Articles

Safety and Efficacy Pharmacogenomics in Pediatric Psychopharmacology

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Abstract

Historically, clinicians have had few resources beyond empiric tools derived from population-based treatment algorithms and patient/family interviews to inform the "best choice" for psychopharmacologic intervention. Previously unappreciated interindividual variance in activity of cytochrome P450 enzymatic activity can lead to abnormal metabolism of many psychotropics and poor outcomes. Fortunately, advances in our understanding and application of psychiatric pharmacogenomic information have the potential to improve the quality of medical care for children at the level of the individual prescription.

Focus Points
• Advances in pharmacogenomics have the potential to improve the quality of medical care for children at the level of the individual prescription.
• Nearly 80% of all drugs in use today, along with most psychotropics, are metabolized via testable metabolic pathways.
• Children and adolescents with metabolic polymorphisms may be at greater risk for adverse drug events than children with normal metabolism.
• Pediatric psychotropic prescribers must consider treatment-resistant patients as potential abnormal metabolizers.

Introduction

A large number of children and adolescents presenting for health care are affected by mental illness and many require psychotropic medications as a component of their overall care.1,2 Despite increasing choices in medication management, many of these patients still experience poor outcomes related to inadequate medication response and significant adverse drug events (ADEs).3 Given ongoing shortages in the specialty of child and adolescent psychiatry,4 the considerable challenge of prescribing psychotropics in the pediatric population is often managed by adult psychiatrists, family physicians, and pediatricians. In considering whether a medication is the “right” one for a given patient, all clinicians must weigh not only issues such as the potential for side effects, family responses to similar psychotropic medications, and the nature and intensity of the patient’s illness, but also psychosocial concerns. This is a process which is complicated by the knowledge that an incorrect choice could result in intolerable side effects, poor efficacy, and ultimately—perhaps most importantly—a negative view towards medication that may have proved helpful. Lack of efficacy and ADEs are frequently cited as reasons for noncompliance in pediatric psychopharmacology.

Currently, children who are treated without the benefit of individualized molecular genotyping have only a 60% chance of successful long-term treatment.5 Fortunately, advances in our understanding and application of individual pharmacogenetic profiles have the potential to improve the quality of medical care for children at the level of the individual prescription.6 Pickar7 has suggested that there is no specialty where the need for pharmacogenetics seems more compelling than for psychiatry. Psychiatric pharmacogenomics is an emerging tool to assist clinicians in developing strategies to personalize treatment and tailor therapy to individual patients, with the goal of optimizing efficacy and safety through better understanding of genetic variability and its influence on drug response. This article provides discussion of the role emerging pharmacogenomic advancement is playing in the clinical practice of individualized psychopharmacology: moving away from “trial and error” prescriptions to individualized prescribing. The article also highlights the growing literature and adoption of pharmacogenomic principles guiding modern psychotropic prescribing practices focusing on the pediatric population.

Background of Psychiatric Pharmacogenomics

Psychiatric pharmacogenomics is the study of how gene variations influence the responses of a patient to treatment with psychotropics. The most commonly studied cytochrome P450 (CYP) enzymes include 2D6, 2C19, and 2C9. Polymorphisms and gene duplications in these enzymes account for the most frequent variations in phase 1 metabolism of drugs since nearly 80% of all drugs in use today, along with most psychotropics (Tables 1 and 2),8,9 are metabolized via these pathways.9 It should also be noted that genetics may account for 20% to 95% percent of variability in drug disposition and effects.10
Historic and current literature divides metabolic phenotypes into four basic categories. These categories presented from least to most efficient metabolism are as follows: poor metabolism (PM; essentially no metabolism at a given enzyme pathway), intermediate metabolism (IM), extensive metabolism (EM; essentially “normal” metabolism), and ultra-rapid metabolism (UM). For the purpose of discussion, this article will highlight safety and efficacy concerns related to the 15% to 25% of pediatric patients that are either PM or UM metabolizers.11

Safety and Efficacy in Abnormal Metabolizers

The two primary tenets considered in all pediatric prescriptions are safety and efficacy, and both can be more precisely addressed through pharmacogenomics. “Safety pharmacogenomics” aims to avoid ADEs and side effects by identifying individuals who are likely to have difficulty with certain medications due to either increased activity of an enzymatic pathway (UMs), or lack of activity (PMs). “Efficacy pharmacogenomics” attempts to predict an individual’s likely response to a medication at the outset of treatment.12

Interindividual variance of activity of CYP enzymes can lead to abnormal metabolism of most antidepressants (Table 1) and antipsychotics (Table 2). These medications have been associated with a variety of ADEs, ranging from milder side effects, such as activation, irritability, sexual dysfunction, and sedation, to more significant ADEs, such as weight gain, extrapyramidal symptoms, metabolic syndrome, hyperprolactinemia, manic-induction, neuroleptic malignant syndrome, and even suicidality.13 Children and adolescents with polymorphisms leading to abnormal drug metabolism may be at greater risk for some of these ADEs than children with normal metabolism, as medications administered at normal therapeutic doses to poor metabolizers may result in toxicity, and consequently ADEs. Conversely, UMs may not attain therapeutic plasma levels on typical therapeutic doses of medications and the treatment may fail or lead to rapid conversion of prodrug to potentially toxic active metabolites.

Table 33-51 includes a list of ADEs that have been linked to abnormal metabolism of neuroleptics by at least one study involving abnormal metabolizers. As pharmacogenomic
Safety and Efficacy Implications in Poor Metabolism

Weight Gain and Metabolic Syndrome

There is no doubt that weight gain can be detrimental to a young person’s physical and mental health and can exacerbate problems with self-esteem during all developmental stages. Obesity, which is common among schizophrenic patients, is further exacerbated by antipsychotics. It has been shown that decreased metabolism due to variations in several CYP genes may contribute to a patient’s risk profile while taking an antipsychotic. For example, decreased metabolism at CYP1A2, which is known to be involved in the metabolism of some antipsychotics, is associated with increased risk for weight gain and a cluster of clinical features including increased visceral adiposity, hyperglycemia, hypertension, and dyslipidemia known as “metabolic syndrome.” Prevalence of metabolic syndrome is higher in women than it is in men as demonstrated in the Clinical Antipsychotic Trials of Intervention Effectiveness schizophrenia trial. Lower activity of CYP1A2 may also contribute to the risk for metabolic syndrome by leading to increased serum concentrations of antipsychotics at standard doses. Children, especially young females, may be more susceptible to weight gain while on antipsychotics, and weight gain may lead to noncompliance and subsequent relapse.

Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) are frequent and serious acute adverse reactions to antipsychotics. These symptoms include pseudoparkinsonism, acute dystonia, akathisia, and tardive dyskinesia, which may be permanent even after removal of the drug.

Several hypotheses and studies indicate that PM at CYP2D6, which metabolizes several of the typical and atypical psychotropics, may increase the risk of developing EPS. Poor CYP2D6 metabolizers are likely to have higher than average plasma concentrations of neuroleptics with an increased risk for developing EPS, including tardive dyskinesia. PM or inhibition of CYP2D6 may be linked to the induction of EPS. CYP2D6 in the brain is involved in the metabolism of dopamine and has a possible functional association with the dopamine transporter. Several selective serotonin reuptake inhibitors and tricyclic antidepressants inhibit CYP2D6, as do a number of non-psychotropic drugs such as quinidine. Methylphenyltetrahydropyridine, a dopamine neurotoxin able to produce Parkinsonism, is metabolized by 2D6 and is also a 2D6 inhibitor. Vandel and colleagues concluded that
inhibition of CYP2D6 may be involved in the genesis of EPS observed in treatment with 2D6 substrate psychotropics.

It follows that poor CYP2D6 metabolizers may be at increased risk for EPS while on certain antidepressants due to high plasma levels. Indeed, it has been shown that there is a significant association between EPS and the CYP2D6*4 and CYP2D6*6 polymorphisms that are both associated with the poor metabolizer phenotype. Furthermore, there may be a relationship between the degree of impaired CYP2D6 activity and the severity of EPS during neuroleptic treatment. One study demonstrating that the development of EPS or tardive dyskinesia while on antipsychotic medication is significantly more frequent among PMs than among matched IM and EM patients, also found a significantly higher prevalence of noncompliance among the same PM patients. These findings highlight the importance of identifying those at greater risk for experiencing these serious ADEs.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening ADE associated with antipsychotics, antidepressants, and other psychotropics. Signs of NMS include hyperthermia, EPS, altered consciousness, fluctuating blood pressure, incontinence, and dyspnea. While some studies were unable to find a significant link between reduced function of CYP2D6 and NMS, more recent case studies suggest pharmacogenetic factors cannot yet be excluded as risk factors for this serious condition. In two separate case studies, four patients who developed NMS were later determined to have mutations in CYP2D6 conferring the PM phenotype. It was concluded that while not all NMS patients have this poor metabolizer phenotype, poor metabolizers at CYP2D6 may be at increased risk for developing NMS.

Hyperprolactinemia

Conventional antipsychotics and certain atypical antipsychotics, such as risperidone, can cause significant elevations in prolactin. Though no studies have yet been conducted to show a link between PM phenotypes and ADEs related to hyperprolactinemia, this link remains not only possible, but an important consideration in the pediatric population. Amongst other potential developmental concerns, complications from early hyperprolactinemia may include bone loss, which in turn could lead to significant consequences upon reaching adulthood. Furthermore, if this increase in prolactin is dose related, PMs may have elevated risk as they may experience higher serum concentrations of poorly metabolized medication.

Additional Considerations

Prescribers should also bear in mind that over sedation, postural hypotension, and cardiovascular complications may be additional significant concerns in poor metabolizers. Likewise, as clinicians follow their natural tendency to optimize dosing in their treatment of psychiatric symptoms, it may be helpful to remember that, in the PM population, so called "somatic symptoms" associated with psychiatric diagnoses (and subsequent treatment) may in fact be medication intolerance exacerbated by dose titration. Without knowledge of the patient's metabolic phenotype, the clinician must "guess" as to the cause of these symptoms and may incorrectly conclude that the patient is just "anxious" or "dramatic." Furthermore, the clinician must also wonder whether or not the patient will be able to adequately tolerate the next medication choice.

Safety and Efficacy Implications in Ultra-Rapid Metabolism

UMs present their own set of treatment challenges as they may not attain therapeutic plasma levels on normal doses of medications, and thus treatment may have a higher propensity to fail. For example, a recent Swedish autopsy study found that among those who died of suicide, there was a higher number carrying >2 active CYP2D6 genes (UM phenotype) as compared with those who died of natural causes. Postulated explanations for this finding include accumulation of higher levels of metabolites at a faster rate which is a known risk of UM. This
buildup may lead to adverse drug reactions if the metabolite is active or toxic. It could also be argued that in this population, UMs did not reach the desired therapeutic concentration of their prescribed medications and thus had not been treated effectively. This hypothesis is supported by Kawanishi and colleagues, who found UMs as more likely to fail to respond to antidepressants. The ultra-rapid metabolizers in the study also had the worst scores on the Hamilton Rating Scale for Depression leading the authors to conclude that ultra rapid metabolism may be a risk factor for persistent mood disorders.

Case studies in UMs suggest that diphenhydramine may be converted to a compound which causes paradoxical excitation due to the abnormally high CYP2D6 activity. More serious consequences might be seen in children treated with other medications like ephedrine whose ultra-rapid conversion might result in toxic accumulation of morphine leading to death. It follows that UMs could be at increased risk of ADEs from higher levels of toxic or active metabolites from psychotropics.

**Discussion**

To date, much of the available literature on pharmacogenomic testing in the pediatric population has focused on the spectrum of efficacy related to cancer treatments. Impressive results in leukemia remission rates have been described as partly due to advancements in pharmacogenomically derived individualized prescribing practices. Cheok and colleagues highlighted the progress made in the treatment of acute lymphoblastic leukemia in children noting the disease as being lethal 4 decades ago to current cure rates exceeding 80%. This progress is largely due to the optimization of existing treatment modalities rather than the discovery of new antileukemic agents. The literature regarding the pharmacogenomics of asthma treatment and research design has also been quite active in the pediatric population in the past few years. In both cancer and asthma research, there are clear outcomes and endpoints to define treatment response and the role that interindividual variability plays.

Historically, the process of initiating psychopharmacologic agents in the child and adolescent population has been empirically based and one in which the clinician considers many variables including age, gender, access to healthcare, and ability to remain compliant with the proposed treatment. Frequently factored into this consideration are quasi-genetic questions relating to family history of illness as well as family history of medication response. Until very recently, the use of family history has been the only tool available to better understand genetic makeup and its resultant interplay with efficacy and ADEs. In fact, as early as the 19th century, Holmes commented, “All medications are directly harmful; the question is whether they are indirectly beneficial.” Fortunately, unlike in Holmes’ day, we now have the potential capability to resolve that very question; pharmacogenomic testing can help determine in advance whether an individual will respond favorably. Ongoing central nervous system maturation coupled with an increased risk for ADEs makes the utility of this advance most relevant in pediatric psychopharmacology.

Though most prescribing in pediatric psychiatry is still off label, treatment algorithms do currently exist for most classes of psychotropics. Unfortunately, none of these algorithms base their recommendations on psychiatric pharmacogenomics. Furthermore, since dosing recommendations are based on “normal” metabolizers, they do not include the estimated 15% to 25% of the population who is either UMs (and therefore at much higher risk for resultant noncompliance due to never reaching therapeutic and/or beneficial levels) or poor with noncompliance resulting from ADEs. These outliers, who frequently end up in treatment-resistant categories of patients, might have entirely different outcomes if medication management were tailored to their genetic—and therefore most fundamental—needs.

When considering the “stakes” involved in the early patient-physician-family relationship, it is clear that prescribing with improved confidence, and less risk of ADEs, will pay significant dividends. For example, if a clinician thoughtfully considers not only the symptoms involved in the patient’s illness process, but also the likelihood that the patient will experience difficulties with certain medications, the patient and family cannot help but be appreciative of the efforts involved at defining their particular risks. This transparency of process and subsequent conversations about the role for medications will allow for greater trust and a sense of improved objectivity.

Widespread adoption of pharmacogenomic testing will be hampered by several factors including costs, limited sample sizes in research reports, and ingrained practice habits fueled by understandable skepticism and access challenges. Each of these issues will need to be individually addressed and overcome in the foreseeable future. Several academic medical centers are
incorporating this form of testing into the comprehensive biopsychosocial workup and results appear promising.\textsuperscript{11,15} Today, the cost of the genotyping of a single gene varies between $300–$700 depending upon the complexity of the variants that are being identified. Fortunately, panels of informative genes can now be ordered for between $800–$1,500. With the rapid improvement in sequencing technologies that is now occurring, these costs will inevitably decrease in the near future.

As psychiatric illnesses are increasingly recognized and treated in the pediatric population, clinicians now have access to an emerging set of pharmacogenomic principles to guide their prescribing practices. The primary principle is to use pharmacogenomic testing to increase the safety of psychotropics. A second principle is to use testing to identify medications that are unlikely to be effective. The ultimate goal of pharmacogenomic testing is to find the “right medication” on the first try. As pharmacogenomic testing becomes more sophisticated, it will be possible to abandon “trial and error” strategies and begin to provide personalized care utilizing metabolic and receptor pharmacogenomics. Using composite data, clinicians will have an unprecedented degree of molecular information available to help them choose effective medication-based treatments while minimizing the potential for ADEs.

Conclusion

As clinicians continue to treat pediatric patients with psychotropics, every relevant clinical observation and laboratory assessment should be considered to increase the likelihood of achieving remission of symptoms with minimal ADEs. Reviewing the results of pharmacogenomic testing prior to writing an initial prescription now provides clinicians useful individualized data that can be reviewed with the patient and family to inform them about the role that metabolism may play in treatment response as well as the possibility of ADEs. It is the authors’ belief that pharmacogenomic testing has a significant role in modern psychopharmacologic practice and that the associated expenses are already outweighed by the potential benefits of more individualized prescriptions.

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