REVIEW ARTICLE

PSYCHOPHARMACOGENOMICS: A NEW TOOL FOR THE PRESCRIBING PHYSICIAN

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ABSTRACT:

The evolution of personalized medicine has begun, and personalized psychiatry is following the approach of personalized medicine. The US Food and Drug Administration (FDA) reports that there are currently over 100 prescription medications that have pharmacogenomic information in their product labels and approximately 30% of these are psychotropic medications. For these psychotropics, the pharmacogenomic information included within the label addresses genotypes of either CYP2D6 or CYP2C19. This makes our understanding of cytochrome P450 enzyme (CYP450) pharmacogenomics especially important. In addition, a high percentage of psychotropic medications are metabolized by these enzymes. Enzymes that are most relevant to the metabolism of psychotropics include CYP450 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4.

The fields of pharmacogenomics and pharmacogenetics have experienced tremendous development. Polymorphisms in the genes which code for the production of CYP450 enzymes can alter the rate at which affected enzymes can metabolize medications (also referred to as substrates). For each enzyme, a patient may be characterized as being an: extensive (normal) metabolizer, intermediate metabolizer, poor metabolizer, or ultra-rapid metabolizer. Extremes in metabolic rates resulting from gene polymorphisms may contribute to either poor tolerability (poor metabolizers), or to poor efficacy (ultra-rapid metabolizers) when using psychotropics that are dosed in anempirical manner. The capacity to genotype a patient's CYP450 enzymes is currently available. Therefore knowing the patient's inherited metabolizer status can be helpful in selecting psychotropic medications that avoid metabolism through a polymorphic pathway, or to adjust a dosing strategy in an effort to avoid poor treatment outcomes when the patient is treated with a medication that is being metabolized through a polymorphic pathway.

This review will focus on the metabolism of psychotropics and important aspects of understanding the genomics of the cytochrome P450 enzymes. This review will also discuss a case scenario which illustrates a process that physicians can use when applying genomic laboratory data to patient care.

KEY WORDS

Cytochrome P450 enzymes, Pharmacogenetics, Pharmacogenomic Testing

INTRODUCTION

Clinical Pharmacogenomics attempts to link identifiable genetic variants to the prediction of drug response.[1] Historically, psychiatrists have used empirical approaches to prescribe medications using a trial and error process combined with close patient monitoring. Unfortunately with this approach there can be a long wait for the patient and physician to find the right medication that will result in symptom relief. If a selected medication results in an inadequate response following an adequate treatment trial, the physician will then either add, or switch to another, medication and begin the process again. During this process, the patient may either continue to experience distressing symptoms, or be at risk for being over-medicated. Pharmacogenomic testing provides us with an innovative tool to help inform the selection of psychotropic medications for our patients. The practical relevance of genotyping drug metabolism enzymes began in 2004 when FDA approved the AmpliChip CYP 450 Test.[2] This genotyping test provides practitioners and patients with a reliable method of identifying common gene variants for the CYP2D6 and 2C19 enzymes.[3] Presently, there are many laboratories in the United States that offer CYP450 enzyme genotype testing.[4]Cytochrome P450 Overview:

The CYP 450 is a collection of enzymes that are responsible for the oxidative phase 1 metabolism of medications. The nomenclature of the enzymes is genetically based and has no functional implication. This system first assigns a family member, then a subfamily letter, and finally an individual enzyme number(e.g.,2D6,2C9).[5] A high percentage of psychotropic medications are metabolized by the cytochrome P450 enzyme system (CYP450; see Table 1). Particularly relevant to psychiatry are CYP450 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4 enzymes. For each of these

enzymes, there are 4 distinct metabolizer status'; the rules that determine a patient's inherited metabolizer status have been described by Black et al: [6]

Ultra-rapid metabolizers (UM): UM represents a metabolic capacity that is greater than normal. Genotypes consistent with UM phenotype include three or more active genes each coding for the production of drug metabolizing enzyme and therefore have increased metabolic capacity. They likely will require an increased dosage due to higher than normal rates of drug metabolism.

Extensive Metabolizers (EM): EM represents normal metabolic capacity. Genotypes consistent with the EM phenotype include two active forms of the gene producing an enzyme with full drug metabolizing capacity. In general, extensive metabolizers are treated with medications that are substrates for these enzymes following standard dosing practices.

Intermediate Metabolizers (IM): IM represents decreased (but not absent) metabolic capacity. Genotypes consistent with the IM phenotype are those with only one active form of the gene producing the drug metabolizing enzyme and therefore have reduced metabolic capacity. Patients who have this genotype may require medication doses that are lower than average.

Poor Metabolizers (PM): PM represents absent metabolic capacity. Genotypes consistent with the PM phenotype are those with genes that code for producing inactive enzyme. These individuals, therefore, are unable to metabolize substrates through the affected enzymatic pathway. Using standard dosing practices, these patients are at increased risk for accumulating the affected medication and drug-induced side effects or lack of therapeutic effect resulting from failure to generate the active form of the drug.

DISCUSSION

In order for a medication to generate the intended therapeutic response for a patient, it must typically be given at a sufficient dose over a sufficient duration of time. For example, when treating major depression in an adolescent patient with citalopram, one typically should give at least X mg/day for at least Y weeks before treatment efficacy is determined. In particular, when dosing any medication, we are attempting to achieve a desirable concentration of that medication at receptor target(s) in the brain so that the patient has the best opportunity to respond. When clinically important gene polymorphisms are present for pertinent CYP450 enzymes, the corresponding alteration in drug metabolism rate and corresponding target site concentrations may potentially lead to poor, and sometimes tragic, treatment outcomes. For example, Sallee et al[7] reported the case of a 9 year-old patient diagnosed with Obsessive-Compulsive disorder, Attention Deficit Hyperactivity disorder and Tourette's disorder who was treated with fluoxetine, methylphenidate and clonidine. Over a ten month period, the patient experienced episodes of disorientation, poor coordination, gastrointestinal distress and low-grade fevers. As time went by, these episodes ultimately lead to the patient having generalized seizures that developed into status epilepticus and cardiac arrest resulting in patient's death. The ensuing autopsy lead to the discovery of fluoxetine toxicity where a subsequent genotyping revealed that the patient had been a CYP2D6 poor metabolizer. Thus, awareness of a patient's CYP450 genotpying can have a therapeutic impact. (Table 2 provides a case example that illustrates the interpretation and application of genotyping results.)

However, a change in the rate of drug metabolism is not the only potential contributor to poor treatment outcomes. Since drug molecules must interact with receptor targets in order to illicit the intended response, alterations in receptor target genetics may also influence treatment outcomes. One example of this may be seen in the genetic variability that has been reported for the serotonin transporter in cases of major depression and when SSRI antidepressant treatment responsiveness is being considered. A meta-analysis performed by Serretti et al[8] supported the findings of other researchers when they concluded that patients who were homozygous for the long-form of the 5-HTTLPR had greater response rates than those patients without this genotype. Therefore, it appears that taking into consideration receptor target genetics may also be important in determining a patient's treatment outcome.

An additional consideration of interpreting and applying genotyping results is to be aware of additional drug therapy that the patient is taking and whether or not any of those medications have effects on CYP450 enzyme activity. In addition to any CYP450 gene polymorphisms a patient may have, the patient may also be taking a medication(s) which may either be an inhibitor or inducer of CYP450 enzyme activity. For example, there are at least five antidepressants that are clinically important CYP450 inhibitors: fluoxetine (2D6 inhibitor), paroxetine (2D6 inhibitor), fluvoxamine (1A2 and 2C19 inhibitor), duloxetine (2D6 inhibitor) and bupropion (2D6 inhibitor). The interplay between CYP450 gene polymorphisms and CYP450 inhibitory effects from co-prescribed medications was illustrated nicely in a case report by Gasche et al[9] who described a case of morphine toxicity from codeine treatment in a patient who was genotyped as a CYP2D6 ultra-rapid metabolizer and who was co-prescribed medications that were CYP3A4 inhibitors.

This testing is currently available in the developed countries but psychiatrists and patients from the underdeveloped countries will benefit if it becomes available to improve outcomes. Interested readers should consider reviewing additional information to inform their understanding of this potentially important clinical data for their patient.[10-13]

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TABLE 1: SUMMARY OF PSYCHOTROPIC MEDICATION CYP45 METABOLISM.

CLASS	1A2	2B6	2C9/19	2D6	3A4
ANTIANXIETY			Diazepam (19)		Alprazolam
					Buspirone
					oxazepam
					Diazepam
ANTIDEMENTIA				Donepezil	Donepezil
				Galantamine	Galantamine
ANTIDEPRESSANT	Amitriptyline	Bupropion	Amitriptyline (19)	Desipramine	Citalopram
	Duloxetine	Sertraline	Citalopram (19)	Duloxetine	Mirtazapine
	Fluvoxamine		Fluoxetine (9)	Fluvoxamine	Nefazodone
	Imipramine		Imipramine (19)	Mirtazapine	Sertraline
	Mirtazapine		Sertraline (9)	Nortriptyline	
				Paroxetine	
				Venlafaxine	
ANTIPSYCHOTIC	Clozapine			Aripiprazole	Aripiprazole
	Haloperidol			Fluphenazine	Asenapine
	Olanzapine			Iloperidone	Clozapine
				Perphenazine	Iloperidone
				Risperidone	Quetiapine
					Ziprasidone
HYPNOTIC	Melatonin		Doxepin (19)	Doxepin	Eszopiclone
	Ramelteon				Quetiapine
					Suvorexant
					Trazodone
					Triazolam
					Zolpidem
MISCELLANEOUS	Propranolol		Benztropine (9)?	Benztropine?	Guanfacine
				Clonidine	
				Propranolol	
MOOD STABILIZER					Carbamazepine
					Tiagabine
STIMULANT				Atomoxetine	Modafinil
				Dextroamphetamine	

TABLE 2: CASE EXAMPLE

Cytochrome P450 testing was ordered for a patient with a diagnosis of Bipolar disorder and Generalized Anxiety disorder due to history of multiple trials of psychotropic medications without much relief of psychiatric symptoms as well as intolerability.
The patient's genotyping results revealed the following:

CYP2C9*1/*1 (*1 allele is normal),CYP2C19*1/*17 (*1 allele is normal, *17 allele codes for increased transcription) and CYP2D6*4 /*35 (*4 allele codes for inactive enzyme, *35 allele codes for normal enzyme activity)

These genotyping results indicated that patient had an extensive (normal) metabolizer status for both CYP2C9 and CYP2C19. For CYP2D6, the patient was anticipated to be an intermediate (sub-normal) metabolizer for drugs metabolized by CYP2D6 which means that careful dose adjustment and monitoring will be required.

There were past medication trials of Aripiprazole, Risperidone and Fluoxetine resulting in inadequate response and or side-effects. Looking at patient's genotype it is most likely that patient did not tolerate these medications due to sub-normal metabolizer status of CYP2D6.

Looking at her genotype profile she was started on lamotrigine which is metabolized primarily through the kidneys and Ziprasidone which is not metabolized by above mentioned enzymes. Patient tolerated these medications well with good symptom control.