam concentrations. Consider dose adjustment. ¹
Chlorpromazine	Possible CYP1A2 Induction	Decreased chlorpromazine concentrations. Consider dose adjustment. ¹
Hexobarbital	Possible CYP3A4 Inhibition	Increased hexobarbital concentrations. Consider dose adjustment. ¹
Ketoconazole	CYP3A4 Inhibition	Increased concentrations of THC/CBD
Rifampicin	CYP3A4 Induction	Decreased concentrations of THC/CBD
Stiripentol	CYP2C19 Induction	Increased concentrations of stiripentol. Consider dose adjustment. ¹
Theophylline	CYP1A2 Induction	Decreased theophylline concentration. Consider dose adjustment. ¹
Valproate	Possible UGT1A9 and UGTB7 Inhibition	Increased LFTs. Assess liver function before taking in combination.
Level 5 Interaction: Co-administration with CBD does not lead to significant changes in drug levels (rufinamide, topiramate, zonisamide, nelfinavir)		

Levels of clinical relevance of drug interactions were determined according to the combination of severity and probability of occurrence.

¹Monitor plasma levels if possible.

Resources:

1. NIDA. What is marijuana? National Institute on Drug Abuse website. <https://nida.nih.gov/publications/research-reports/marijuana/what-marijuana>. April 13, 2021 Accessed March 22, 2022.
2. “Cannabis.” *Cannabis - Alcohol and Drug Foundation*, Alcohol and Drug Foundation, 10 Nov. 2021, <https://adf.org.au/drug-facts/cannabis/>.
3. Meds Safety. “List of Drugs That Interact with Marijuana (Cannabis).” *Meds Safety*, Meds Safety, 10 Jan. 2022, <https://medssafety.com/list-of-drugs-that-interact-with-marijuana-cannabis/>.
4. Peter Grinspoon, MD. “Medical Marijuana.” *Harvard Health*, Harvard Health Publishing, 10 Apr. 2020, <https://www.health.harvard.edu/blog/medical-marijuana-2018011513085>.
5. Lopera V, Rodríguez A, Amariles P. Clinical Relevance of Drug Interactions with Cannabis: A Systematic Review. *Journal of Clinical Medicine*. 2022; 11(5):1154. <https://doi.org/10.3390/jcm11051154>
6. John R. Horn, PharmD, and PharmD Philip D. Hansten. “Drug Interactions with Marijuana.” *Pharmacy Times*, Pharmacy Times, 8 Mar. 2021, <https://www.pharmacytimes.com/view/drug-interactions-with-marijuana>.
7. Antoniou T, Bodkin J, Ho JM. Drug interactions with cannabinoids. *CMAJ*. 2020;192(9):E206. doi:10.1503/cmaj.191097
8. CBD drug interactions. NCPA CBD Source Powered by PRS. <https://ncpacbdsource.com/pharmacist-education/cbd-drug-interactions/>. Published July 16, 2020. Accessed August 12, 2021.