Pharmacogenomic Testing and Drug–Drug Interactions With Cannabinoids

Jahan Marcu, PhD, speaks to conference attendees at Columbia University in New York City.

New York, NY—Pharmacogenomic testing is a promising strategy for predicting drug–drug interactions (DDIs) with cannabinoids, preventing addiction, lowering side-effect risk, informing dosage guidelines, and personalizing strategies for health care, Jahan Marcu, PhD, told attendees at the inaugural meeting of Medical Cannabis: The Science. The Research. The Risks, held at Columbia University.[1]

Genomic, genetic variability influences the efficacy and tolerability of the 2 major pharmacologically active cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD),[2] Dr. Marcu said. Pharmacogenomic influences may include variability in drug transporters (eg, P-glycoprotein), which may impact drug absorption and distribution. Additionally, variability in drug metabolizing enzymes, most commonly the cytochrome P450 (CYP450) family, resulting from genetics or drug interactions may affect cannabis metabolism and the risk for side effects.[3]

PHARMACOKINETIC	PHARMACODYNAMIC
Cannabinoid as "**victim**": • Cannabinoid levels are changed by another drug	• Both drugs contribute to **overlapping side effects** • Concepts of "victim" and "perpetrator" don't apply
Cannabinoid as "**perpetrator**": • Cannabinoid causes change in levels of another drug	

Figure. Types of drug–drug interactions with oral cannabinoids.

Image credit: M. Tagen

"The activity of these CYP450 enzymes, whether patients are ultra-rapid or ultra-slow metabolizers, can vary 10-fold between individuals due to genetic mutations or polymorphisms," Dr. Marcu told attendees.[3,4] Notably, this effect applies to oral administration of cannabis, which undergoes extensive first-pass metabolism. In contrast, inhaled administration has no significant first-pass metabolism and sublingual administration avoids first-pass metabolism with the exception of a small portion that is swallowed.[5]

For example, the CYP2C9*3 polymorphism, which is present in approximately 8% of the white population and leads to reduced enzyme activity, is associated with 3-fold higher plasma levels of THC with oral administration compared with the CYP2C9*1 polymorphism, Dr. Marcu explained.[6,7] Thus, what might be an effective dose for a patient with the CYP2C9*1/*1 polymorphism may be intolerable for a patient with the CYP2C9*3/*3 polymorphism. The clinical implication is that patients with the CYP2C9*3 polymorphism may require a 2- to 3-fold reduced oral THC dose, but do not require a dosing adjustment for inhaled THC, Dr. Marcu said.

If proven effective, "pharmacogenomics could speed up the trial-and-error period with cannabis therapy, improving therapy and lowering cost to patients," Dr. Marcu said.

Additionally, pharmacogenomics testing could identify patients at risk for cannabis or substance use disorders, in whom cannabis may not be the best option. The findings also have legal implications given that some patients taking medical cannabis may fail a roadside sobriety blood test because of genetic factors leading to high serum levels of THC, even when they are not actually impaired,[8] Dr. Marcu told attendees (see **DWIC,** page 42).

Are Cannabinoids Acting as Victims or Perpetrators of Drug–Drug Interactions

Dr. Marcu likened oral cannabinoids to either victims or perpetrators in DDIs (Figure). Cannabinoids are victims when administered with strong CYP3A4 inhibitors, including clarithromycin, telithromycin, itraconazole, ketoconazole, and protease inhibitors. When combined with these agents, THC and CBD levels increase 1.8-fold each and 11-OH-THC levels (the major metabolite of THC) increase 3.5-fold.[9]

An example of a cannabinoid acting as a perpetrator in a DDI is high-dose CBD (5–20 mg/kg/d) and the antiepileptic agent clobazam. Here, high-dose CBD significantly increases serum levels of the active metabolite of the antiepileptic agent (*N*-desmethylclobazam) with a 150% to 200% increase over baseline, according to a randomized safety trial of CBD in children with Dravet syndrome,[10] Dr. Marcu explained.

Unanswered Questions

"There are definitely are a lot of yellow lights when it comes to cannabis and pharmaceutical drug interactions when cannabinoids are taken orally," Dr. Marcu said.

"Unanswered questions remain around the extent that THC and CBD can be inhibitory or activating when combined with other drugs," Dr. Marcu told attendees. "There is insufficient evidence around CYPs contributing to bioavailability. And there is a lack of consistency of THC and CBD exposure in a lot of studies."

The Future of Pharmacogenomic Testing

Availability of noninvasive direct-to-consumer pharmacogenomic testing is increasing exponentially, Dr. Marcu explained. However, he warned that patients should make sure that these

tests are CLIA certified and FDA compliant, and also protect patient privacy.

Pharmacogenomic clinical trials of cannabis are currently underway, including those examining the effects of the catechol-*O*-methyltransferase (*COMT*) gene on the effects of CBD and THC.[11,12] Additionally, researchers are investigating the role of pharmacogenomic mechanisms associated with cannabis-associated psychosis.[13] Furthermore, researchers are examining genes related to dopamine, γ-aminobutyric acid, glutamate, and CB_1 receptors and their effects on cannabinoids, according to Dr. Marcu.

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> ***—Jahan Marcu, PhD***

The vast majority of pharmacogenomics testing (90%) for medical cannabis is focused on CYP polymorphisms, which is limiting given that there are many other genetic factors that may affect response to cannabinoids, Dr. Marcu continued.

"Many of these factors are going to turn out to be more important than CYPs," Dr. Marcu concluded.

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Dr. Marcu *provides consulting, advising, and education services to licensed cannabis operators, private companies, regulatory bodies, and universities. He serves on the PAX Health Advisory Board and as an advisor to Navigator Genomics.*