

July 2014

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Abstract

Pharmacogenetics (PGt), the study of a gene's influence on patient response to a drug, shows strong potential for explaining issues with efficacy related to antidepressant medications. Each year, antidepressants are one of the most commonly prescribed medications due to the millions of Americans affected by depression. Importantly, it is recognized that there is wide interpatient variability in drug response to antidepressants caused by genetic mutations, which can alter the pharmacodynamic (PD) and pharmacokinetic (PK) properties of various drugs used to treat depression. Proteins that are mainly involved in how patients respond to medications include receptors, drug-targeted proteins, drug transport proteins and drug-metabolizing enzymes. Specifically in depression, variations in the serotonin reuptake transporter (SERT-1 or 5-HTT), N-acetyltransferase (NAT2), cytochrome P450 (CYP) 2C19, 2D6, and 1A2 can affect the outcomes of patients receiving certain antidepressant medications. Utilizing PGt can help prevent the trial and error in prescribing antidepressants and lead to better patient outcomes in the treatment of depression. Pharmacists can utilize genetic information to help primary care physicians choose drug regimens that are more likely to benefit their patients. Although advances are being made in this subject matter, some major efforts of future research will evaluate the efficacy of drug regimens and the dosing of drugs based on patient genetics.

Glossary:¹

Allele—Alternate sequences or versions of the same gene inherited from each parent.

Extensive Metabolizers/Normal Metabolizer (EM/NM)—An individual with two “normal-function” alleles relative to a drug-metabolizing enzyme.

Genotype—The specific set of alleles inherited at a locus on a given gene.

Haplotype—A series of polymorphisms that are inherited together.

Indel—Insertion or deletion of deoxyribonucleic acid (DNA) either as single nucleotides or spanning regions of DNA involving many nucleotides.

Intermediate Metabolizers (IM)—In general, an individual with one “loss-of-function” allele and one “normal-functional” allele relative to a drug-metabolizing enzyme.

Personalized medicine—The use of patient-specific information and biomarkers to make more informed choices regarding the optimal therapeutic treatment regimen for a given patient.

Pharmacodynamics (PD)—The relationship between drug exposure and pharmacologic response.

Pharmacogenetics (PGt)—The study of a gene involved in response to a drug.

Pharmacogenomics (PGx)—Studying and understanding the genes, in some cases the entire genome, involved in response to a drug.

Pharmacokinetics (PK)—The relationship of time and drug absorption, distribution, metabolism and excretion.

Phenotype—An individual's expression of a physical trait or physiologic function due to genetic makeup and environmental and other factors.

Polymorphisms—A mutation in DNA in a given population that may be observed at greater than 1 percent frequency.

Poor Metabolizer (PM)—In general, an individual with two “reduced-function” or “loss of function” alleles relative to a drug-metabolizing enzyme.

Reference Sequence Number (rs)—A unique and consistent identifier of a given single nucleotide polymorphism (SNP).

Single Nucleotide Polymorphism (SNP)—A variant DNA sequence in which a single nucleotide has been replaced by another base.

Ultra Metabolizers (UM)—An individual with a “gain-of-function” allele (e.g., overexpression of a metabolic enzyme).

Wild-Type Gene—The typical or normally occurring genotype of an organism.

Introduction/Background

According to statistics, one of every 10 adults in America have reported symptoms of depression, and specifically, major depressive disorder (MDD) is one of the most commonly diagnosed disorders in the United States.^{2,3} These current numbers aside, it is also estimated that at least 10 percent of Americans will experience MDD at some point in their lives.⁴ This trend in disorders is reflected in drug use as well. According to the U.S. Centers for Disease Control and Prevention, in 2010, prescribers wrote nearly 122 million prescriptions for antidepressant drugs—the third highest of any other type of medication prescribed out of the total 3.2 billion prescriptions written in both hospitals and doctors' offices.⁵ Altogether, the number of depressed patients plus the antidepressant medications they are prescribed each year makes it obvious that this type of mental disorder utilizes a significant portion of our health care system resources.

In terms of current treatment guidelines for depression, health care professionals are first advised to manage patients with sleep hygiene and low-intensity psychosocial interventions such as cognitive behavioral therapy.⁶ After employing this nonpharmacologic therapy, the first-line drugs of choice for depression are antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs).^{6,7} Depression is a disorder

der of the brain involving neurotransmitters. The SSRIs, and other antidepressants, successfully target specific neurotransmitters, including serotonin, norepinephrine and sometimes dopamine.⁸

As mentioned previously, SSRIs are the first-line pharmacologic choice for treatment of depression. In comparison to other antidepressant drugs, in general SSRIs are safer and have fewer intolerable side effects.⁹ Some of the most commonly prescribed SSRIs are fluoxetine (Prozac®), sertraline (Zoloft®), escitalopram (Lexapro®), Paroxetine (Paxil®), and citalopram (Celexa®).⁸ Another factor to consider regarding the popularity of antidepressant drug use is the high frequency of a comorbid anxiety disorder. Almost 50 percent of patients diagnosed with depression are diagnosed with an anxiety disorder as well.¹⁰ Some of the most common types of mental disorders diagnosable by Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria are depressive disorders, anxiety disorders, trauma- or stressor-related disorders, and obsessive-compulsive and related disorders.¹¹ More specific examples include generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), seasonal affective disorder (SAD) and obsessive compulsive disorder (OCD), all of which have a first-line treatment that includes SSRIs per the American Psychological Association guidelines for treatment.¹²⁻¹⁴

Overall, considering the popularity in use of antidepressant drugs, based on the number of prescriptions written per year, it would seem that antidepressants must be a successful treatment strategy regarding depression and anxiety disorders. However, there is a downside to this type of treatment that cannot be ignored. Despite the medication successfully treating patients for their mental disorders, the actual response to these drugs is very slow and delayed. It can take four to six weeks before patients will see the full effect of antidepressants.⁸ According to current treatment guidelines it is recommended that individuals undergo an initial therapeutic trial of four to eight weeks to determine their response to the medication.⁷ Not only does it require this period of waiting to see the full therapeutic effects of the drug, but this also includes a delay in time before patients may exhibit adverse side effects from drug use as their body adjusts to the medication.^{7,9}

The requirement of patience when using antidepressants can be a difficult feat to achieve when treating individuals with mental disorders. These patients are already experiencing symptoms that are negatively impacting their lives and are requiring treatment. Adding on the stress of "waiting" to see if the drug will work can prove to be a definite challenge for many individuals who seek an immediate "fix." Also, unfortunately, there is the chance that the drug will not even reach therapeutic effects in the patient regardless of how long he or she waits (i.e., treatment-resistant depression). Another problem is that physicians use trial and error prescribing as the primary method of prescribing antidepressants. Trial and error prescribing is a method by which the physician "blindly" chooses a medication that tends to work, in hope that a response will be seen. This is very inefficient because it

can take months before discovering an efficacious therapeutic regimen for patients. The National Institute of Mental Health has published research that shows that patients who do not find success from their first medication usually find resolution with their second treatment on a different type of medication.⁸ However, this fact can make it even more difficult for patients to accept when asked to "wait" for their therapy to reach full effect. "It has been estimated that about 20 to 30 percent of patients with major depression fail to respond to treatment with a single antidepressant drug given in adequate dosage for an appropriate period."¹⁵ This is a problem to be addressed, and the answer may be a consequence of pharmacogenetics (PGt).

Like all other drugs, antidepressants possess pharmacodynamic (PD) and pharmacokinetic (PK) properties. The PD characteristics relate to the therapeutic effects antidepressants have on neurotransmitters in the brain, while the PK properties can result in increased drug exposure leading to adverse effects, or decrease exposure leading to treatment failure. Pharmacogenomics (PGx), looking across a larger number of genes relative to drug response, takes both PD and PK into account. Therefore, it can be assumed that PGx could be used to "screen and predict whether patients will respond to antidepressants and be able to tolerate the medications."⁷

Depression and antidepressants actually serve as a perfect platform for PGx research since genetics play a large role in both the disease and drug therapy. First, most antidepressant drugs are metabolized via CYP450 enzymes, and it has already been proven through many studies that the CYP450 enzymes have numerous variations and mutations based on different genes and alleles that exist within the human population.^{7,15} Therefore, if professionals can identify specific polymorphisms in patients they can predict their inherent metabolic capacity to metabolize antidepressant drugs before ever beginning treatment. Second, depression itself has shown to be 40 to 50 percent due to "heritability." This means that nearly 50 percent of all cases of depression are actually related to genetics.⁴ That being said, if a family member has previously responded well to a certain antidepressant, this could be a positive indication that the same drug will also work for a relative with a similar genetic profile. Ultimately, health care professionals can use genetics first to designate a patient's predisposition for depression, and then add the use of PGx to determine their metabolic capacity to process antidepressant drugs. As a result, health care providers can have some expectation of treatment effects before beginning therapy and, thus, they can better predict drug responses to antidepressant medications and minimize the burdensome requirement to "wait."⁷

In an attempt to transform subjective data into objective data, four distinct phenotypic categories have been created for placement of individuals based on their CYP450 genotype "star nomenclature." These include: poor metabolizer (PM), intermediate metabolizer (IM), extensive (normal) metabolizer (EM;NM), and ultrarapid metabolizer (UM).¹ For example, PMs cannot metabolize the drug as efficiently as needed

which may result in increased side effects or even toxicity as the drug accumulates. If the medication is a prodrug, metabolism by a CYP enzyme is required for activation, and in this case would be compromised leading to decreased efficacy. Conversely, a UM would metabolize an active drug very efficiently, resulting in a decrease in efficacy and a greater dose would be required to achieve therapeutic levels.

Due to the variance in patient outcomes and the need to know a patient's genetic composition for predicting the effectiveness of an antidepressant, genetic testing of the genes that code for enzymes that metabolize antidepressant medications would help optimize therapy. Various companies exist that can perform this type of genetic testing for patients. One such company is Genelex Corporation. This company provides a software product called YouScript® which is a tool that can help pharmacists and other health care providers in the interpretation of genetic information. YouScript® includes a three-step process for patients interested in having individual SNPs identified that are relevant to their disease state. First, the patient would need to talk with his or her physician to have a prescription form completed for the testing. Depending on what genes are being tested and a patient's insurance, the testing may be covered. Next, the prescriber would follow the kit instructions and send in a cheek swab sample from the patient. After about five to seven days, the results of the genetic testing would be returned, which could be used by a physician to assess the likelihood of how effective a medication would be. Although there is some lag time to get the results of a genetic test, this is still less than the typical time to analyze the efficacy of an antidepressant through standard practice as described earlier. For a patient starting a new antidepressant therapy, he or she will not need their entire genome sequenced. Genetic variance needs to be identified for genes that are relevant to the antidepressant medications a patient will be taking. As it relates to antidepressants, the genetic information for the genes that code for the enzymes NAT2, CYP2D6, CYP2C19, and CYP1A2, and the reuptake transporter 5-HTT may be needed depending on the medications being prescribed.¹⁶ Although these four enzymes and transporter are involved, the majority of antidepressants are metabolized in the liver by either CYP2D6 and/or CYP2C19.¹⁷ By knowing and understanding a patient's genetic profile, physicians and pharmacists will be better able to serve a patient and individualize his or her therapeutic regime.

Cytochrome P450 2D6 (CYP2D6)

Cytochrome P450 2D6 (CYP2D6) is an enzyme coded by CYP2D6 gene which is found on chromosome 22 and is expressed in many tissues, particularly the liver.¹⁷ This enzyme (CYP2D6) biotransforms approximately 25 percent of known drugs that are metabolized by the CYP family and is one of the most important enzymes for metabolism of antidepressants.¹⁷ The CYP2D6 gene has more than 100 different variations, some of which are shown in Table 1.^{16,18,19} Depending on the SNPs, the enzyme could have active, inactive or partially active function. Additionally, CYP2D6 is not considered an inducible enzyme (via drug interactions) and varied responses of the action of this enzyme among patients is due to their inherited genetics.²⁰ Because there are so many different alleles of CYP2D6, it can be a challenging gene in terms of determining if a medication will likely be effective.²⁰ For antidepressants, CYP2D6 is important for the metabolism of SSRIs and tricyclic antidepressants (TCA).¹⁶ Tricyclic antidepressants are hydroxylated by CYP2D6 to less active forms. The polymorphisms that a patient has will influence his or her likelihood to experience a therapeutic response or adverse events. For example, a patient that is a poor metabolizer because of inactive or partially active forms of the enzyme is at increased risk of experiencing adverse events because of elevated TCA plasma levels. In these individuals, alternative medications may be needed.¹⁸ In addition, medications can be metabolized by other enzymes, which may also be controlled by genes with many variants.

Cytochrome P450 2C19 (CYP2C19)

In addition to the CYP2D6 enzyme, cytochrome P450 2C19 (CYP2C19) is also an important enzyme for the metabolism and activation of antidepressants. CYP2C19 is the gene coding for this enzyme which is found on chromosome 10 and also has a wide range of variation with as many as 34 polymorphisms identified.^{19,21} Some antidepressant medications such as amitriptyline, clomipramine, doxepin, imipramine and trimipramine are in a less active form and have to be demethylated to active metabolites by CYP2C19 in order to induce their therapeutic effect.¹⁸ In a patient that has a genotype for partially active or inactive CYP2C19 enzyme (Table 2), this individual may not achieve the desired response because not enough of the compound is in the active form. By knowing the PGt of an individual prior to antidepressant medication prescribing, a health care professional could recognize that the patient would likely not respond to

Table 1. Polymorphisms for CYP2D6¹⁶

	CYP2D6 Polymorphisms
Active	*1, *2, *35
Inactive	*3, *4, *5, *6, *7, *8, *11, *12, *14, *15, *19, *20
Partially Active	*9, *10, *17, *29, *41

Table 2. Polymorphisms for CYP2C19¹⁶

	CYP2C19 Polymorphism
Active	*1
Inactive/ Loss-of-Function	*2, *3, *4, *5, *6, *7, *8, *12
Partially Active	*9, *10
Gain-of-function	*17

amitriptyline if he or she has a certain polymorphism of the CYP2C19 enzyme. This would help eliminate the guessing game of prescribing antidepressant medications. The variations of the enzymes that are genetically determined yet again demonstrate the need for genetic testing for people being prescribed a new antidepressant therapy.

Cytochrome P450 1A2 (CYP1A2)

Cytochrome P450 1A2 (CYP1A2) is another important cytochrome P450 metabolic enzyme (comprising of 13 percent of all CYP proteins) that is coded by the CYP1A2 gene located at chromosome 15 with other CYP1 genes (CYP1A1 and CYP1B1).^{22,23} Over 100 substrates for CYP1A2 have been reported including drugs such as caffeine (major substrate), procarcinogens and endogenous substrates.²² Some important inducers of CYP1A2 include cigarette smoking, proton pump inhibitors (esomeprazole and omeprazole), cruciferous vegetables (cauliflower, cabbage, broccoli and similar green leafy vegetables), whereas some important inhibitors include ciprofloxacin (Cipro®) and other fluoroquinolones, fluvoxamine (Luvox®) (SSRI), oral contraceptives, verapamil (Calan®) and grapefruit juice; a more complete list can be found at <http://youscript.com/uploads/P450chart.pdf>.¹⁶ Also, similar to other main drug-metabolizing CYPs, a number of allelic variants have been identified that clearly explain the phenotypic variability in CYP1A2 gene expression or inducibility.²⁴

Over 40 haplotype variants have been discovered in CYP1A2 and only 12 of these variants have been clearly associated with one of four phenotypes including normal enzymatic activity, inducer of enzymatic activity, decreased or abolished expressivity, or decreased enzymatic activity (inhibitor) with most being classified as inhibitors.^{19,25} The allele accounting for normal enzymatic activity is CYP1A2*1A. One important allelic variation in CYP1A2 is a SNP at nucleotide position 163 where adenosine (A) replaces cytosine (C) which is designated by 163C>A. This SNP has been reported to result in increased (induced) enzymatic activity and is noted by the reference sequence number (rs #, refSNP, rs) rs762551.^{25,26} Three other allelic variations that decrease or abolish expression of CYP1A2 include *3, *4, and *6. The remaining seven allelic variations are clearly associated with phenotypes linked to decreased enzymatic function include *1C, *1K, *7, *8, *11, *15, *16.^{19,25} Relatively little

is known about other CYP1A2 polymorphisms (SNPs) in terms of their functional consequences possibly due to lack of research because CYP1A2 is not as prevalent as other CYP enzymes and is not a major metabolizing enzyme of most drugs.²⁶

Within the classes of antidepressant drugs, fluvoxamine (Luvox®) is the only SSRI in which CYP1A2 plays a minimal role (5-10%) in metabolism.²² The metabolic pathway for fluvoxamine through CYP1A2 is methyl-ether demethylation, which is when a methyl ether is replaced with a hydroxyl group that causes the drug to be inactivated.²² Since CYP1A2 plays a very minimal role in fluvoxamine metabolism, it is highly unlikely that the dosage will need to be adjusted in these patients. Coincidentally, a study done by Christensen et al. found that fluvoxamine is a strong inhibitor of CYP1A2 and CYP2C19 due to results showing significant (40-50%) inhibitory effect on both enzymes even at low doses.²⁷ Patients taking fluvoxamine need their medication profiles reviewed to identify medications that utilize CYP1A2 or CYP2C19 as a major metabolic pathway, due to the inhibitory effect of fluvoxamine. Primary care physicians will need to make dose adjustments for some medications or switch patients to a different drug regimen to avoid drug toxicity from occurring. Furthermore, patients may need therapy adjustments if they choose certain diets or lifestyles (e.g., smoking) that induce or inhibit enzymatic activity of CYP1A2. There are a few other antidepressants that are major substrates for CYP1A2 including amitriptyline (Elavil®), chlorpromazine (Thorazine®), duloxetine (Cymbalta®), imipramine (Tofranil®), olanzapine (Zyprexa®); a more complete list including antidepressants that are metabolized by CYP1A2 and additionally CYP2D6, CYP2C19, and other enzymes can be found at http://www.plasmaspiegel.at/TDM_consensus_document_2011.pdf.²⁸ Undoubtedly, there is still an unmet need for research in determining variant allele associations with phenotype groups for CYP1A2. The hope is that future studies will be able to adequately guide recommendations for treatment adjustments for patient phenotypes that either affect metabolic efficiency or expressivity of CYP1A2.²⁵

Table 3. Polymorphisms for CYP1A2^{19,25}

Phenotype	CYP1A2 Allele
Wild-Type	*1A
Abolished / Decreased Expression	*3, *4, *6
Enzyme Inducer	*1F
Decrease Enzyme Activity (Inhibitor)	*1C, *1K, *7, *8, *11, *15, *16

Not all factors of drug response rely on hepatic metabolism. In the case of antidepressants, as well as many anticancer agents and other drugs, drug response is also determined by mutations in the expression of transporters and other cell proteins.¹⁶ In other words, a patient's CYP genotype is not the sole factor in determining their response to antidepressant therapy. Currently, the U.S. Food and Drug Administration (FDA) recognizes 155 clinically significant biomarkers directly affecting patients' response and tolerance to medications.²⁹ In a study by Lee and associates, a mutation in the gene coding for an intracellular signaling protein was associated with a significantly better response to SSRI therapy.³⁰ Dysfunctions in a protein controlling the activation of brain-derived neurotrophic factor (BDNF) as well as the enzyme catechol O-methyltransferase (COMT) gene have also been established in predicting antidepressant response outcomes.^{31,32} These newly identified biomarkers affecting drug metabolism and response serve as future drug targets for better patient-specific therapy.

N-acetyltransferase 2 (NAT2)

N-acetyltransferase 2 (NAT2) is an enzyme coded by the gene NAT2 which is found at chromosome 8 (specific location: p21.3-p23.1). This enzyme is responsible for acetylation of the nitrogen atom in many drugs, including antidepressants.³³ N-acetyltransferase 2 acts on 1 percent of drugs in current clinical use and is thought to contribute to the breakdown of different classes of drugs including antidepressants. The proportion of slow, intermediate, and rapid metabolizers (acetylators) is known to differ between different ethnic populations.¹⁶ The only specific inhibitor for NAT2 is acetaminophen which weakly inhibited the enzyme by 30.9 percent in rapid acetylators and 19.3 percent in slow acetylators (no data for intermediate acetylators given).³⁴ There are currently over 87 variants that have been identified in NAT2 with the wild-type identified as NAT2*4.²⁵ Allelic variations are associated to low enzymatic activity (*5, *6, *7, *14, *17, *22), rapid (normal) enzymatic activity (*11, *12, *13, *18, *20, *21, *23, *24, *25, *27), and no enzymatic activity (*15, *19A, *19B).²⁵ Three phenotypes are identified between varying alleles in these categories that can be classified as rapid (normal) acetylators (two rapid activity alleles), intermediate acetylators (one low activity one rapid activity allele), or slow acetylators (two low activity alleles).³⁵ Assigning acetylator phenotype according to alleles is very challenging due to the fact that six different SNPs influence the phenotype presentation in which patients can have any

different number of them. In order to determine if patients are rapid, slow, or intermediate acetylators, a free online program called the NAT2 website predictor (NAT2PRED), <http://nat2pred.rit.albany.edu>, implements a pattern recognition according to the combination of SNPs found in NAT2 at positions 282, 341, 481, 590, 803 and 857.³⁵ Patient SNPs in NAT2 can be identified by genetic testing, and the website allows selection between the different SNPs the patient may contain. Once submitted, the predictor assigns one of the three NAT2 phenotypes based on the combination of SNPs inputted whereby health care providers can make adjustments to dosing of medications.³⁵ Clinicians should also be aware that NAT2 activity is also dependent upon hepatic and renal function status and age.¹⁶ Some dosing recommendations (for drugs impacted by NAT2) provided by youscript.com include starting at the lowest dose possible of a drug in which efficacy can be seen and employing therapeutic drug monitoring in intermediate acetylators and slow acetylators.¹⁶ Further studies are required to determine whether genotyping of NAT2 is clinically useful for determining a patient's dosage for efficacy of treatment and to avoid drug toxicity, especially in antidepressants.²⁵

Serotonin Reuptake Transporter (SERT-1 or 5-HTT)

The serotonin reuptake transporter 1 (SERT-1 or 5-HTT) is coded by the gene, SLC6A4, and is a protein mainly found on serotonergic presynaptic neurons in the brain, playing a primary role in the termination of the synaptic effects of serotonin (5-hydroxytryptamine or 5-HT) following its presynaptic release.³⁷⁻³⁹ The role of the transporter is to carry extracellular 5-HT across the cell membrane into the neuron, via a conformational change, which allows the cell to either recycle intracellular 5-HT into storage vesicles or metabolize unpackaged intracellular 5-HT with enzymes.³⁷⁻³⁹ The promoter activity of SLC6A4 is located at chromosome 17 (specific location: q11.1-q12) and may contain an indel (insertion or deletion of DNA) polymorphism in a region known as the 5-HTT gene-linked polymorphic region (5-HTTLPR). A polymorphism in this region can alter transcriptional efficiency (production) of the transporter protein itself causing problems with the regulation of serotonin.^{38,39}

About 40 percent of the North American population, especially in populations of European ancestry, have a genetic variation in 5-HTTLPR which is associated with reduced efficacy of SSRIs, a slower overall onset of treatment, and often times an indication for a change in therapy.¹⁶ The short (S)

Table 4. Polymorphisms for NAT2 ^{25,35}

Phenotype	NAT2 Allele
Wild-Type (Rapid Enzymatic Activity)	*4
Slow Enzymatic Activity	*5, *6, *7, *14, *17, *22
Rapid Enzymatic Activity	*11, *12, *13, *18, *20, *21, *23, *24, *25, *27
No Enzymatic Activity	*15, *19A, *19B

allele is associated with lower transcriptional efficiency of 5-HTT (due to a deletion with an overall length of 44 base pairs), whereas the long (L) allele maintains normal transcriptional efficiency of 5-HTT.³⁸⁻⁴⁰ Patients will contain one of three possible allele pairs (genotypes) including homozygous L/L, heterozygous S/L and homozygous S/S.¹ Depressed patients containing the L/L or L/S variant genotypes have demonstrated a better response to SSRIs than those patients with the S/S (short) variant.¹ Although the L allele is significantly associated with better treatment outcomes with SSRI therapy, it is unclear exactly why the L allele would confer a favorable outcome. One proposed mechanism surmises that the L allele makes the HTTLPR region better able to regulate the transporter's response to dynamic changes in extracellular concentrations of 5-HT; such as those affected by environmental changes and/or administration of SSRIs (mainly due to the activation of a stronger feedback mechanism).⁴¹ Some more recent studies now suggest that the presence of promoter binding elements may increase with antidepressant treatment due to evidence from a differential effect (the effect of applying one treatment instead of the other) with the promoter region insertion.⁴¹ Other studies have proposed possible mechanisms explaining the association between the L allele and better treatment outcomes, however, future research should evaluate these mechanisms to define a more distinct answer. Furthermore, studies have not researched the possible genotype effect on a dose response curve which would indicate whether dosing could optimize antidepressant treatment based on the patient's genotype.⁴¹ Clinically, there are no clear recommendations for dosing medications based on individual genotypes, however, educating patients about their individual genotypes can be beneficial in optimizing treatment. Patients carrying a genotype that is associated with a less beneficial treatment outcome compared to others should be made aware of possible alternative approaches if SSRI treatment fails. In addition, patients could also be encouraged to try alternative therapies due to the different mechanisms that other treatments target.

Clinical Relevance

In addition to genetic differences related to PK, drug-drug interactions also have their place regarding antidepressant dosing and medication choice. Citalopram primarily undergoes its metabolism by the enzymes CYP3A4 and CYP2C19 while sertraline is subject to CYP2D6 metabolism.^{42,43} These SSRIs, both of which are in the top 20 most prescribed drugs of 2012, demonstrate a high potential for interaction with medications sharing the same enzyme.⁴⁴ The easy-to-acquire, over-the-counter proton pump inhibitors, omeprazole and lansoprazole, also require metabolism by CYP2C19 and can decrease the metabolism of other 2C19-dependent medications.⁴³ These enzymes are also known metabolizers of many of the top 100 prescribed drugs, and substrates of these enzymes may compete for the enzyme's activity, resulting in a drug-drug-gene interaction known as a phenotype conversion or phenoconversion. These interactions can either be synergistic or antagonistic and can enhance or decrease a drug's effect, respectively, possibly rendering a previous EM to a UM or PM.

With knowledge of patients' genotypes, both pharmacists and prescribers are able to personalize therapy and provide the optimal drug and/or dose for better patient outcomes. Depression and mental disorders can now be managed accurately and aggressively, and traditional guess-and-check methods will no longer need to be employed for starting antidepressant treatment. In a recent study by Ferreri and associates, community pharmacists performed PGt testing for the CYP2C19 genotype in patients currently taking clopidogrel.⁴⁵ The CYP2C19 enzyme is responsible for converting the prodrug, clopidogrel, to its active metabolite, and its gene is found to have at least one loss-of-function allele in 30 percent of the population.^{46,47} It was found that half of the patients in the study had at least one variant allele (*2 or *17). Recommendations of therapy were made by the pharmacist based on the genotype outcome, and were approved by the prescriber 89 percent of the time.⁴⁵ The remaining 11 percent consisted of therapy changes, including the prescriber knowing the patient's intolerance (via prior experience) to the suggested treatment, and a discontinuation of clopidogrel for a patient not supposed to be receiving it. The knowledge of a patient's genotype allowed the pharmacists to make recommendations to change therapy and perhaps improve outcomes in 50 percent of those who participated.

This study demonstrates the potential for pharmacists' genetic testing in a community setting and direct involvement with improving patients' health and well-being. Initiation of a collaborative agreement between providers (prescriber and pharmacist) will help to streamline therapy regimens and decrease any risk of drug-drug or drug-gene interactions. A comprehensive medication review will most likely become required with PGx testing as to eliminate any potential for adverse events. The possibility to improve outcomes exists prior to initiating treatment by ordering testing upon diagnosis, whether by a primary care physician, specialist or a clinical pharmacist. For antidepressants, preemptive genetic testing before prescribing can provide the greatest immediate benefit by determining an effective medication with which to begin treatment.

Significant barriers exist for implementing PGx testing, especially in a community pharmacy setting. The average time spent by a pharmacist from initially performing the testing and communicating with prescribers to counseling the patient totals over one hour, with lab results averaging over five days, and almost two weeks to receive approval from the prescriber.⁴⁵ At first glance, this laborious process can be seen as a suboptimal business model in the world of fast paced retail chains, but as health care information technology catches up with this blueprint of highly integrated transition of care, we can expect this timeline to dramatically decrease. Billing and reimbursement also remain a factor as all claims sent to medical insurance companies, including Medicare Part D plans, were initially rejected for having the pharmacist listed as the provider, and not the prescriber. Also related to cost are the implications of PGx testing and its overall cost/benefit profile for antidepressant drugs. Additional research is necessary to provide solid evidence dis-

playing increased patient remission rates for depression directly related to genetic testing.

Fortunately, all of these barriers can be overcome with correct implementation of health care information technology and laws. As more and more clinically relevant outcomes are proven relating an individual's genotype to his or her drug response, we can expect to see a paradigm shift in the prescribing and treatment regimen for antidepressant medications as well as other CYP dependent medications. Over 130 FDA-approved drugs currently include PGx information in the package labeling, with 30 of them being classified for psychiatry and/or neurology.²⁹ The increase in evidence will help validate the need for genetic testing and, combined with the decreasing cost of DNA sequencing, will accelerate the acceptance of reimbursement by insurance companies.

Conclusion

Pharmacists maintain a major role in applying and utilizing personalized medicine and are beginning to base many clinical decisions on PGt in both the community and health-systems setting. Personalized medicine is reaching antidepressant therapy due to the increased research in PGt and the reduction of cost in genetic testing.¹⁷ Pharmacists can utilize genetic information to help primary care physicians choose drug regimens that are more likely to be beneficial to their patients. Pharmacists can also make recommendations to patients' diet and lifestyle choices (e.g., smoking) that might cause an increase or decrease in drug efficacy. It is also important for pharmacists to be aware of medications that may induce or inhibit the normal enzymatic activity and to understand what enzymes are major metabolic pathways of each drug which ultimately affects what treatment regimens are chosen.

The future of personalized medicine, including PGt testing related to PK and PD, could ultimately lead to better clinical outcomes. Studies show that patients utilizing individualized therapy based on genotypes have better outcomes and achieve efficacious therapeutic regimens quicker. Although most antidepressant treatment does not have distinct pharmacotherapy guidelines based on polymorphisms, the expectation is that more extensive research will result in the development of guidelines for dosing and drug selection based on patient genotypes. Nevertheless, pharmacotherapy adjustment guidelines are currently seen for drugs in diseases that present less complex heritability models such as warfarin and clopidogrel.³⁹ Recently, many discoveries have been made toward the pathophysiology of mood disorders and their treatment mechanisms, however a major target for research should be to evaluate the efficacy of therapies and dosing based on patient genotypes. Another major target for future research is the development of genotyping kits at lower costs in order to individualize patient treatments more effectively.³⁹ Genotyping, especially for patients on antidepressants, will prevent the primary care physician from having to use trial and error prescribing to find an effective drug and dose for their patients. Furthermore, screening a patient's genotype eliminates therapeutic options that would have been deemed effective in most other patients.

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