Personalized Medicine Corner

Pharmacogenetics and SSRIs in the Treatment of Depression

Nearly 7% of U.S. adults have at least one major depressive episode annually.[1,2] SSRIs (e.g., sertraline, escitalopram) are first-line treatment options for major depressive disorder. Although SSRIs have been shown to be equally effective, approximately half of patients fail to respond well to their initial SSRI and require treatment modification.[3,4]

Optimizing therapy is further confounded by the slow onset of SSRI response, with the full therapeutic benefit often taking up to 8 weeks. This delay is important because of the potential for self-harm, suicidality, and other adverse events related to untreated depression. While data demonstrating a clear link between genetic factors and SSRI antidepressant effectiveness are lacking, recent studies show a genetic link with the risk for adverse effects.

Cytochrome P450 enzymes 2D6 (CYP2D6) and 2C19 (CYP2C19) are key metabolizers of several SSRIs. These genotypes confer the normal, intermediate, poor, rapid, and ultra-rapid metabolizer phenotypes. The Clinical Pharmacogenetics Implementation Consortium (CPIC; https://cpicpgx.org/) has released guidelines for incorporating CYP2D6 and CYP2C19 phenotype information into prescribing decisions for certain SSRIs - sertraline, escitalopram, citalopram, paroxetine, and fluvoxamine.[4] Guidelines do not address whether genotyping should be done, but rather provide guidance for use of genotype information when available. The recommendations from these guidelines are summarized as below.

Recommendations for Citalopram, Escitalopram, and Sertraline based on CYP2C19 Phenotype[4]

CYP2C19 Phenotype	Recommendation
Rapid or Ultrarapid Metabolizer	Consider alternative drug not predominantly metabolized by CYP2C19
Normal or Intermediate Metabolizer	Initiate therapy with recommended starting dose
Poor Metabolizer	Consider 50% reduction of starting dose or alternative drug not predominantly metabolized by CYP2C19

Recommendations for Fluvoxamine and Paroxetine based on CYP2D6 Phenotype[4]

CYP2D6 Phenotype	Recommendation
Rapid or Ultrarapid Metabolizer	Paroxetine: Consider alternative drug not predominantly metabolized by CYP2D6 Fluvoxamine: No recommendation due to lack of evidence
Normal or Intermediate Metabolizer	Initiate therapy with recommended starting dose
Poor Metabolizer	Consider 50% reduction of starting dose or alternative drug not predominantly metabolized by CYP2D6

Genotyping is likely to have the most clinical benefit in patients being newly initiated on an SSRI to help guide drug and dosage selection. Contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu) for more information about these findings or for assistance with interpreting *CYP2D6* or *CYP2C19* pharmacogenetic test results clinically.

Contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu) for more information about these findings or for assistance with interpreting CYP2C19 pharmacogenetic test results clinically.

References:
1. Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). Retrieved from http://www.samhsa.gov/data
2. Murray CJ et al. U.S. Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA. 2013;310:591–608.
3. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct (available at https://psychiatryonline.org).
4. Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015;98:127–34.

The Personalized Medicine Corner appears quarterly and is provided by the UF Health Personalized Medicine Program. To find out more or submit a question, email PMP-HELP@ctsi.ufl.edu.

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida