Question: What medications could potentially interact with marijuana?

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Twenty-six states and the District of Columbia currently have laws broadly legalizing marijuana in some form.[1] But, regardless of legal status, recreational and medicinal use of marijuana is common across the United States. With this increasing availability and also the increasing potency of marijuana,[2] it is important for both users and healthcare professionals to be aware of the potential drug interactions associated with marijuana use.

Tetrahydrocannabinol (THC) is the primary psychoactive cannabinoid found in marijuana.[2] Cannabidiol (CBD) is also found in high concentrations in marijuana but is not psychoactive; it has an antagonistic effect at the cannabinoid receptors and appears to block some of the effects of THC.[3] Cannabinol (CBN) is a relatively weak psychoactive cannabinoid existing in very small quantities within the marijuana plant but is one of the primary metabolites of THC.[4] The marijuana plant contains more than 50 other cannabinoids, but synthetic medications approved by the US Food and Drug Administration (eg, dronabinol and nabilone) contain only THC without any CBD. The pharmacologic effect of these products may differ from that of natural cannabis.[5] Data are limited regarding the potential drug interactions associated with marijuana use; however, unstudied interactions can be theorized based on the metabolism of the primary cannabinoids in marijuana.

CYP450 Enzymes

Cytochrome P450 (CYP450) enzymes are responsible for the metabolism of most chemicals and medications that enter the human body. Humans have roughly 60 CYP genes. CYP450 enzymes occur primarily in liver cells where drug metabolism occurs.

Chemicals or drugs may be substrates, inhibitors, or inducers of CYP450 enzymes. Substrates are substances that are metabolized by the enzyme. Inhibitors reduce the activity of the enzyme, preventing the metabolism of its substrates and thus increasing the substrate concentration and effect. Inducers, on the other hand, increase the activity of the enzyme, enhancing the metabolism of its substrates and thus decreasing the substrate concentration and effect.[6]

The CYP1A2, CYP3A4, CYP2C9, and CYP2C19 enzymes are known to be affected by marijuana use.[7,4]

CYP1A2

Smoking marijuana regularly is believed to cause induction of the CYP1A2 enzyme, which may decrease serum concentrations of 1A2 substrates.[10] One study reported that theophylline clearance was 48% greater in individuals who smoked more than 2 joints weekly.[10] Marijuana would be expected to have a similar effect on other 1A2 substrates.

Other 1A2 substrates. Aminophylline, caffeine, clozapine, duloxetine, estradiol, estrogens, flutamide, fluvoxamine, frovatriptan, lidocaine, melatonin, mexiteline, mirtazapine, olanzapine, propranolol, ramelteon, rasagiline, ropinirole, tizanidine, triamterene, zolmitriptan.

CYP3A4

The CYP3A4 enzyme is involved in the metabolism of both THC and CBD.[2] Therefore, 3A4 inhibitors may increase serum concentrations of these cannabinoids, while 3A4 inducers may decrease the serum concentrations. In one study performed in the United Kingdom, rifampin (3A4 inducer) reduced the concentration of THC by 40% and CBD by 20%. In the same study, ketoconazole (3A4 inhibitor) was found to increase the concentration of THC by 20%.[11] It would be expected that other 3A4 inhibitors and inducers would produce a similar effect.

Strong 3A4 inducers. Carbamazepine, enzalutamide, fosphenytoin, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's wort.

Strong 3A4 inhibitors. Clarithromycin, darunavir, grapefruit juice, itraconazole, ketoconazole, lopinavir, mifepristone, nefazodone, nelfinavir, ombitasvir, paritaprevir, rilronavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil, voriconazole.
CYP2C9
In addition to CYP3A4, CYP2C9 is the other known enzyme responsible for metabolism of THC.\[^{12}\] In a study of patients who were poor metabolizers of 2C9, THC concentrations were found to be threefold higher than in those with normal 2C9 function.\[^{13}\] While no known studies have looked specifically at the effects of 2C9 inhibitors and inducers on THC concentrations, they would be expected to have similar effects as the 3A4 inhibitors and inducers.

**Strong 2C9 inducers.** Barbiturates, carbamazepine, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort.

**Strong 2C9 inhibitors.** Amiodarone, cimetidine, clopidogrel, delavirdine, disulfiram, fluconazole, fluoroouracil, gemfibrozil, metronidazole, phenytoin, sulfadiazine, sulfamethoxazole, tolbutamide, valproic acid, voriconazole.

CYP2C19
In addition to CYP3A4, CYP2C19 is the other known enzyme responsible for metabolism of CBD.\[^{13}\] In one study, omeprazole (2C19 inhibitor) did not increase serum concentrations of CBD.\[^{13}\] Even with these unexpected results, 2C19 inhibitors and inducers should be assumed to have similar effects on CBD concentrations as the 3A4 inhibitors and inducers until further studies provide a better understanding.

**Strong 2C19 inducers.** Barbiturates, carbamazepine, phenytoin, primidone, rifampin, rifapentine, St. John's wort.

**Strong 2C19 inhibitors.** Chloramphenicol, cimetidine, clopidogrel, delavirdine, efavirenz, esomeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, isoniazid, modafinil, omeprazole, oxcarbazepine, ticlopidine, voriconazole.

Other Potential Drug Interactions With Marijuana

Central nervous system (CNS) depressants. Clear evidence exists that THC can enhance sedative, psychomotor, respiratory, and other effects of CNS depressant drugs and alcohol.\[^{14-16}\]

Anticholinergic agents, cocaine, sympathomimetics. Cannabinoids are known to cause tachycardia. Several drug monographs and clinical studies have been published indicating that concomitant use of marijuana with anticholinergics, cocaine, or sympathomimetic agents can further enhance tachycardic and hypertensive effects of cannabinoids.\[^{17-19}\]

Disulfiram and fluoxetine. At least two case reports of individuals taking disulfiram and at least one case report of an individual taking fluoxetine while also using marijuana indicate a possible interaction causing symptoms of hypomania.\[^{20-22}\] Prescribing information for nabilone and dronabinol also includes this drug interaction to warn prescribers of the potential risk.\[^{19, 23}\]

Warfarin. A single published case report describes an interaction with a patient taking warfarin who also regularly smoked tobacco and marijuana. The patient had multiple comorbidities and was taking at least 10 other medications. On at least two occasions, the patient's international normalized ratio (INR) increased to values over 10 with episodes of bleeding. The only change reported for both occasions was an increase in the amount and frequency of marijuana smoking.\[^{24}\] Patients who take warfarin and use marijuana regularly should receive close INR monitoring for any potential interaction.

Antiepileptic drugs (AEDs). A recent study examined baseline serum AED levels to identify drug-drug interactions between CBD and 19 AEDs during an open-label safety study in 81 patients (39 adults, 42 children) with refractory epilepsy.\[^{25}\] As doses of CBD were increased, the researchers noted an increase in the serum levels of topiramate (P<.01), rufinamide (P<.01), and desmethylclobazam (P<.01) and a decrease in the levels of clobazam (P<.01) in both adult and pediatric patients. In adult patients, a significant increase in the serum levels of zonisamide (P=.02) and eslicarbazepine (P=.04) was observed with increasing CBD dose. No other drug interactions among the 19 AEDs were noted. The authors recommended monitoring serum AED levels in patients receiving CBD, as drug-drug interactions may be correlated with adverse events and laboratory abnormalities.

Be Aware and Educate Patients

Patients using marijuana should be educated to avoid drugs that affect associated CYP450 enzymes. When these drugs cannot be avoided, and marijuana use is expected to continue, the patient should be monitored closely for potential drug interactions.

Smoking more than two joints weekly is likely to increase the risk for drug-related interactions.\[^{5, 19}\] No data exist monitoring large-scale marijuana use in the United States. However, in Washington, a state in which marijuana use is legal, the average user is estimated to smoke two to three joints per week.\[^{26}\]

With growing legalization and use throughout the nation, healthcare professionals must exercise heightened caution in the situation of concomitant use of medications and marijuana.

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