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Pharmacogenetic testing in children: What to test and how to use it

ANTONIO GUILLEM/PAULISTA/SHUTTERSTOCK

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Pediatric-specific evidence is limited, but testing can inform treatment, improve outcomes

The use of pharmacogenetic testing to help drive decisions for medication management of patients with psychiatric illnesses is growing. It's becoming increasingly common for patients or the parents of pediatric patients to request pharmacogenetic testing or to bring the results of prior testing to their appointment. In these situations, patients may ask clinicians to consider the recommendations from these testing reports, which rarely provide guidance specific to pediatric patients. However, this can be difficult for clinicians who did not receive education in pharmacogenetics and may not be familiar with the evidence or options for pharmacogenetic testing. Many of the pharmacogenetic associations identified thus far have been discovered in adults, but studies in pediatric patients are relatively rare. This article reviews pharmacogenetic testing and the evidence supporting it, and describes implementation of routine pharmacogenetics testing at a children's hospital.

CASE

Testing leads to dose adjustment, improvement

Ms. R, age 16, presents with treatment-resistant major depressive disorder that is characterized by a significant neurovegetative burden and prominent anhedonia, as well as intermittent suicidal ideation without intent or plan. She reportedly did not improve after multiple medication trials, including citalopram (maximum dose 30 mg/d, treatment duration 8 weeks, good compliance), sertraline (maximum dose 150 mg/d, treatment duration 10 weeks, good compliance), fluoxetine (maximum

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dose 40 mg/d, treatment duration 8 weeks, good compliance, mild improvement in neurovegetative symptoms and depressed mood), and duloxetine (maximum dose 90 mg/d, treatment duration 6 weeks, good compliance, mild benefit but intolerable nausea).

Augmentation strategies included risperidone, 1 mg/d at bedtime, but it failed to ameliorate her depressive symptoms. At the time of pharmacogenetic testing, she is taking aripiprazole, 2 mg/d at bedtime, and venlafaxine ER, 37.5 mg/d. Some benefit was noted, but her symptoms recrudesced within several weeks. Because both of these medications are metabolized by the cytochrome P450 (CYP) 2D6 enzyme, Ms. R is tested for CYP2D6 variants and is determined to be a CYP2D6 ultra-rapid metabolizer. Her venlafaxine ER is quickly titrated from 37.5 to 112.5 mg/d and aripiprazole is titrated from 2 to 10 mg/d. The patient's anergia, amotivation, and mood improve.

Drug metabolism and genetic variants

It is common for patients with psychiatric disorders to receive trials of multiple psychotropic medications prior to identifying one that reduces symptom burden without producing intolerable adverse effects. Due to the high frequency of toxicity-related adverse effects (observed in 20% to 70% of patients),[1] these medications are frequently initiated at low doses and titrated slowly until the patient either experiences an intolerable adverse effect or achieves symptomatic remission.[1,2] The practice of slow titration at the start of treatment increases the risk of undertreatment in many patients, and may ultimately lead to a medication change due to the lack of response.

Many of the medications used to treat psychiatric illnesses are primarily metabolized by 2 CYP enzymes expressed in the liver, encoded by the CYP2D6 and CYP2C19 genes[3] (***Table 1,***[3-7] ***page 32,*** and ***Table 2,***[3,6,7] ***page 33***). These drug-metabolizing enzymes affect the pharmacokinetics of many medications. Some medications are converted to an active form by these enzymes, and some are inactivated. The contributions of CYP enzymes to the pharmacokinetics of neuropsychiatric medications have been well-described; however, there is less evidence on whether variants in these genes are associated with treatment efficacy, especially in pediatric patients.[8,9] CYP2D6 enzyme activity reaches adult levels soon after birth, but children may have higher CYP2C19 activity than adults.[4] CYP3A4 also contributes to the metabolism of many medications; however, there is only weak evidence that genetic variants in CYP3A4 contribute to variability in the pharmacokinetics of these medications, and there are currently no dosing guidelines based on pharmacogenetics available for this gene.[10]

As is common in the pharmacogenetic field, genotypes are denoted with a "star allele" (eg, *2) rather than positional nomenclature (eg, c.681G>A). The normal allele is usually designated as *1, and this result is given in the absence of the tested alleles. There is no consensus on the minimum set of alleles to be tested for most genes,[11] so commercially available tests vary widely in what alleles are tested (and therefore what they exclude before calling a normal allele).[12] The metabolizer phenotype for a patient is determined by taking into account the activity of each of the patient's 2 alleles (eg, *1/*2). A patient is categorized as a poor-, intermediate-, normal- (extensive-), or ultra-rapid metabolizer. Generally, the allele definitions are widely agreed upon (what genetic variant or variants comprise the *2 allele) due to nomenclature committees for each gene; however, because there are no standards for interpretation, the interpretation of the activity of the alleles and conversion to metabolizer phenotype varies among clinics.[13]

Guidelines help with genotype-guided dosing

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines describing the allele definitions, allele activity, and phenotypic interpretation.[14] Evidence-based guidelines for genotype-guided dosing of selective serotonin reuptake inhibitors (SSRIs)[4] and tricyclic antidepressants[5,15] are available from CPIC. There is less guidance for antipsychotics,

Clinical Point

CYP2D6 enzyme activity reaches adult levels soon after birth, but children may have higher CYP2C19 activity than adults

Clinical Point

Evidence-based guidelines for genotype-guided dosing of SSRIs and tricyclic antidepressants are available from CPIC

Table 1

Antidepressants: Pharmacogenetic guidelines and metabolizing enzymes

Medication	Guidelines[a]	Metabolizing enzyme(s)
Tricyclic antidepressants		
Amitriptyline	CPIC and DPWG	CYP2D6 and CYP2C19
Clomipramine	CPIC and DPWG	CYP2D6 and CYP2C19
Desipramine	CPIC and DPWG	CYP2D6
Doxepin	CPIC and DPWG	CYP2D6 and CYP2C19
Imipramine	CPIC and DPWG	CYP2D6 and CYP2C19
Nortriptyline	CPIC and DPWG	CYP2D6
Trimipramine	CPIC	CYP2D6 and CYP2C19
Atypical antidepressant		
Vortioxetine	FDA	CYP2D6
Selective serotonin reuptake inhibitors		
Citalopram	CPIC, DPWG, and FDA	CYP2C19
Escitalopram	CPIC and DPWG	CYP2C19
Fluoxetine	CPIC	CYP2D6
Fluvoxamine	CPIC	CYP2D6
Paroxetine	CPIC and DPWG	CYP2D6
Sertraline	CPIC and DPWG	CYP2C19
Vilazodone		
Serotonin-norepinephrine reuptake inhibitors		
Atomoxetine	FDA and DPWG	CYP2D6
Desvenlafaxine		
Duloxetine		
Levomilnacipran		
Venlafaxine	DPWG	CYP2D6

Source: References 3-7

[a]Guideline indicates whether there is a published guideline from the Dutch Pharmacogenetics Working Group (DPWG) or Clinical Pharmacogenetics Implementation Consortium (CPIC), or whether the FDA includes pharmacogenetic-related dosing recommendations on the drug label. The FDA recommends monitoring plasma concentrations of the tricyclic antidepressants in poor metabolizers of the associated enzyme(s).

CPIC: Clinical Pharmacogenetics Implementation Consortium; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2D6: cytochrome P450 family 2 subfamily D member 6; DPWG: Dutch Pharmacogenetics Working Group

although the Dutch Pharmacogenetics Working Group (DPWG) provides some guidance for aripiprazole and haloperidol.[6,7]

Each CPIC guideline specifically addresses use in pediatric patients, indicating that there are relatively few studies in pediatrics, but "it may be appropriate to extrapolate these recommendations to adolescents or possibly younger children with close monitoring."[4] The DPWG guidelines do not mention whether or not the recommendations are applicable to children. Neither CPIC nor the DPWG provides guidance on when to test; however, the French National Network of Pharmacogenetics (Réseau national de pharmacogénétique) recommends CYP2D6 and CYP2C19 genotyping before initiating antidepressant treatment, especially in patients with a high risk of toxicity.[16]

In the case above, Ms. R was determined to be a CYP2D6 ultra-rapid metabolizer. Because she showed some initial response to aripiprazole and venlafaxine ER, which are both metabolized by CYP2D6, these medications were very quickly titrated up, and the increased dosages produced the desired response. Venlafaxine is metabolized to the active metabolite O-desmethylvenlafaxine by CYP2D6. The DPWG recommends increasing the dose of venlafaxine in

CYP2D6 ultra-rapid metabolizers to 150% of the normal dose based on the decreased serum concentrations of venlafaxine and O-desmethylvenlafaxine in these patients.[6] Aripiprazole is also metabolized by CYP2D6; however, the FDA and DPWG give no recommendations for ultra-rapid metabolizers, but do recommend reducing the dose of aripiprazole in CYP2D6 poor metabolizers.

Multiple studies in adults have analyzed the association between pharmacokinetic (CYP2D6 and CYP2C19) or pharmacodynamic genes (SLC6A4, HTR2A, and GRIK4) and outcomes,[17] including some large clinical trials that conducted genome-wide association studies[18-20] and meta-analyses across multiple studies.[21,22] Most pharmacogenetic studies in psychiatric patients are small, and very few have included pediatric patients. However, with more interest in neuropsychiatric pharmacogenetics, these studies are becoming more common.[23-26]

Limited evidence from studies of commercially available tests

Several pharmacogenetic tests are commercially available, including some that focus on providing information that can be used specifically when prescribing psychiatric medications, such as the GeneSight Psychotropic test, CNSdose, Genomind, and Neuropharmagen.

In an industry-sponsored, nonrandomized clinical trial that included patients for whom prescribing decisions were made based on the GeneSight test, outcomes in adults were improved compared with treatment as usual,[27] inpatient stays were shorter,[28] and pharmacy costs were reduced.[29] In one of these studies, the authors noted that the traditional, single-gene analysis was not associated with improved outcomes, whereas the multiple gene combination (pharmacokinetic and pharmacodynamic genes) was associated with improved outcomes among patients with depression.[27] However, when GeneSight was compared with treatment as usual in a small randomized trial, there was not a significant association between use of the test and improved outcomes among patients with treatment-resistant depression.[30] The results of a much larger randomized trial (N = 1,167) are available[31] and expected to be published, but patients younger than age 18 were excluded from this study.[32] A retrospective study conducted in adult psychiatric patients found that patients whose treatment followed recommendations of a pharmacogenetic test including 20 genes were almost 4 times more likely to improve than patients whose treatment did not follow the recommendations.[33]

Table 2

Antipsychotics: Pharmacogenetic guidelines and metabolizing enzymes

Medication	Guidelines[a]	Metabolizing enzyme
First-generation antipsychotics		
Chlorpromazine		
Fluphenazine		
Haloperidol	DPWG	CYP2D6
Perphenazine		
Thioridazine	FDA	CYP2D6
Thiothixene		
Second-generation antipsychotics		
Aripiprazole	DPWG and FDA	CYP2D6
Asenapine		
Brexpiprazole	FDA	CYP2D6
Cariprazine		
Clozapine	FDA	CYP2D6
Iloperidone	FDA	CYP2D6
Lurasidone		
Olanzapine		
Paliperidone		
Quetiapine		
Risperidone	DPWG	CYP2D6
Ziprasidone		

Source: References 3,6,7

[a]Guideline indicates whether there is a published guideline from the Dutch Pharmacogenetics Working Group (DPWG) or Clinical Pharmacogenetics Implementation Consortium (CPIC), or whether the FDA includes pharmacogenetic-related dosing recommendations on the drug label.

CYP2D6: cytochrome P450 family 2 subfamily D member 6

continued

Clinical Point

The FDA and DPWG recommend reducing the dose of aripiprazole in CYP2D6 poor metabolizers

Pharmacogenetic testing in children

Clinical Point

Each commercially available pharmacogenetic test has a different way of presenting results

Pharmacogenetic testing at our pediatric inpatient unit

The Cincinnati Children's Division of Child and Adolescent Psychiatry is the largest psychiatric inpatient service in a U.S. pediatric hospital. Starting in 2004, we adopted pharmacogenetically-guided dosing of psychiatric medications.[34] CYP2D6 and CYP2C19 were chosen for testing because the enzymes encoded by these genes metabolize many of the antidepressants and antipsychotics that patients admitted to our unit will receive, and the clinicians wanted all available tools to help improve the care of these patients. To date, the Genetic Pharmacology Service (GPS) has performed >25,000 tests for variants in CYP2D6 and CYP2C19 as part of inpatient care. Patients provide a specimen (blood or buccal swab) at the time of admission to inpatient psychiatry, genotyping is performed onsite by the Molecular Genetics Laboratory (certified by the College of American Pathologists [CAP]/Clinical Laboratory Improvement Amendments [CLIA]) and the results are posted to the medical record within 2 business days. The report contains the patient's alleles for CYP2D6 and CYP2C19, the genotype-predicted metabolizer phenotype, and dosing recommendations for 19 drugs (provided as a percentage of the standard dose). Insurance is billed for the test, and reimbursement is usually received when the test is performed as part of an inpatient stay.

The GPS team performed a retrospective chart review after the first panel was implemented in 2005.[23] The study included 279 patients who were receiving a medication metabolized by one of the 2 genes tested. The poor metabolizers had the highest efficacy and highest number of adverse drug reactions, while ultra-rapid metabolizers had the lowest efficacy and lowest number of adverse reactions during their initial inpatient stay. In patients not treated with medications metabolized by CYP2D6 or CYP2C19, there was no association between metabolizer status and efficacy or adverse drug reactions. In this retrospective study, there was no association between metabolizer status and length of stay.

Overcoming the challenges

One challenge with many of the pharmacogenetic tests is interpretation of the results. The reports can span more than 20 pages, and clinicians may not have time to thoroughly read and understand how best to use all of this information. Sometimes the reports can make it seem like the first-line medication for the patient's condition is not the best choice, but it could work well when dosed appropriately based on the patient's genotype. Each commercially available test has a different way of presenting results,[13] so when choosing a pharmacogenetic test, one should be sure to see a sample report. Vo et al[35] recently reviewed factors to consider when choosing a pharmacogenetic test.

Because patients and families also have difficulty understanding the reports, we created patient education sheets,[36] written at an eighth grade level with feedback from parents and modeled on those provided by St. Jude Children's Research Hospital.[37] St. Jude Children's Research Hospital also has pharmacogenetic competencies that pharmacists and nurses must pass.[38,39] The following is a sample explanation that one of our nurses uses to educate parents on what is being tested and what effect the results will have on the treatment plan.

> "During your child's stay we will be completing a genetic test to help us understand how he/she processes the types of medications that we may be likely to start during their hospitalization. This does not tell us which medication will be best—unfortunately within the field of psychiatry there is still some unavoidable trial and error; rather, what it will do is tell us how to make sure that the dosing is at a level that would be safe for the way your child's body breaks down the medicine, so that he/she can get the intended benefit of the medicine's effects, while decreasing the risk of uncomfortable side effects, where possible."

Other challenges in pharmacogenetic testing are the cost, disease risk, and concern about how genetic information will be used. Because these tests are often not covered by health insurance, some commercial

pharmacogenetic testing companies offer an out-of-pocket maximum in the $250 to $350 range to reduce the cost to the patient. Some pharmacogenetic testing companies also test for genes associated with disease, so if a clinician orders the test, he or she may be responsible for sharing that information with the patient. For most pharmacogenetic testing companies, the turn-around time is 2 to 10 days. Genetic information is protected by federal laws, including Genetic Information Nondiscrimination Act (GINA) and Health Insurance Portability and Accountability Act (HIPAA).

The choice of psychotropic medication is complex, and although we would like pharmacogenetics to be the only answer to why every patient does or does not respond to a medication, it is not. Response to medication is influenced by age, comorbidities, illness severity, illness duration, compliance, gender, concomitant medications, and potentially more.[40] Pharmacogenetics is another tool at the clinician's disposal to help in choosing a medication and dose. There is a clear association between CYP2D6 and CYP2C19 and exposure to many antidepressants and antipsychotics (reviewed by Stingl et al[3]); however, the link between exposure and response is much weaker. It may be strengthened by the inclusion of pharmacodynamic information (the level of expression of the drug target), which can be influenced by genetic variants.[41] At the present time, the most evidence exists for testing CYP2D6 and CYP2C19, and the CPIC[4,5,15] and DWPG[6] guidelines provide evidence-based recommendations for how to adjust medication dosages based on the results.

There is clearly much more research that needs to be done in the field of neuropsychiatric pharmacogenetics, especially in pediatric populations. As we see increased utilization of pharmacogenetic tests in psychiatry, there is also a need for pharmacogenetic education of patients, families, nurses, pharmacists, and psychiatrists. Several good pharmacogenetic resources that contain up-to-date summaries of the available evidence linking pharmacogenetic variants to medication response, implementation resources, and educational resources are available. These include CPIC (www.cpicpgx.org), PharmGKB (www.pharmgkb.org), and the IGNITE Spark Toolbox (https://ignitegenomics.org/spark-toolbox/clinicians/).

Related Resources

- Deardorff OG, Jeanne V, Leonard L. Making sense of CYP2D6 and CYP1A2 genotype vs phenotype. Current Psychiatry. 2018;17(7):41-45.
- Ellingrod VL, Ward KM. Using pharmacogenetics guidelines when prescribing: What's available. Current Psychiatry. 2018;17(1):43-46

Drug Brand Names

Amitriptyline • Elavil, Endep
Aripiprazole • Abilify
Asenapine • Saphris
Atomoxetine • Strattera
Brexpiprazole • Rexulti
Cariprazine • Vraylar
Chlorpromazine • Promapar, Thorazine
Citalopram • Celexa
Clomipramine • Anafranil
Clozapine • Clozaril
Desipramine • Norpramin
Desvenlafaxine • Pristiq
Doxepin • Silenor
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluphenazine • Prolixin
Fluvoxamine • Luvox
Haloperidol • Haldol
Iloperidone • Fanapt
Imipramine • Tofranil
Levomilnacipran • Fetzima
Lurasidone • Latuda
Nortriptyline • Pamelor
Olanzapine • Zyprexa
Paliperidone • Invega
Paroxetine • Paxil
Perphenazine • Trilafon
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Thioridazine • Mellaril
Thiothixene • Navane
Trimipramine • Surmontil
Venlafaxine • Effexor
Vilazodone • Viibryd
Vortioxetine • Trintellix
Ziprasidone • Geodon

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continued

Bottom Line

Pharmacogenetically-guided dosing of psychiatric medications may help improve clinical outcomes, including for pediatric patients. Guidelines from the Clinical Pharmacogenetics Implementation Consortium and other organizations can help with interpretation of the results of pharmacogenetic testing.

Clinical Point

Presently, the most evidence exists for testing CYP2D6 and CYP2C19

Pharmacogenetic testing in children

Clinical Point

To reduce the cost to the patient, some testing companies offer a $250 to $350 out-of-pocket maximum

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