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Depression and Pharmacogenetics

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ABSTRACT

Depression is the most common and leading devastating psychiatric illness that affects a majority of the world population. The treatment of depression has been a challenge for a majority of patients and healthcare practitioners. The advent of pharmacogenomics (PGx) empowered the Food and Drug Administration to approve some antidepressant biomarkers for PGx model of treatment. The PGx testing identifies whether an individual is a poor metabolizer, ultra/rapid metabolizer, intermediate metabolizer, or essential metabolizer of an antidepressants before prescription. This is a cutting edge treatment that eliminates trial and error. PGx testing has shown to precisely identify the effective medication and dose for a patient.

Ms. Holmes is a young female Caucasian medical student who was diagnosed with major depressive disorder at the age of 25. She weighs 158 lb at 6 ft tall with athletic build, blonde hair, and blue eyes, prior to the diagnosis. She had just started a brighter life in medical school, hoping to become a healthcare professional one day, keeping to the family legacy of medical professionals. Unfortunately for Ms. Holmes, in her second year in medical school, she began to experience body aches, loss of interest in daily activities, loss of appetite, hyper-insomnia, difficulty concentrating, and suicidal ideation. Ms. Holmes was put on several antidepressants to improve her condition. For three and half years, none of the recommended medications could stabilize her condition for more than six months. In addition to the relapses she experienced while on the antidepressants, there were side effects she describes as more depressing than the disease. Ms. Holmes' physicians recommended pharmacogenomics testing, and it was discovered she was an ultra-rapid and poor metabolizer of the antidepressants she was taking. The right antidepressants were determined and prescribed with the right dose. Today, Ms. Holmes has returned to medical school hoping to become a psychiatrist and to promote pharmacogenomics testing for patients suffering from mental illness.

There are many people across the globe afflicted with depression who are not fortunate as Ms. Holmes. Depression is a biochemical dysregulation of mood and emotions associated with psychosocial stressors. Depression can cripple an individual, preventing them from functioning normally. It is the most *camouflaged* devastating disease that triggers myocardial infarction and suicide in many individuals (Bondy, 2002). This disease claims many lives disguised as heart attack and suicide. The World Health Organization (2015) describes depression as a global crisis and the number one cause of disability and illness. The alarming statistics for depression are that one out of every four college students are depressed. Globally, there are more than 800,000 suicides annually related to depression, and 7.6% of Americans age 12 and over are depressed (Kerr & Krucik, 2012; Pratt & Brody, 2014; World Health Organization, 2015). The biological and molecular pathophysiology of depression evolved from the middle of the twentieth to the twenty-first century and is strongly supported by pharmacogenomics. It is the most common mental illness that affects the majority of the population and has been well researched in pharmacogenomics. The therapeutic effectiveness of the current pharmacologic therapy for depression focuses on preventing relapses through pharmacogenomic testing. This paper highlights the genetic variants involved in antidepressant metabolism, provides some recommendations from experts, and explains the synopsis of the metabolic pathway of a medication with approved cytochrome P450 (CYP) labeling by the Food and Drug Administration (FDA) for treating depression as well as some recommendations for treating depression.

GENETIC VARIANTS AND ANTIDEPRESSANTS

Pharmacogenomics of antidepressant medications focus on the pharmacokinetics and pharmacodynamics of the medication. In pharmacokinetics of antidepressants, the well-researched genes for distribution, absorption, metabolism, and elimination are CYP and adenosine tri-phosphate binding cassette (ABC; Hornstmann & Binder, 2009). Geneticists have identified 50 of the CYP enzymes, out of which 10 of the most important medication metabolizing CYP genes are known. Six of the 10 CYP genes are essential for metabolizing antidepressant medications: CYP2D6, CYP2C19, CYP3A4, and CYP1A2 (Sim & Sundberg, 2011). The CYP2D6 is the most investigated gene with over 78 functional alleles. The variant phenotypes of the alleles are

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based on whether an individual is an ultra-rapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM). This means that therapeutic effect and adverse effect susceptibility to antidepressants are dependent on the individual's CYP2D6 gene-phenotype (Kyu-Man, Hun, Byung-Joo, & Minn-Soo, 2013). For instance, an individual with the alleles for PMs will accumulate a higher concentration of an antidepressant medication in the plasma leading to a potential serious adverse effect. In addition, some selective serotonin reuptake inhibitors (SSRIs) for treating depression, such as Paxil (paroxetine), Prozac (fluoxetine), and Celexa (citalopram), inhibit the activity of CYP2D6, which could eventually change EMs to IMs or PMs.

The ABC is subdivided into seven specific proteins that transport molecules across extra- and intra-cellular membrane. The seven subfamilies are ABC1, MDR/TAP, MRP, ALDP, OABP, CCN20, and white proteins. The protein of interest to antidepressants is p-glycoprotein of the ABC1 gene located on chromosome 7q21, which can regulate antidepressant medications in the brain (Hornstmann & Binder, 2009). Numerous studies show that p-glycoprotein prevents most SSRIs from crossing the blood-brain barrier (O'Brien, Clarke, Dinan, Cryan, & Griffin, 2013). This explains why a patient may have a higher concentration of SSRIs in the plasma but will not respond to treatment.

Pharmacodynamics is still in the preliminary stages in terms of the direct effect of the genes on antidepressant medications. There is the need for more studies on the psychodynamics of antidepressant medications. The serotonin transporter gene, identified as the most investigated genetic variant predictor of antidepressants, revealed a slight correlation of the serotonin gene response to antidepressants in Caucasians only and showed no significance in Asians in a meta-analysis study (Porcelli, Fabbri, & Serretti, 2012).

The recommendations provided so far in pharmacokinetics are based mostly on CYP2D6. A convened panel of expert recommends testing only individuals with major depressive disorder for CYP2D6 because there is currently no significant clinical data available to support its effectiveness in the treatment of depression (Evaluation of Genomic Applications in Practice and Prevention [EGAPP], 2015). The FDA recommends genetic testing before starting patients on most of the SSRIs (Torkamani & Vaux, 2014).

FDA APPROVED ANTIDEPRESSANTS

Many of the common antidepressants have an FDA label with specific CYP2D6 gene alleles that may cause an adverse effect in individuals undergoing treatment for depression. Some of these medications are amitriptyline, clomipramine, codeine, desipramine, doxepin, fluoxetine, imipramine, nortriptyline, paroxetine, and trimipramine. The guidelines for these medications provide the CYP2D6 gene alleles and their specific metabolizers. Based on the metabolizer, the exact medication and dosing limit for a patient with the corresponding phenotype could be recommended for treatment. For instance, a patient about to start fluoxetine with a CYP2D6 1*1* will be recommended to start on a low dose and then to increase over several days to the recommended steady-state dose (Pharmacogenomics Knowledge Implementation ([PharmGKB], 2015). Using the FDA approved biomarkers and other approved pharmacogenomic organization recommendations for antidepressants could enhance prescribers' decision making for patients suffering from depression.

METABOLIC PATHWAY OF FLUOXETINE (PROZAC)

Fluoxetine (Prozac) is a SSRI with four distinct, compound *R*- and *S*-enantiomers. The racemic mixture is different in their inhibiting mechanism and kinetics. The most effective inhibiting serotonin reuptake is *S*-norfluoxetine. Kinetically, the plasma concentration of *S*-enantiomer is twice higher than that of *R*-enantiomer (Whirl-Carrillo et al., 2012). The schematic diagram (Fig. 1) explains how fluoxetine prevents the reabsorption of serotonin and increases the amount of serotonin in the synapse.

For fluoxetine to accomplish its work of inhibition, it must undergo biotransformation in the liver to release the compound for inhibition into the synapse.

The next diagram (Fig. 2) explains the metabolic pathway of fluoxetine. Fluoxetine is completely absorbed after oral administration but is hugely deposited in the liver and other tissues because of its lipid and fat solubility. Fig. 2 shows how fluoxetine deposited into the liver is biochemically transformed by CYP2D6, CYP2C19, CYP2C9, CYP3A4, and CYP3A5 to *R*- and *S*-fluoxetine to their *N*-desmethyl metabolites. Genetic polymorphism in the CYP affects the catalytic activity of this biotransformation (PharmGKB, 2015). Studies confirmed that CYP2D6 alleles are highly responsible for the formation of *S*-norfluoxetine and CYP2C9 catalysis the formation of *R*-fluoxetine (Foley & Quigley, 2010). The inactive byproducts and norfluoxetine and fluoxetine gluconate are eliminated through the kidney with 10% unchanged as fluoxetine gluconate (Whirl-Carrillo et al., 2012).

CLINICAL AND RESEARCH IMPLICATIONS OF FLUOXETINE IN GENETIC VARIANTS OF CYP2D6: POOR, INTERMEDIATE, EXTENSIVE, OR ULTRA-RAPID METABOLIZERS

The tremendous role CYP2D6 plays in the biotransformation of fluoxetine to *S*-norfluoxetine, the main potent inhibiting factor of serotonin reuptake, implies that a wrong variant can affect the efficacy of the medication. Additionally, cytochrome isoenzymes contribute to numerous drug metabolisms in the liver for detoxification, which means the potential of fluoxetine and norfluoxetine inhibitory effects of CYP2D6 affecting other drugs or causing drug interaction is very high. The complexity of the metabolic pathway of most psychotropic medications is gradually being simplified by PGx testing. However, there is greater need for understanding how other drugs may enhance or inhibit the efficacy of psychotropic drugs like fluoxetine.

There is also the need for more research regarding p-glycoprotein on the single nucleotide polymorphism that prevents some individuals from responding to antidepressants. The current studies are inconsistent, as some studies refute the clinical relevance of p-glycoprotein association with antidepressants (O'Brien et al., 2013). A solidified research that supports the usefulness of all the identified CYP and p-glycoprotein can be enhanced with current clinical application of PGx testing for depression.

A major research implication is putting the pieces together in pharmacodynamics. The number of reported cases in the literature of individuals stopping their antidepressants because of major side effects such as weight gain and sexual dysfunction is numerous, and these cases cannot be ameliorated without identifying the specific variants responsible for the adverse effects using pharmacodynamics (Reichenpfader et al., 2014). A clear understanding of the metabolic pathway of antidepressants and their genetic variants may provide a better treatment for the 30% to 50% of individuals who stop responding to antidepressants during treatment and those who stop due to the adverse effects.

Although pharmacogenomics appears promising for psychopharmacology even with the many unanswered questions and weak public confidence in this advanced and evolving molecular pharmacology, treating and managing debilitating illness such as depression require innovative approaches like pharmacogenomics in addition to psychosocial interventions. For this new and emerging method of treating patients with depression to thrive, providers must embrace the idea through education and engage patients about the possibility of genetic testing, advocating FDA approval of the psychotropic medications with identified pharmacogenomic metabolic pathways. The number of depressed patients relapsing every year is alarming and continues to be a strong factor in high rates of suicide in the United States. Practitioners, administrators, educators, and researchers will