Pharmacogenomic testing in child and adolescent psychiatry: An evidence-based review

Anna M. Wehry, MD,[a] Laura Ramsey, PhD,[b] Shane E. Dulemba, MSN, ARNP,[c] Sarah A. Mossman, BS,[a] and Jeffrey R. Strawn, MD[a]

Significant advances have been made in the application of pharmacogenomic testing for the treatment of patients with psychiatric disorders. Over the past decade, a number of studies have evaluated the utility of pharmacogenomic testing in pediatric patients with psychiatric disorders. The evidence base for pharmacogenomic testing in youth with depressive and anxiety disorders as well as attention/deficit hyperactivity disorder (ADHD) is reviewed in this article. General pharmacogenomic principles are summarized and functional polymorphisms in P450 enzymes (and associated metabolizer phenotypes), the serotonin transporter promoter polymorphisms, serotonin 2 A receptor genes (e.g., HT2AR) and catecholamine pathway genes (e.g., COMT) are reviewed. These commonly tested pharmacogenomic markers are discussed with regard to studies of drug levels, efficacy and side effects. The translation of pharmacogenomics to individualized/precision medicine in pediatric patients with ADHD, anxiety and depressive disorders has accelerated; however, its application remains challenging given that there are numerous divergent pathways between medication/medication dose and clinical response and side effects. Nonetheless, by leveraging variations in individual genes that may be relevant to medication metabolism or medication target engagement, pharmacogenomic testing may have a role in predicting treatment response, side effects and medication selection in youth with ADHD, depressive and anxiety disorders.

Curr Probl Pediatr Adolesc Health Care ▮▮▮▮;▮:1-9

Introduction

The promise of personalized medicine and of genetically informed treatment selection that heralded the beginning of this millennium has yet to be fully realized. However, great advances have been made with regard to the application of pharmacogenomic testing to the treatment of patients with psychiatric disorders. To date, much of this work has been conducted in adults treated with antidepressants, stimulants, second generation antipsychotics, and antiepileptic medications. The last decade has seen an increasing number of studies examining the utility of pharmacogenomic testing as a predictor of treatment response and medication tolerability in pediatric patients.

Pharmacogenetic testing—in its most basic application—leverages variations in individual genes relevant to medication metabolism or targets to predict treatment response and may guide treatment selection. Ideally, this testing would maximize the likelihood that a specific psychotropic medication produces the best therapeutic benefit while minimizing adverse effects. Initial use of pharmacogenomic testing focused on single genes (e.g., cytochrome P450 genes) related to medication metabolism and consequently medication exposure. The first FDA-approved pharmacogenetic test, the AmpliChip CYP450 employed a DNA microarray to assess two polymorphisms in *CYP2D6* and *CYP2C19* (Roche molecular Systems, Inc: AmpliChip CYP450 Test for in vitro diagnostic use). However, more recent strategies utilize combinatorial strategies that rely on (usually proprietary) algorithms; such a test might utilize the genotype for a series of genes [several cytochromes, the serotonin transporter (*SLC6A4*), and the serotonin 2 A receptor ($5HT_{2A}$), etc.] to generate a profile that aims to guide prescribing for several classes of psychiatric medications.

Given the increase in pharmacogenomic testing and the rapid pace at which data are accumulating in pediatric patients, we sought (1) to summarize the underlying principles of pharmacogenomic testing in youth with psychiatric disorders, (2) to review current

From the [a]University of Cincinnati, College of Medicine, Box 0559, Cincinnati, OH 45267-0559; [b]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; and [c]Division of Child and Adolescent, Cincinnati Children's Hospital, Cincinnati, OH.

Curr Probl Pediatr Adolesc Health Care ▮▮▮▮;▮:▮▮▮-▮▮▮
1538-5442/$ - see front matter

https://doi.org/10.1016/j.cppeds.2017.12.003

data that support its use, and (3) to discuss potential limitations.

Cytochrome P450 enzymes

The cytochrome P450 system refers to a group of enzymes called monoxygenases that are critical for elimination of many drugs. They are expressed in every tissue although greatest expression is observed in hepatic tissue. Collectively, these enzymes represent Phase I metabolism; they catalyze the transformation of lipophilic drugs into more polar compounds that are then excreted by the kidneys. The genes, and consequently the proteins that they encode, are highly variable as multiple alleles exist for each cytochrome (e.g., *CYP2D6*—more than 100 alleles have been identified). Specific alleles may code for a fully functional enzyme or an enzyme with decreased or absent activity. In addition, an individual may express multiple copies of an active allele or an allele with enhanced activity, resulting in an increased metabolic rate compared to the wild type (i.e., the prevailing phenotype or "normal" form in the population). A "star" designation is used to refer to specific alleles, with *1 denoting the standard by which the activity of enzymes encoded by other alleles is measured.

An individual's metabolizer phenotype for a particular cytochrome takes into account the activity of each of the patient's two alleles (e.g., *1/*2). Given the variation associated with each cytochrome, classifying patients into four main groups based on metabolic phenotype represents the most common approach to assigning phenotypes. Using the current standard terminology from the Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network,[1] individuals are classified as extensive (normal), poor, intermediate, and ultrarapid metabolizers (Table 1). This classification system may have significant limitations that are most problematic in the extreme phenotypes (i.e., ultrarapid and poor metabolizers). Thus, some laboratories have reported metabolic phenotypes using a seven-category classification system, that adds phenotypes: enhanced extensive, enhanced intermediate, and reduced intermediate. Examples of allele combinations which could theoretically give rise to these phenotypes are given in Table 2.

A patient's response to a medication is highly dependent on cytochrome P450 enzymatic activity. This phenotypic variance is clinically significant; a patient who is a "poor metabolizer" for a particular P450 enzyme may require lower doses of a medication that is metabolized through that system or he/she will

TABLE 1. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for consideration of genotype and medication dosing or selection for antidepressant medications

Medication	Cytochrome	Phenotype	Recommendation	Strength of recommendation
Paroxetine	*CYP2D6*	Ultrarapid	Select alternative drug not metabolized by *CYP2D6*	Strong
		Extensive	Initiate therapy at standard starting dose	Strong
		Intermediate	Initiate therapy at standard starting dose	Moderate
		Poor	Consider 50% reduction of recommended starting dose or select alternative drug	Optional
Fluvoxamine	*CYP2D6*	Ultrarapid	No recommendations due to lack of data	
		Extensive	Initiate therapy at standard starting dose	Strong
		Intermediate	Initiate therapy at standard starting dose	Moderate
		Poor	Consider 25–50% reduction of starting dose or use alternative drug	Optional
Citalopram and escitalopram	*CYP2C19*	Ultrarapid	Consider using alternative drug	Moderate
		Extensive	Initiate therapy at standard starting dose	Strong
		Intermediate	Initiate therapy at standard starting dose	Strong
		Poor	Consider 50% reduction of standard starting dose or select alternative drug	Moderate
Sertraline	*CYP2C19*	Ultrarapid	Initiate therapy at standard starting dose and consider alternative drug if patient does not respond	Optional
		Extensive	Initiate therapy at standard starting dose	Strong
		Intermediate	Initiate therapy at standard starting dose	Strong
		Poor	Consider 50% reduction of standard starting dose or select alternative drug	Optional