Editorial

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Pharmacogenomics

Pharmacogenetics of treating pediatric anxiety and depression

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"We advocate for evidence-based guidelines for PGx use in children and adolescents with anxiety and depressive disorders, while planning larger and more comprehensive PGx studies in these patients."

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Anxiety and depressive disorders are the most common mental health conditions affecting children and adolescents [1,2], and rank among the biggest drivers of healthcare burden for individuals under the age of 18 [3,4]. Despite early onset [5,6], and significant burden [4], pediatric anxiety and depressive disorders are often unrecognized and untreated [7], despite the availability of evidence-based treatments: cognitive behavioral therapy, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) [8]. Among SSRI and SNRI treatments for major depressive disorder (MDD), anxiety disorders (i.e., generalized anxiety disorder, separation and social anxiety disorders), and obsessive–compulsive disorder (OCD), five medications have US FDA indications for patients less than 18 years of age: escitalopram (MDD), fluoxetine (MDD, OCD), fluvoxamine (OCD), sertraline (OCD) and duloxetine (generalized anxiety disorder). However, these medications (and others) are commonly utilized 'off label' based on data supporting their use. Despite the evidence base for these medications, there is tremendous heterogeneity in response. In fact, nearly two in five patients with anxiety disorders or MDD [9–11] fail to respond to these medications. Accumulating data indicate that pharmacogenetic (PGx) factors likely account for variability in improvement and tolerability, and may be helpful in optimizing drug selection and dosing.

Most studies of SSRI PGx are performed in adults with MDD, and translation across ages and to other disorders is not clear. There are significant differences between adult and pediatric patients in the frequency and magnitude of side effects of these medications. They may be due, in part, to differences in activity of drug metabolizing enzymes that change throughout development impacting the pharmacokinetics of these medications. For instance, escitalopram and sertraline exposure may be up to 30% lower in youth compared with adults given the same dose [12] while fluoxetine and fluvoxamine exposure may be up to threefold higher in youth than adults given the same dose [13,14].

SSRIs are primarily metabolized by hepatic cytochrome P450 enzymes, including CYP2D6 and CYP2C19. There are common genetic variants that influence the activity of these enzymes. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published an evidence-based guideline that provides a review of the literature, genotype to phenotype interpretation and dosing recommendations for SSRIs [15]. However, the authors caution the use in children as the guideline was largely based on evidence from adults and there are differences in the pharmacokinetics of these medications between adults and pediatric patients.

Future Medicine

In addition to the CPIC guidelines, PharmGKB [16] curates PGx literature and summarizes pathways, including SSRI pharmacokinetics [17] and pharmacodynamics [18]. Additionally, the pharmacokinetic and pharmacodynamic genes associated with SSRI/SNRI response in pediatric patients were recently reviewed [19]. Currently, the most commonly investigated pharmacokinetic genes are *CYP2D6* and *CYP2C19*, and the pharmacodynamic gene most often investigated, *SLC6A4*, encodes the target of the SSRIs, the serotonin transporter.

There is considerable evidence for the association of CYP2C19 metabolizer status and plasma escitalopram/citalopram concentrations and discontinuation in adults [20,21], which is consistent with one retrospective pediatric study [22]. CYP2C19 poor and intermediate metabolizers (PMs and IMs) have higher escitalopram exposure and are more likely to discontinue treatment (likely due to side effects), whereas the ultrarapid metabolizers are more likely to have subtherapeutic levels and discontinue treatment (likely due to lack of efficacy) compared with normal metabolizers [21].

Sertraline is metabolized by CYP2D6 and CYP2C19, although, its pharmacokinetics seem to be primarily influenced by *CYP2C19* variants. In a small study of sertraline-treated children with Fragile X, CYP2C19 PMs and IMs were more likely to respond [23] and in youth with anxiety and depressive disorders, sertraline was titrated more slowly in PMs and IMs. [24] This study also examined the influence of variants in *SLC6A4* and *HTR2A* (encoding the 5-HT_{2A} receptor), on the dose of sertraline at the time of response. Pharmacodynamic variants had greater influence on the response dose and maximum tolerated dose than pharmacokinetic variants (i.e., *CYP2C19*).

As fluvoxamine is less frequently prescribed in children than other SSRIs, there is less PGx evidence available, and the sample sizes are very small. In one study, CYP2D6 PMs required lower doses to achieve similar plasma concentrations to normal metabolizers [25]. As plasma fluvoxamine concentrations are associated with activation [26], a larger study examining the effect of CYP2D6 on activation in fluvoxamine-treated patients is warranted. Another group demonstrated an influence of *SLC6A4* genotype on fluvoxamine response in children [27].

Fluoxetine is metabolized by CYP2D6 to its active metabolite, norfluoxetine. In CYP2D6 PMs, fluoxetine to s-norfluoxetine ratios are greater compared with non-PMs [28]. However, when the active components are compared between PMs and non-PMs, there is no difference [13,29], and CYP2D6 metabolizer status did not influence 8- or 12-week outcomes in youth receiving fluoxetine [28]. For this reason, there are no current CPIC guidelines for fluoxetine dosing based on CYP2D6. However, based on the perceived possibility of CYP2D6 impact on metabolism, some institutions consider *CYP2D6* genotype to guide fluoxetine therapy [30,31] and a number of PGx testing laboratories include 'guidance' based on this drug–gene pair. There are, however, many investigations into how pharmacodynamic variants influence fluoxetine response (e.g., *HTR1B* [a serotonin receptor]) [32,33] in younger patients.

Many of the studies of antidepressant PGx in children examine a single gene–drug pair or candidate genes; however, the commercially available PGx testing that is most accessible to clinicians includes many genes, and provides recommendations based on algorithms that includes the combination of the genes tested [34]. At this time, the published trials on the utility of commercially available tests exclude pediatric patients. However, the tests are commonly ordered by mental health practitioners working with children and adolescents despite frequently lacking pediatric-specific recommendations and not following CPIC's evidence-based dosing guidelines.

Child and adolescent psychiatrists and other mental health clinicians working with pediatric patients vary considerably in how they use PGx testing. For some, PGx is utilized to select medications while others leverage PGx testing to inform target doses or titration; another group may combine these approaches. Additionally, some utilize combinatorial testing while others use single gene testing (often CYP450-related polymorphisms). In some institutions, clinical pharmacists may be involved in the determination of whether or not ordering a test may be informative, the general interpretation of results or specific application as related to dose or titration modifications. In the community setting, pharmacists are a common accessible point of contact for patients who have general questions about PGx testing or about how results obtained elsewhere may relate to other medications they are taking. Few institutions have implemented PGx testing routinely in child and adolescent psychiatry [31].

PGx education varies across medical and pharmacy schools, residency and fellowship training programs. Even in institutions where PGx education is incorporated, this may lag behind its use in clinics. This may result in misapplication or misinterpretation of PGx testing. In this regard, some believe that a non-normal metabolizer phenotype for an enzyme precludes the use of medications metabolized by that pathway. As another example, medications for which evidence is lacking (e.g., bupropion), where there is evidence of poorer tolerability (e.g., a tricyclic antidepressant being selected in favor of an SSRI) may be selected based on testing. Some antidepressants (e.g., desvenlafaxine) do not have notable PGx relationships, but as presented in results could be misinterpreted

as being an optimal choice for patients. These issues, which largely stem from a lack of education, underscore the need for incorporation of PGx into training and continuing education programs for doctors, pharmacists, genetic counselors and nurses.

Just as the education of healthcare providers is important, so is the education of patients and their parents or guardians. There is no current requirement or standard approach to counseling before or after PGx testing. However, in our opinion, information about what one might reasonably expect from a PGx test is important in managing expectations. Patients (or parents) may be disappointed if they believe that PGx testing will definitively answer the question: Which medication will work best? Further, they may be at risk for misinterpreting results with regard to current or prior treatments. Understanding that PGx is just one factor to consider, and is not a definitive test, is important for patients and their parents to understand prior to testing. Additionally, just as a test may identify genetic factors related to drug response or tolerability, the absence of significant findings may also be helpful in reassuring patients that current or possible next step therapies are not confounded by genetic factors. Just like education related to medications, education related to PGx testing is best if reinforced in a consistent manner across heathcare professionals involved with a patient's care. If done appropriately, this also may help to engage patients (and their caregivers) with their treatment and, in doing so, improve adherence.

As clinicians, we must remind ourselves that PGx testing, like other clinical procedures (e.g., physical examination, laboratory tests, psychological testing) requires that findings be considered in the context of clinical and demographic factors, history and treatment focus (or differential diagnosis). We advocate for evidence-based guidelines for PGx use in children and adolescents with anxiety and depressive disorders, while planning larger and more comprehensive PGx studies in these patients. Through the use of PGx-guided care, we may be able to avoid side effects and hasten treatment response for pediatric patients with anxiety and depression.

Authors' contributions

LB Ramsey, JR Bishop, JR Strawn all made substantial contributions to the conception or design of the work, drafted/revised the work, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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