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Gene-Based Dose Optimization in Children

Laura B. Ramsey[1,2], **Jacob T. Brown**[3], **Susan I. Vear**[4], **Jeffrey R. Bishop**[5], **Sara L. Van Driest**[6]

[1]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio 45267, USA

[2]Divisions of Research in Patient Services and Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229, USA

[3]Department of Pharmacy Practice and Pharmaceutical Sciences, University of Minnesota College of Pharmacy, Duluth, Minnesota 55812, USA

[4]Department of Hematology & Oncology, Nationwide Children's Hospital, Columbus, Ohio 43205, USA

[5]Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy, and Department of Psychiatry, University of Minnesota Medical School, Minneapolis, Minnesota 55455, USA

[6]Departments of Pediatrics and Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, USA

Abstract

Pharmacogenetics is a key component of precision medicine. Genetic variation in drug metabolism enzymes can lead to variable exposure to drugs and metabolites, potentially leading to inefficacy and drug toxicity. Although the evidence for pharmacogenetic associations in children is not as extensive as for adults, there are several drugs across diverse therapeutic areas with robust pediatric data indicating important, and relatively common, drug–gene interactions. Guidelines to assist gene-based dose optimization are available for codeine, thiopurine drugs, selective serotonin reuptake inhibitors, atomoxetine, tacrolimus, and voriconazole. For each of these drugs, there is an opportunity to clinically implement precision medicine approaches with children for whom genetic test results are known or are obtained at the time of prescribing. For many more drugs that are commonly used in pediatric patients, additional investigation is needed to determine the genetic factors influencing appropriate dose.

Keywords

pharmacogenomics; pediatrics; infectious disease; psychiatry; oncology; immunology

sara.van.driest@vumc.org.

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1. INTRODUCTION

Precision medicine has been described as the “right drug for the right patient at the right time” (1, p. 11) and has received over $4 billion in global financial support (2). One important component of precision medicine is pharmacogenetics. Pharmacogenetic research aims to explain the heritable portion of individual variability in medication response. Clinical implementation incorporates information from inherited genetic variants into prescribing decisions for drug selection or dosing strategies. Although the bulk of pharmacogenetic research has been performed in adults, many medications with known drug–gene interactions are also used in children, and recommendations to alter dosage, or change the drug choice altogether, may apply to children as well as adults.

Pharmacogenetics is one of myriad factors that contribute to interindividual variability in drug exposure and response (Figure 1), and there are pediatric-specific nuances to these factors. For example, some hepatic metabolic enzymes have expression patterns that change throughout development, particularly in infancy (e.g., CYP3A enzymes) (3); thus, genetic variation in these enzymes will not explain individual differences in drug exposure until the enzymes are expressed. Weight, body surface area, and lean body mass can also influence variability in exposure and change significantly over the course of infancy, childhood, and adolescence. Drug exposure is potentially affected by kidney and liver dysfunction; developmental trajectories (e.g., pubertal status), chronic disease, and acute processes such as inflammation can impact organ function in children. Concomitant medications have long been recognized as influencing drug exposure, as they can inhibit or enhance metabolic capacity. Some foods can also influence medication exposure through changes in drug absorption, altered drug metabolism, or differences in drug response. Other external factors that can influence medication exposure are adherence, formulation, route of administration, dosing regimen, and time of day, all of which can be influenced by the age and developmental stage of the pediatric patient. This review focuses on the impact of genetic variation on dosing for children, as this is an important, nonmodifiable risk factor for drug inefficacy or toxicity.

There have been several recent advances that have increased the interest in and implementation of gene-guided prescribing for children. These advances include the decreased cost of genotyping, increased knowledge of how genetic variants influence medication exposure such as that curated by the Pharmacogenomics Knowledge Base (PharmGKB) (4), establishment of clinical guidelines such as those from the Clinical Pharmacogenetics Implementation Consortium (CPIC) (5) and the Dutch Pharmacogenetics Working Group (6), and availability of commercial and direct-to-consumer genetic testing. CPIC guidelines specifically address pediatrics and include resources for implementation, although not all of their guidelines contain pediatric-specific recommendations. Here we review several drugs with potential for the clinical implementation of gene-guided dosing in children, including codeine, thiopurines, selective serotonin reuptake inhibitors (SSRIs), atomoxetine, tacrolimus, and voriconazole. We also identify common themes among the evidence and clinical implementations in pediatrics and strategies for advancing gene-based dosing for children.

2. BASIC PRINCIPLES OF PHARMACOGENETIC MECHANISMS

Genetic variants influence the outcomes of drug therapy through multiple mechanisms. Most well-established pharmacogenetic associations involve genes encoding drug metabolism enzymes or drug transporters. These variants have the potential to impact pharmacokinetics. For example, genetic variants that decrease enzyme function can lead to slower conversion of the active drug to inactive metabolites, contributing to high active drug concentrations and the potential for toxicity (Figure 2). Genetic variants that increase enzyme function lead to faster inactivation and may be associated with inefficacy. Examples of well-established drug–gene interactions of this type include thiopurine drugs with *TPMT* and *NUDT15*; escitalopram, sertraline, and voriconazole with cytochrome P450 (*CYP*)*2C19*; fluvoxamine and atomoxetine with *CYP2D6*; and tacrolimus with *CYP3A5*. For prodrugs that are converted from inactive compounds to active forms by drug metabolism enzymes, the relationships between enzyme function and active drug levels are reversed. Decreased enzyme function prevents formation of the active form, leading to inefficacy, while increased enzyme function generates high levels of the active form and the potential for toxicity. An example of this type of drug–gene interaction is codeine with *CYP2D6*. For pharmacokinetic drug–gene interactions, dose optimization or alternative medications can be recommended for individuals with atypical function. The proportion of individuals with atypical function is highly variable across genes and across populations. For example, fewer than 1% of individuals with European or African ancestry lack NUDT15 enzyme function, whereas the no function allele is seen in nearly 10% of East Asians (7). In contrast, 80–85% of individuals with European ancestry are poor metabolizers for CYP3A5, while most individuals with African ancestry have two functional alleles (8). Most individuals have at least one actionable pharmacogenetic variant; an assessment of nearly 10,000 individuals genotyped for variants for five drug-related genes revealed actionable variants in 91% of all individuals and in 96% of African American individuals (9). Throughout this review, we use the consensus terms for enzyme functional status (poor, intermediate, normal, rapid, and ultrarapid metabolizers) whenever possible (10).

Some genetic variants affect pharmacodynamics. For example, individuals may have specific genetic variants that affect the affinity of a drug for the target receptor or an off-target protein binding site. For these drug–gene interactions, clinical implementation often includes recommendations to use alternative medications in individuals who harbor variants associated with hypersensitivity or inefficacy (Table 1).

3. EXAMPLES OF CLINICALLY IMPLEMENTED GENE-GUIDED DOSING OPTIMIZATION IN CHILDREN

3.1. Codeine

Codeine is an opioid commonly used for the relief of mild to moderate pain. Single-ingredient codeine is US Food and Drug Administration (FDA) approved only for use in adults (11, 12), whereas codeine with acetaminophen was previously approved by the FDA in patients over three years of age (13). Codeine is *O*-demethylated to morphine by CYP2D6. Morphine binds to μ-opioid receptors to provide analgesia. Codeine has been used

as an antitussive agent, although early studies indicating efficacy across common causes of cough (14, 15) have been contradicted by more recent placebo-controlled studies (16–18).

Codeine metabolism is complex, and the majority of parent drug is converted to inactive metabolites by CYP3A4 and UGT2B7. An estimated 5–10% of the drug is biotransformed to morphine by CYP2D6. The morphine compound is further metabolized by UGT enzymes to the active compound morphine-6-glucuronide and inactive morphine-3-glucuronide. Morphine and morphine-6-glucuronide have 200-fold higher affinity for the μ-opioid receptor than does codeine (19, 20).

Since codeine is a prodrug dependent on CYP2D6 for activation, CYP2D6 poor metabolizers are unable to convert codeine to morphine and thus have no therapeutic effect. Depending on the population, the frequency of poor metabolizers varies from ≤1% (East Asian, South Central Asian, and Oceanian populations) to ~5% (European and Ashkenazi Jewish populations) (21). Conversely, CYP2D6 ultrarapid metabolizers generate excess morphine and are at risk for toxicity, including respiratory depression and death. The frequency of ultrarapid metabolizers is ~1% in East Asians; 3–5% in Africans, Europeans, South Central Asians, and Americans; and >10% in Middle Eastern, Ashkenazi Jewish, and Oceanian populations (21). Although much of the high-quality evidence for the drug–gene interaction comes from adults (22, 23), there is ample evidence from pediatric studies. There are several case reports of infant mortality and respiratory failure after exposure to morphine via breastmilk, following biotransformation of codeine in infants whose mothers were CYP2D6 ultrarapid metabolizers, and of additional children with codeine toxicity, some after adeno/tonsillectomy (24–29). Furthermore, higher morphine levels and risk for adverse events are observed in children with ultrarapid CYP2D6 function (30–35).

The FDA added a black box warning to the codeine label in February of 2013, stating that respiratory depression and death have occurred in children who received codeine following adeno/tonsillectomy and that CYP2D6 inhibitors may impact drug response (36). In April of 2017, a contraindication (the FDA's strongest warning) was added, stating that codeine should not be used for pain or cough in children younger than 12 years old. The new guidance also includes a warning against codeine use in adolescents 12–18 years of age who are obese, have obstructive sleep apnea, or have severe lung disease and a strengthened warning against codeine use while breastfeeding.

Guidelines for codeine use based on CYP2D6 metabolizer status have been published (22, 23), and multiple centers have implemented *CYP2D6* testing to guide codeine prescribing *CYP2D6* genotyping for children with sickle cell disease has been successfully implemented to ensure that patients with ultrarapid or poor metabolizer phenotypes are not prescribed codeine (38). Some advocate for the continued use of codeine for analgesia in children when CYP2D6 functional status can be assessed (39). With the removal of codeine from the formulary for many children's hospitals (40), the use of codeine in children is on the decline (41, 42), but it may be replaced by other opioid drugs that are also metabolized by CYP2D6.

3.2. Thiopurine Drugs

The thiopurine drugs azathioprine, mercaptopurine, and thioguanine are key components of therapy for pediatric patients with acute lymphoblastic leukemia, inflammatory bowel disease, and autoimmune disorders. The principal cytotoxic effect of thiopurine drugs is the result of the production of 6-thioguanine nucleotides, thioguanine mono- and di-phosphates, which are converted to thioguanine triphosphates. Thioguanine triphosphates are incorporated into RNA, while thio-deoxyguanosine triphosphates are incorporated into DNA, resulting in cytotoxicity (43).

The metabolism of thiopurine drugs is highly complex, involving multiple competing enzymatic steps of the salvage purine pathway (43). Azathioprine, mercaptopurine, and thioguanine are all inactive prodrugs that require intracellular activation by multiple enzymes. The first extracellular step of azathioprine activation involves conversion to mercaptopurine via metabolism by GSTM1, GSTA1, and GSTA2 (44). Once mercaptopurine or thioguanine are transported into the hepatocyte, there are multiple metabolic pathways. One important pathway involves thiopurine methyltransferase (TPMT), which methylates mercaptopurine and thioguanine compounds (45). Another important component of thiopurine metabolism involves the NUDT15 enzyme, which converts the active 6-thioguanine nucleotide into inactive metabolites (7).

The complex and competing nature of the thiopurine metabolic pathway can make achieving the clinical balance between efficacy and toxicity challenging. To date, preemptive testing of two genes, *TPMT* and *NUDT15*, has been clinically implemented to achieve that balance. There is an inverse relationship between TPMT activity, a heritable trait, and the level of the cytotoxic 6-thioguanine nucleotide metabolites (46). There are three well-characterized variants in *TPMT* that result in unstable TPMT protein and enhanced protein degradation. These three variants account for 90% of TPMT low-activity phenotypes (47–49) and are present in 5% of white populations, 3% of Asian populations, and 6% of black populations (47).

Patients who are TPMT poor metabolizers have a significantly increased risk of hematopoietic toxicity and cytopenia when compared to patients with normal TPMT activity, with dose reductions due to mercaptopurine toxicity required in 100% of poor metabolizers versus 35% of intermediate metabolizers and 7% of normal metabolizers (46). Thus, the recommendation for TPMT poor metabolizers requiring this drug for treatment of malignancy is to drastically reduce the thiopurine dose (e.g., a tenfold dose reduction) and to consider alternative therapy for nonmalignant conditions (47). TPMT intermediate metabolizers also have a significantly increased risk of hematopoietic toxicity and cytopenia when compared to patients with normal TPMT activity (46). However, 40–70% of TPMT intermediate metabolizers tolerate full doses of thiopurine drugs (47), demonstrating the complex nature of thiopurine metabolism. Therefore, the dosing recommendation for TPMT intermediate metabolizers is a more moderate dose reduction (e.g., 50–80% of the typical dose, depending on dose and indication) (47). All active Children's Oncology Group protocols for acute lymphocytic leukemia currently recommend testing for *TPMT* variants at diagnosis and adjusting initial doses of thiopurine drugs accordingly.

Clinical decision support for TPMT-based thiopurine dosing is available via the PharmGKB website (https://www.pharmgkb.org/) for 34 different *TPMT* star alleles and their combinations, based on CPIC guidelines. Some institutions have also incorporated electronic health record–based decision support into their practice, which automatically advises providers ordering thiopurine drugs for patients with *TPMT* variants that their patient may require a dose adjustment based on their genotype or phenotype and provides links to current guidelines, such as CPIC (47).

NUDT15, which inactivates 6-thioguanine nucleotides, was initially recognized as a clinically important enzyme in the thiopurine pathway via genome-wide association study of patients treated with thiopurine drugs for acute lymphocytic leukemia and inflammatory bowel disease (7, 50). The *NUDT15* variant rs116855232 was associated with thiopurine-related hematopoietic toxicity in several studies of mercaptopurine, and further studies identified a similar toxicity profile for azathioprine and thioguanine. Additional variants have been identified, with varying degrees of effect on NUDT15 activity (47). The frequency of poor metabolizer phenotypes ranges from 1% to 10%, with higher frequencies reported among Asian and Hispanic populations (51, 52).

NUDT15 poor metabolizers who require thiopurines for treatment of malignancy are recommended to start at a significantly decreased dose, and those being treated for nonmalignant conditions are recommended to use an alternate therapy. For NUDT15 intermediate metabolizers and those with variants with uncertain functional activity, reduced dosing is recommended, with careful dose adjustment after 2–4 weeks based on toxicity and response (47). CPIC guidelines also include guidance for patients for whom both *TPMT* and *NUDT15* genotypes are known. All recommended dose reductions are based on a standard mercaptopurine starting dose of 75 mg/m^2/day; lower starting doses may not require a dose reduction, particularly in intermediate metabolizers (47).

While preemptive testing of both *TPMT* and *NUDT15* prior to thiopurine drug exposure can mitigate some of the toxicity associated with these drugs, thiopurine metabolism is complex and involves multiple additional enzymes of potential significance (e.g., XO, ITPA, MTHFR, IMPDH1, and IMPDH2) (53–55). Therefore, it is crucial that providers initiating thiopurine therapy continue to monitor patients for toxicity rather than interpreting normal metabolizer status for TPMT or NUDT15 as a guarantee against encountering significant toxicity.

3.3. Antidepressant Medications: Selective Serotonin Reuptake Inhibitors

SSRIs are commonly prescribed for the treatment of mood and anxiety disorders. In children and adolescents, these medications are often trialed after nonpharmacological approaches (e.g., cognitive behavioral therapies) have been ineffective. Studies of adolescent depression suggest that the combination of an antidepressant and cognitive behavioral therapy is better than either intervention alone (56, 57). While there are many SSRIs approved for adults, only four currently have FDA indications for depression, anxiety, or obsessive-compulsive disorder in patients under 18 years of age: escitalopram, sertraline, fluvoxamine, and fluoxetine (although others are used off-label in young patients).

The metabolism of SSRIs is primarily mediated through hepatic enzymes, including CYP2D6 and CYP2C19. While each SSRI mentioned above is approved for use in adults and younger patient populations, it is important to recognize that there may be some differences in pharmacokinetic parameters across age ranges that impact dosing strategies. For example, escitalopram and sertraline have steady-state concentrations or exposures that are approximately 15–30% lower in children and adolescents than in adults due to faster clearance in the younger patients and clinically relevant shorter half-lives (~10 h or ~30% shorter) (58). On the other hand, fluoxetine and fluvoxamine may have two- to threefold higher steady-state plasma concentrations and exposure in younger patients (59, 60). Presently, the relationships between drug metabolism genotypes and clinical or pharmacokinetic phenotypes are largely informed by data from adults.

Among SSRIs, perhaps the best-described pharmacogenetic relationships are between CYP2C19 metabolizer status and escitalopram. A meta-analysis of nearly 1,000 individuals (patients and healthy controls) from pharmacokinetic studies identified 95% increases in overall exposure in poor metabolizers (2–15% of individuals, depending on the population) as compared to normal metabolizers. Rapid and ultrarapid metabolizers (**1/*17* or **17/*17*, 2–30% of individuals) had decreased exposure of 14–36% as compared to normal metabolizers (61). Additionally, in a retrospective study of more than 2,000 patients (including some adolescents), escitalopram discontinuation was more common in the extremes than normal metabolizers (62), a finding that was replicated in a study that included only children and adolescents (63). CPIC guidelines recommend alternative therapy (a drug metabolized by another enzyme) for individuals who are CYP2C19 ultrarapid metabolizers and consideration of an alternative therapy or a 50% dose reduction of the starting dose for CYP2C19 poor metabolizers (64).

Despite two major CYP pathways (CYP2C19 and CYP2D6) and a number of secondary pathways for sertraline metabolism, variants in the *CYP2C19* gene appear to have the greatest impact on the pharmacokinetic parameters of this drug (64). CYP2C19 poor metabolizers have a slower rate of formation of the active metabolite (desmethylsertraline), a longer half-life (~36 h, or 50% longer than normal metabolizers), and an increased (~55%) overall exposure to the parent drug as compared to normal metabolizers (65, 66). Not surprisingly, and likely due to the contributions of multiple enzymatic pathways to sertraline's metabolism, heterogeneity exists across pharmacogenetic studies, with other investigations not finding a significant impact of *CYP2C19* variants on response to sertraline (67, 68). CPIC guidelines suggest the selection of an alternative therapy in CYP2C19 ultrarapid metabolizers and either the selection of an alternative therapy or a 50% reduction in the starting dose for poor metabolizers (64).

Fluvoxamine metabolism is mediated primarily through CYP1A2 and CYP2D6. There is moderate evidence that CYP2D6 poor metabolizer status leads to higher peak plasma concentrations (~50% higher), greater overall exposure (200%), or longer half-life (~60% longer) (60, 64). CPIC guidelines suggest a 25–50% reduction of the recommended starting dose or selection of an alternative therapy in patients who are known CYP2D6 poor metabolizers.

Arguably the most clinically relevant (for younger patients) and controversial SSRI, with respect to pharmacogenetic influence from CYP2D6, is fluoxetine. Fluoxetine is commonly recommended as the first-line SSRI for consideration in patients under 18 years of age who are in need of a pharmacological treatment for depression (69). While adult studies identify some small increases in concentrations of fluoxetine and the most active metabolite (*S*-norfluoxetine), comparisons of the total active components (parent + metabolites) between poor and nonpoor metabolizers were largely equivocal (59, 64). However, this is one example in which the relationship between genotypes and clinical and pharmacokinetic phenotypes has been directly examined in subjects under 18 years of age (70). In younger patients, CYP2D6 poor metabolizers had increased ratios of fluoxetine to *S*-norfluoxetine (the active metabolite), even after adjusting for patient weight and drug dose. However, the total active component (fluoxetine + *S*-norfluoxetine) did not differ across genotype groups, nor did clinical response measures that were examined at 8- and 12-week time points in this study. Based on these data, there are currently no genotype-informed dosing guidelines for fluoxetine.

As previously noted, much of the pharmacogenetic data for SSRIs have been derived in adult populations. At this time, there are few systematic implementation efforts to incorporate genotype-guided dosing of SSRIs into routine clinical care (71). Most clinical pharmacogenetic testing for children (and adults) being treated with an SSRI is currently done using commercial laboratories that examine a constellation of pharmacokinetic and pharmacodynamic genes. While drug dosing recommendations from these tests may be similar to those presented above, the added influences of pharmacodynamic genes (i.e., serotonin receptors and transporters) are also important and in some cases difficult to separate from drug metabolism pharmacogenetic results. The genes/alleles tested, interpretation of metabolizer phenotypes, and treatment recommendations also vary widely between commercial testing companies (72, 73). While the American Psychiatric Association Task Force for Biomarkers and Novel Treatments recognizes the potential influence of drug metabolism pharmacogenetics in relation to adverse effects, they have concluded that data determining how and when to obtain pharmacogenetic testing are lacking (74). Therefore, at this time, pharmacogenetic tests for SSRIs are not considered standard of care and, if ordered, are done so predominantly by prescribers who determine that genotype guidance may be informative for a specific patient.

3.4. Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor (75) approved for the use of attention-deficit hyperactivity disorder (ADHD). Initially introduced in 2002, atomoxetine was the first nonstimulant option approved for the treatment of ADHD and is typically prescribed to children when stimulants are contraindicated or not tolerated. Atomoxetine is thought to exert its therapeutic effect primarily through increased extracellular concentrations of norepinephrine in the prefrontal cortex (76).

Atomoxetine is an active compound predominantly metabolized by CYP2D6 to the active metabolite 4-hydroxyatomoxetine; however, this metabolite is present at low concentrations and is rapidly glucuronidated to the inactive 4-hydroxyatomoxetine-*O*-

glucuronide metabolite (77). To a lesser extent, CYP2C19 also contributes to atomoxetine metabolism, forming *N*-desmethylatomoxetine, which is further broken down by CYP2D6 to *N*-desmethyl-4-hydroxyatomoxetine (4).

CYP2D6 variation wields considerable impact on atomoxetine exposure. A single-dose pharmacokinetic study of 0.5 mg/kg of atomoxetine in 23 children with ADHD showed significantly higher atomoxetine exposures in poor metabolizers as compared to intermediate and normal metabolizers (78). CYP2D6 poor metabolizers experienced 11.4-fold higher dose-corrected exposures as compared to normal metabolizers, while there was a 30-fold range in exposures across all participants. Poor metabolizers have also been shown to require lower doses of atomoxetine, be more likely to have a therapeutic response to atomoxetine, and have lower discontinuation rates as compared to nonpoor metabolizers (79, 80).

Atomoxetine is one of the few CYP2D6 substrates with genotype-guided dosing recommendations for children in the FDA label. Standard dose recommendations in children and adolescents up to 70 kg are to initiate atomoxetine therapy at 0.5 mg/kg/day and titrate up to 1.2 mg/kg/day after a minimum of three days, while dose increases in known CYP2D6 poor metabolizers are recommended only after four weeks if a lack of response is observed. Although FDA labeling provides dose recommendations for poor metabolizers, it is important to recognize that, in clinical studies, CYP2D6 poor metabolizers were more likely to respond to treatment as compared to CYP2D6 normal or ultrarapid metabolizers. Thus, individuals who are normal or ultrarapid metabolizers should be closely monitored for a lack of efficacy. A recently published CPIC guideline for CYP2D6 and atomoxetine recommends initiating dosing at 0.5 mg/kg/day and increasing to 1.2 mg/kg/day after three days in normal and ultrarapid metabolizers, while also utilizing plasma concentrations to attain peak concentrations approaching 400 ng/mL if there is no clinical response or adverse events after two weeks. In poor or intermediate metabolizers, the recommendation is to initiate dosing at 0.5 mg/kg/day and wait two weeks before utilizing peak plasma concentrations to guide dose adjustments in the absence of clinical response and adverse events (81). The Royal Dutch Pharmacists Association Pharmacogenetics Working Group also provides therapeutic dose recommendations for atomoxetine (6). Specifically, they state that poor metabolizers should be closely monitored for adverse drug events and that dose increases are likely unnecessary in this subset. They also note that, while there are insufficient data to allow for dose adjustments in ultrarapid metabolizers, these individuals should be closely monitored for reduced efficacy or prescribed an alternative ADHD medication.

Institutions that have currently implemented *CYP2D6* pharmacogenetic testing into clinical care are well positioned to expand their utilization of this information for atomoxetine dosing. Clinical decision support tools can alert providers to individuals known to be CYP2D6 poor metabolizers and provide them with dose recommendations from both the FDA label and the CPIC guideline. Conversely, these tools may also alert clinicians to ultrarapid CYP2D6 metabolizers who may be at an increased risk of nonresponse to standard doses. Additionally, many commercially available pharmacogenetic testing companies include atomoxetine and *CYP2D6* on their test panel and provide interpretation

on its usage. To date, pharmacogenetic-guided dosing strategies for atomoxetine have predominantly focused on variants in the *CYP2D6* gene that result in considerable differences in atomoxetine plasma concentrations; however, future studies assessing atomoxetine response and variation in the norepinephrine transporter gene (*SLC6A2*) may eventually provide additional insight into which individuals are most likely to respond favorably (82, 83).

3.5. Tacrolimus

Tacrolimus is the most widely used immunosuppressant after kidney transplant. This calcineurin inhibitor is also used after other solid organ transplantations to prevent and treat allograft rejection and to treat glomerulonephritis and graft-versus-host disease in recipients of blood and marrow transplants (84). The inhibition of calcineurin prevents T cell activation and interleukin-2 production, leading to immunosuppressant effects. Tacrolimus use is complicated by the narrow therapeutic window and high interindividual variability in drug disposition. Therapeutic drug monitoring (TDM) of tacrolimus concentrations is used to optimize exposure for each patient; however, under- and overexposure are still common and put patients at risk for graft rejection and toxicity.

The metabolism of tacrolimus is predominately through CYP3A5 (and some contribution of CYP3A4) in enterocytes and hepatocytes. Many metabolites are formed, with one minor metabolite, 31-*O*-demethyl-tacrolimus, having comparable immunosuppressive activity to tacrolimus. Other metabolites, including the most prevalent 13-*O*-demethyl-tacrolimus, have little pharmacological activity. Tacrolimus is effluxed by the P-glycoprotein transporter, which is expressed on epithelial cells, endothelial cells, and lymphocytes.

CYP3A5 variants explain 40–50% of the variability in blood concentrations of tacrolimus (85, 86). There are a multitude of studies of transplant patients demonstrating that carriers of the *CYP3A5∗1* allele (CYP3A5 expressers) have significantly lower dose-adjusted trough concentrations of tacrolimus compared to noncarriers (8). A CPIC guideline exists for *CYP3A5*-based dosing of tacrolimus (8), recommending a one-and-a-half- to twofold increase in dose for CYP3A5 expressers for both pediatric and adult patients. One of two randomized clinical trials demonstrated that a higher proportion of patients in the *CYP3A5* genotype–guided group achieved a therapeutic dose after three days of tacrolimus compared to standard bodyweight-based dosing in adults after kidney transplant (87), but the other did not (88). Of note, there were no differences between the genotype-guided versus bodyweight-based dosing in graft survival, acute rejection, delayed graft function, or tacrolimus-related toxicities in either trial. In the only pediatric trial to assess *CYP3A5*-guided tacrolimus dosing in solid organ transplant patients, the therapeutic concentration was reached sooner in the *CYP3A5*-guided group compared to the unguided group (3.4 days versus 4.7 days), and there were no differences in adverse events (89). *CYP3A5*-guided dosing is not intended to replace TDM but to be used in conjunction with TDM to achieve target concentrations more quickly and stably than TDM alone, as several studies have suggested (8). The addition of the *CYP3A4* genotype may improve dose predictions, as one study found that tacrolimus dose requirement was better predicted by *CYP3A4* and *CYP3A5* alleles than either gene alone (90).

CYP3A5 genotyping is available clinically and has been implemented in some academic medical centers, including Vanderbilt's PREDICT program (9), the Mayo Clinic's Center for Individualized Medicine (91), and St. Jude Children's Research Hospital's PG4KDS program. Clinical decision support for tacrolimus dosing based on *CYP3A5* is fairly straightforward in nonliver transplant patients (8), but in patients receiving liver transplants, the donor liver must be genotyped since it will influence the pharmacokinetics of tacrolimus posttransplant.

3.6. Voriconazole

Voriconazole is a broad-spectrum triazole antifungal agent. It is recommended as a first-line agent for the treatment and prophylaxis of invasive *Aspergillus* infections and an alternative therapy for *Candida* infections (92, 93). The mechanism of action is the inhibition of ergosterol synthesis via inhibition of lanosterol 14α-demethylase. Voriconazole has a narrow therapeutic window; subtherapeutic drug concentrations are associated with mortality from treatment failure, and supratherapeutic levels lead to toxicities, including neurotoxicity and hepatotoxicity (94–97). Due to significant interindividual variability in pharmacokinetics attributed to age, weight, liver function, concomitant medications, and genotype, TDM is recommended (96, 98).

Voriconazole is primarily inactivated by CYP2C19, with minor contributions by CYP3A enzymes and CYP2C9. Decreased CYP2C19 function is associated with higher concentrations of voriconazole and/or drug toxicity. Increased CYP2C19 function is associated with low voriconazole concentrations, subtherapeutic drug levels, and treatment failure. CPIC guidelines recommend that alternate agents be used for CYP2C19 rapid and ultrarapid metabolizers and that alternate agents or lower doses of voriconazole be used in CYP2C19 poor metabolizers (99).

Age is an important consideration for voriconazole dosing. The standard dosing to achieve therapeutic concentrations is higher for children than for adults. For example, for invasive *Aspergillus* infection treatment, adult maintenance requires a 4 mg/kg intravenous (IV) dose every 12 h, whereas children require an 8 mg/kg IV dose every 12 h (92). In children who are CYP2C19 ultrarapid metabolizers, even higher voriconazole doses are required (100, 101). Given the difficulty of achieving therapeutic concentrations in this group, alternate therapy is recommended when treatment is urgent (99). For children who are rapid metabolizers, guidelines suggest initiation of standard dosing with dose titration guided by TDM, in contrast to adult rapid metabolizers, where alternative agents are recommended (99). This pediatric-specific recommendation stems from a lack of data demonstrating a difference between CYP2C19 normal and rapid metabolizers in children. There is a case report of a 10-year-old CYP2C19 rapid metabolizer who required voriconazole dosing of 14 mg/kg twice daily to achieve therapeutic levels (102). Rapid metabolizers under 12 years of age were predicted to need higher doses of voriconazole than normal metabolizers (30 versus 20 mg/kg/day, respectively) (101). However, there is tremendous variability in voriconazole pharmacokinetics in children, making it difficult to accurately predict voriconazole dosing.

For CYP2C19 poor metabolizers, alternative therapy or lower doses (with careful TDM) are recommended. The limited data for this subgroup in children (101, 103, 104) support extrapolation from adults, as children without CYP2C19 function have high plasma concentrations, which may put them at risk for adverse effects.

Genotype-guided voriconazole dosing has been implemented by some medical centers. In pediatric patients, adjusting voriconazole dosing based on CYP2C19 metabolizer status in pediatric patients needing antifungal prophylaxis resulted in a significant reduction in the time required to achieve target drug concentrations (105). However, genotype is one of many factors influencing voriconazole pharmacokinetics. Ideally, individualized dose calculations will incorporate genotype and other factors to accurately forecast the dose required (98). Timely generation of these sophisticated models could be facilitated by consolidating data from many pediatric centers.

4. COMMON THEMES IN GENE-BASED DOSE OPTIMIZATION FOR CHILDREN

Review of the pediatric-specific evidence for pharmacogenetic associations that are well-established in adults reveals that, in most instances, few studies (and in only relatively small cohorts) of children have been published. These small studies, particularly if they fail to replicate the drug–gene interaction (perhaps due to inadequate power), may not be convincing to pediatric providers who are considering pharmacogenetic implementation in their clinical practice. Although each of the drug–gene interactions discussed herein has been clinically implemented for pediatric patients, most children who are treated with these drugs do not receive preprescription pharmacogenetic testing, as these tests are localized to a few early adopters.

The validation of pharmacogenetic associations in pediatric patients is, however, an important step prior to implementation. The complex physiology of growth and development can lead to pediatric-specific effects. As discussed above, voriconazole variability, after accounting for *CYP2C19* variation, is more pronounced in children than adults, indicating additional genetic or nongenetic factors influencing exposure. SSRIs have age- and drug-specific pharmacokinetic profiles, which should ideally be incorporated into dosing recommendations. It has also been demonstrated that the effect size for the *SLCO1B1* variant on simvastatin disposition in children is twofold that of adults (106), providing another example of the impact of age on drug–gene interactions.

The population health impact of gene-guided dose optimization for children depends on the frequency of drug exposures and genetic variants and the severity of the adverse outcomes. A study in one tertiary care children's hospital demonstrated that exposures to sertraline and escitalopram were common (over 500 children exposed per year), atomoxetine and tacrolimus were less common (200–400 per year), and fluvoxamine and voriconazole were rare (30–40 per year) (107). Given the frequency of atypical CYP2D6 and CYP2C19 function, gene-guided therapy for drugs such as the SSRIs can improve therapeutic outcomes for many children. Conversely, while thiopurine drug exposures and the problematic genotypes are relatively uncommon in children, the potential adverse events

(life-threatening cytopenias) are severe, emphasizing the value of pre-exposure genetic testing.

There are several drugs commonly used in children for which there is emerging evidence for pharmacogenetic associations. Methylphenidate, a mild central nervous system stimulant prescribed for ADHD (108), is predominantly metabolized through carboxylesterase 1 (CES1). One of the many variants in *CES1*, rs71647871, considerably reduces methylphenidate metabolism, increases methylphenidate exposure, and reduces the dose requirement for children (109–112). Risperidone is an atypical antipsychotic drug used in the management of schizophrenia, bipolar disorder, autism, and other mental/behavioral health diagnoses. Risperidone is metabolized by CYP2D6, and CYP2D6 metabolizer status is associated with adverse events, including weight gain (113–116). Proton pump inhibitors (PPIs) are one of the most commonly prescribed drugs in the United States and are metabolized predominately by CYP2C19 (117). CYP2C19 metabolizer status has been demonstrated to impact PPI exposure, drug efficacy, and adverse events in children (118–126).

For many drugs with well-established pharmacogenetic associations in adults, there are no data in children. In some cases, this is due to the infrequent use of the drug in pediatric patients (e.g., the antiplatelet drug clopidogrel), but other drugs with potential pharmacogenomic associations are commonly used in children (107). The anti-nausea drug ondansetron is metabolized by CYP2D6, and adult ultrarapid metabolizers are frequently nonresponders to therapy. Ondansetron is one of the most commonly used drugs in pediatrics, which may facilitate investigation of the impact of CYP2D6 function on ondansetron response in children.

Most clinically implemented pharmacogenetic drug-gene pairs involve drug metabolism genes. The sentinel observations of genetic variation influencing drug response were in the drug metabolism enzymes and set the precedent for the importance of these enzymes (127–129). The ability to analyze drug concentrations as an outcome in pharmacokinetic studies has facilitated further discoveries. Given the complexity of drug responses, it is likely that genetic variation in drug targets and the downstream pathways make significant contributions to variability in therapeutic outcomes. Modern genomic techniques and the definition of pharmacodynamic outcomes have the potential to fuel additional discoveries of important drug–gene interactions in adults and children.

5. STRATEGIES FOR ADVANCING GENE-BASED DOSE OPTIMIZATION FOR CHILDREN

The generation of high-quality, validated, generalizable evidence for pediatric pharmacogenetics is necessary for pediatric patients to reap the benefits of precision medicine. One strategy for gathering this evidence is to use real-world data generated during the routine care of pediatric patients to validate known pharmacogenetic findings and discover novel associations. Real-world data have the advantage of representing the target population for therapy, thus including the appropriate ages, demographics, and disease states. Real-world data also may overcome some practical barriers to pediatric research

studies, using strategies such as analysis of remnant blood specimens to avoid additional blood draws. Careful attention must be paid to data quality to ensure that findings are robust (130).

Establishing evidence for the benefits of gene-based dosing for children is perhaps the most effective way to facilitate the implementation of this approach. Demonstration of the costs and benefits (e.g., decreased length of stay for oncology patients who undergo gene-guided dosing of chemotherapy) will increase enthusiasm among health-care institutions and payers. Demonstration of improved outcomes (e.g., reduction in organ rejection for transplant patients with gene-based tacrolimus dosing) will convince health-care providers, patients, and parents of the utility of pharmacogenetic testing. Pragmatic trials of gene-based dosing may be an efficient way to generate this evidence (131, 132). However, given that only about 1–10% of patients (depending on the relevant gene) harbor an actionable pharmacogenetic variant, the sample size needed to evaluate these outcomes is large. Collaboration across pediatric centers through national networks will facilitate the timely accumulation of data.

The implementation of pharmacogenetic testing and clinical decision support is not a straightforward task (71, 133–138). Resources for implementation are being developed by CPIC (139) and IGNITE. The implementation barrier may be difficult to overcome in many settings with limited laboratory resources and information technology support. The generation of low-cost, easy-to-interpret pharmacogenetic testing technology and interoperable clinical decision support for pharmacogenetic test results generated from a variety of sources are required for widespread adoption of gene-based dose optimization outside of major academic children's hospitals.

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Glossary

Pharmacogenetics
the effects of genetic variation on an individual's response to a drug

CPIC
international team facilitating genotype-guided therapy by creating, curating, and posting peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines

Pharmacokinetics
movement of drugs/metabolites within the body, including absorption, distribution, metabolism, and excretion; "What the body does to the drug"

Cytochrome P450
family of enzymes that metabolize drug compounds; star allele nomenclature used to denote variations within the gene, with ∗1 typically indicating fully functional protein product

Pharmacodynamics

effects of a drug through the mechanism of action, e.g., binding to a drug receptor leading to downstream signaling cascades; “What the drug does to the body”

Therapeutic drug monitoring

clinical practice of measuring a specific drug’s concentration in a patient’s blood to achieve a target concentration through dose titration

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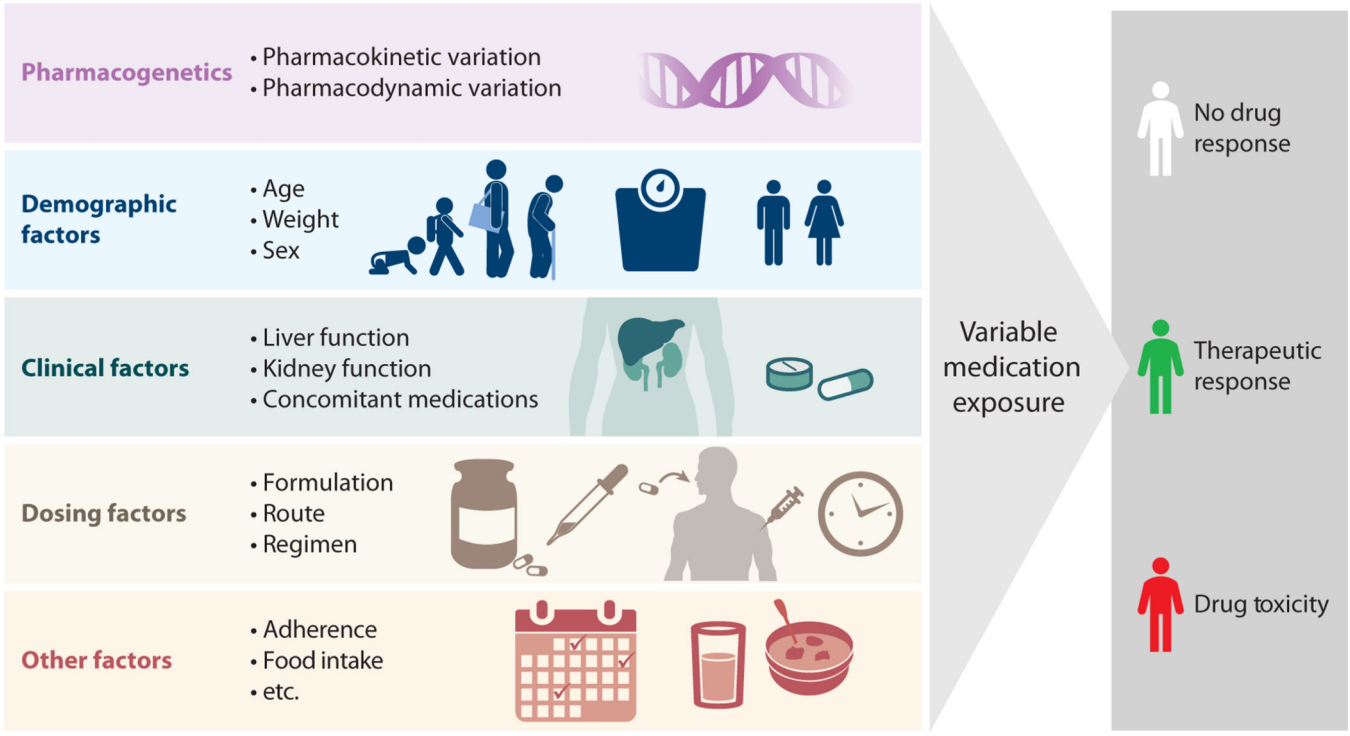

Figure 1.

Illustration of factors contributing to individual differences in drug exposure. In addition to pharmacogenetics, demographic factors (age, weight, and sex), clinical factors (organ function and other drugs), dosing factors (formulation, route, and timing), and issues such as adherence and food intake are important determinants of drug exposure. Interindividual differences in drug exposure can lead to differences in drug response, including inefficacy or toxicity.

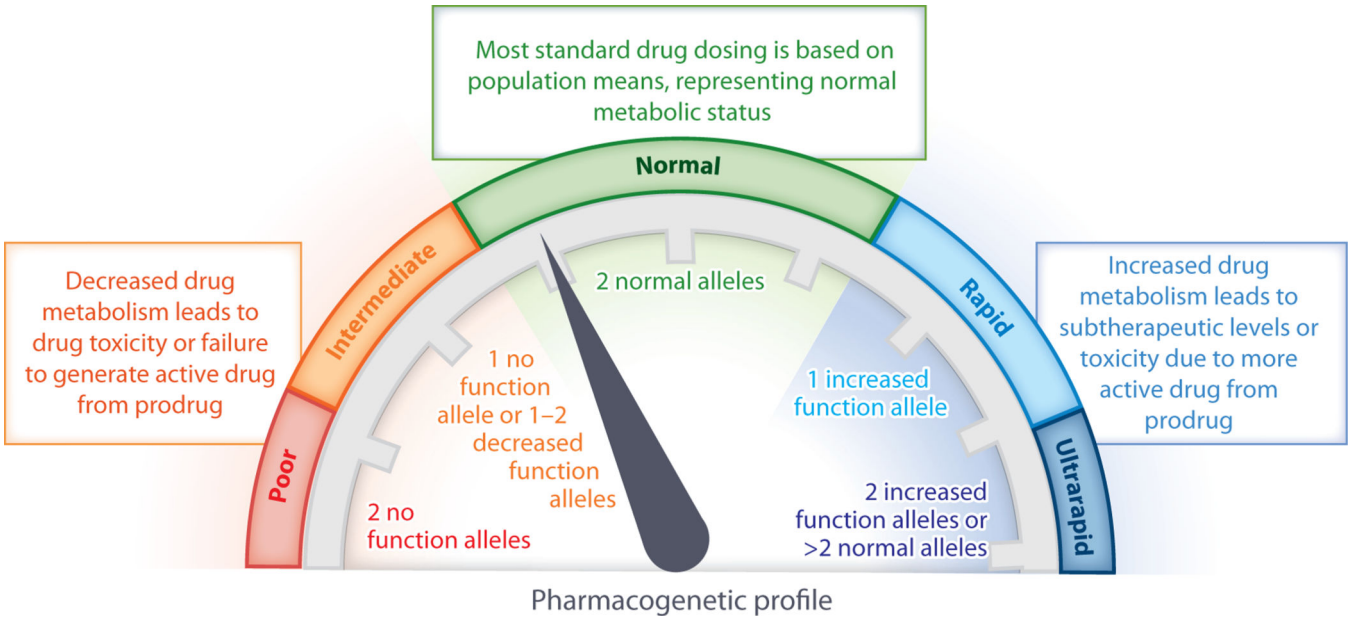

Figure 2.

The impact of genetic variants on metabolizer status. Due to genetic differences, the functional activity of a drug metabolism enzyme may be absent, decreased, normal, or increased. Depending on the combination of alleles present, each individual can be classified regarding their functional status for each drug metabolic enzyme as a poor, intermediate, normal, rapid, or ultrarapid metabolizer.

Table 1

Selected drug–gene interactions with clinical guidelines relevant to pediatric populations

Drug	FDA-approved pediatric indications (age)	Additional clinical uses	Gene(s)	Gene-based dose adjustments
Codeine	Pain (ages 12+ as part of combination drug)	None[a]	*CYP2D6*	Use alternate therapy for CYP2D6 UM and PM
Azathioprine	None	Renal transplant Inflammatory bowel disease Autoimmune disease Other malignancies	*TPMTNUDT15*	Drastically reduce dose for TPMT PM Reduce dose for TPMT IM Reduce dose for NUDT15 IM and PM
Mercaptopurine	Acute lymphocytic leukemia (all ages)			
Thioguanine	Acute nonlymphocytic leukemia (all ages)			
Escitalopram	Major depression (ages 12+)	Anxiety Autism and pervasive developmental disorders	*CYP2C19*	Use alternate therapy for CYP2C19 UM 50% dose reduction for CYP2C19 PM
Sertraline	Obsessive-compulsive disorder (ages 6+)			
Fluvoxamine	Obsessive-compulsive disorder (ages 8+)	Anxiety Major depression	*CYP2D6*	25% dose reduction for CYP2D6 PM
Atomoxetine	Attention deficit hyperactivity disorder (ages 6+)	None	*CYP2D6*	Aggressive dose titration (increase) for CYP2D6 NM, UM
Tacrolimus	Liver transplant (all ages)	Heart and kidney transplant Nephrotic syndrome	*CYP3A5*	Increase dose 1.5–2 times for CYP3A5 expressers
Voriconazole	Invasive fungal disease (ages 12+)	Antifungal prophylaxis	*CYP2C19*	Use alternate therapy for CYP2C19 UM Decrease dose for CYP2C19 PM

[a]Children under 18 years of age should not be given prescription cough and cold medicines containing codeine.

Abbreviations: FDA, Food and Drug Administration; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.