Southern Illinois University Edwardsville School of Pharmacy

Potential For Adverse Effect Reduction With Pharmacogenomic Guided Dosing of Delta-9-Tetrahydrocannabinol

Josh Beane Ph.D Candidate In collaboration with Professor Ronald Worthington, Ph.D SIUe

Background

- **Growing Marijuana Use**
  - 37 states with medical use, 20 with full recreational use
  - Near 70% of US population support federal legalization
- **Changing Patient Population**
  - Fastest growing demographic of medical marijuana users are seniors
  - Expanding use presents more opportunity for interactions and adverse effects
- **Limited Resources Available for Prescribers**

Methods

- **primary literature searches**
  - Pubmed, SCOPUS, EBSCOhost platforms
- **PharmGKB**
  - Clinical guidelines
  - Gene-drug associations
- **CPIC**
  - Clinical Pharmacogenetics Implementation Consortium
- **YouScript**
  - Clinical decision support database
  - Phenotype variations and resulting pharmacokinetic effects
  - Therapeutic effects and monitoring recommendations

Results

CYP2C9

In vitro data has shown CYP2C9 to be involved with formation of THC metabolites, specifically psychoactive and primary metabolite 11-OH-THC, as well as with the elimination of active metabolites. Each allele functional status is assigned an activity value ranging from 0 to 1. 0 for no function, 0.5 for decreased, and 1.0 for normal function, which are then used to calculate the activity score, AS, for each diplotype.

Likely phenotype[a,b]	Activity score	Genotypes	Examples of diplotypes
Normal metabolizer	2	An individual carrying two normal function alleles	*1/*1
Intermediate metabolizer	1.5 1	An individual carrying one normal function allele plus one decreased function allele; OR one normal function allele plus one no function allele OR two decreased function alleles	*1/*2 *1/*3, *2/*2
Poor metabolizer	0.5 0	An individual carrying one no function allele plus one decreased function allele; OR two no function alleles	*2/*3 *3/*3
Indeterminate	n/a	An individual carrying allele combinations with uncertain and/or unknown function alleles	*1/*7, *1/*10, *7/*10, *1/*57

COMT

COMT is the enzyme responsible for the methyl conjugation of the catecholamines adrenaline, noradrenaline, and dopamine. The most widely studied variant of COMT is rs4680, Val158Met, and produces 3 to 4 times lower activity for methylation of dopamine compared to the wild-type allele. Research has shown potential connections of COMT variations resulting in adverse effect presentation and neural system dysfunction clinically relevant to substance abuse and potential initiation of marijuana therapy. COMT variation and resulting therapeutic response combined with the increasing effect THC has on dopamine levels requires close monitoring of patients with Met variant when on or initiating marijuana treatment.

CPIC

CYP2C9	dronabinol	B/C	Provisional	Actionable PGx

The Clinical Pharmacogenetics Implementation Consortium gives CPIC levels to gene-drug pairs based upon PharmGKB Clinical Annotation Levels of Evidence or PharmGKB PGx level based upon FDA approved drug labels. Level B rating means that genetic information could be used to change prescribing because it would likely be as effective and safe as non-genetically guided dosing. This requires that at least one optional action is recommended, such as change in prescribing. Actionable designation is given because the Dronabinol label may contain information on changes in efficacy, dosage, metabolism, or toxicity due to genetic variants.

YouScript

Intermediate and Poor Metabolizers are associated with increased THC exposure. CYP2C9*3 allele significantly increased THC exposure more than the *2 allele. Pharmacokinetic studies have shown single-dosed oral THC 15 mg resulted in a 209% increase in THC AUC, a 133% increase in Cmax and a 34% increase in the AUC of the main THC active metabolite in poor metabolizers, 2C9*3/*3, compared to normal metabolizers. Clinical relevance for these results are an increased risk of marijuana adverse effects: dizziness, abdominal pain, altered mental status, somnolence, nausea and vomiting. The research also showed sedation scores were also found to be higher for poor metabolizers, 2C9*3/*3, when compared to normal metabolizers. Normal metabolizer status and COMT variations were not shown to have any effects on dosing adjustment recommendations

Cause	Drug Exposure (PK)
CYP2C9 Poor metabolizer	↑ >200%

Limitations

- **Studies on COMT relationship are not definitive**
  - Inadequate amount of powered studies to make true correlation
  - Available data does suggest connection
- **Racial and ethnic disparities in genetics research**
  - Most commonly researched variants are most predominant in European and Caucasian populations
  - Disproportional enrollment of African American and African-descent patients in primary studies

Conclusions

- **Pharmacogenomic testing**
  - **Becoming more accessible**
    - Increasing insurance coverage
    - Growing clinical utility and adoption
  - **Personalized Medicine**
    - Treatment decisions supported by individual genomic results
  - **Prescriber Support**
    - Treatment decisions simplified by preferred and excluded therapies based on patient results
  - **Improved Patient Outcomes**
    - Greater adverse effect prediction/ avoidance
    - Optimization of therapy promotes greater adherence